IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

DEFENDANT ELI LILLY AND COMPANY'S NOTICE OF FILING UNDER SEAL

Defendant Eli Lilly and Company, by and through counsel of record, hereby files its Motion Requesting Confidential Protections of Regulatory Communications Not Subject to Public Disclosure, and accompanying Affidavit of Timothy R. Franson, under seal, attached to this notice. Portions of the content of the Motion and the Affidavit have been deemed confidential.

DATED this 28th day of February, 2008.

PEPPER HAMILTON LLP
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George A. Lehner, admitted *pro hac vice*
John F. Brenner, admitted *pro hac vice*
Andrew R. Rogoff, admitted *pro hac vice*
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and
LANE POWELL LLC
Attorneys for Defendant

By _____
Brewster H. Jamieson, ASBA No. 8411122
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I certify that on February 28, 2008, a copy of the foregoing was served by hand-delivery on:

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009867 0038/163655.1

See 6/13/08 order of Judge Rindner pages 12 and 13 Documents Unsealed 8/11/08 Made

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Pages 5659A-5672

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, v. ELI LILLY AND COMPANY, Defendant.	Case No. 3AN-06-05630 CI **[FILED UNDER SEAL]**

DEFENDANT ELI LILLY AND COMPANY'S MOTION REQUESTING CONFIDENTIAL PROTECTIONS OF REGULATORY COMMUNICATIONS NOT SUBJECT TO PUBLIC DISCLOSURE

Although Eli Lilly and Company agrees that public access to this trial is appropriate, it seeks a narrowly tailored order that would bar Courtroom View Network from videotaping for public transmission that portion of the trial that would involve the disclosure of highly confidential, valuable trade secret information contained in regulatory submissions and exempt from disclosure under the Freedom Of Information Act ("FOIA"). Lilly also requests that the Court exclude the public from these portions of the trial.

Specifically, Lilly requests that the Court protect from disclosure Lilly's 2007 confidential submissions to the Food and Drug Administration ("FDA") and the related communications between Lilly and the FDA.[1] These documents contain trade secret

[1] Lilly's request encompasses the documents themselves, as well as references to same through testimony or briefing.

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information, the confidentiality of which Lilly and the FDA vigilantly protect, and which would not otherwise be subject to public disclosure.

I. RULE 26 PERMITS THIS COURT TO PROTECT LILLY'S CONFIDENTIAL DOCUMENTS.

Rule 26(c) of the Alaska Rule of Civil Procedure authorizes a court to enter, "on such terms and conditions as are just," any order "which justice requires to protect a party or person from annoyance, embarrassment, oppression, or undue burden or expense." The court may enter such an order to protect, *inter alia*, Lilly's "trade secret[s] or other confidential research, development, or commercial information."[2] Given the "potential for abuse" attendant to liberal discovery rules,[3] Rule 26(c), like its federal counterpart, permits a party to seek a protective order prohibiting dissemination of information produced in discovery upon a showing of "good cause." "This provision . . . applies primarily to commercially sensitive information that might cause the defendant some competitive harm."[4] As a result of such protections, federal and state courts have protected the confidentiality of Lilly's internal documents, as well as its confidential communications with the FDA.

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[2] *Phillips v. General Motors Corp.*, 307 F.3d 1206, 1211 (9th Cir. 2002) (courts have "broad latitude to grant protective orders to prevent disclosure of materials for many types of information, including *but not limited to*, trade secrets or other confidential research, development, or commercial information.").

[3] *Seattle Times Co. v. Rhinehart,* 467 U.S. 20, 34-35 (1984).

[4] Jack B. Weinstein, *Secrecy in Civil Trials: Some Tentative Views*, 9 J.L. & Pol'y 53, 57 (2000).

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II. REGULATORY SUBMISSIONS AND COMMUNICATIONS BETWEEN LILLY AND THE FDA CONTAIN TRADE SECRETS AND CONFIDENTIAL COMMERCIAL INFORMATION.

The confidential documents at issue in this motion contain current trade secret information and confidential commercial information, including data recently submitted to the FDA.[5] They reflect statutorily protected, private communications between Lilly and the FDA,[6] would not be subject to disclosure under FOIA,[7] and should not be publicly disclosed at trial. The documents include:

- Plaintiff's Ex. No. 10094: Mar. 27, 2007 Letter from T. Laughren to R. Wojcieszek.
- Plaintiff's Ex. No. 10105: Feb. 20, 2007 Chronological Timeline of Regulatory Submissions.
- Plaintiff's Ex. No. 10104: May 10, 2007 Regulatory Response.
- Plaintiff's Ex. No. 10106: Feb. 20, 2007 Regulatory Response.
- Plaintiff's Ex. No. 10107: June 29, 2007 Regulatory Response.
- Plaintiff's Ex. No. 10108: Aug. 28, 2007 letter from T. Laughren to R. Wojcieszek.
- Plaintiff's Ex. No. 10109: Sept. 4, 2007 FDA Briefing Document.
- Plaintiff's Ex. No. 10110: Sept. 2007 Meeting Minutes.

[5] Affidavit of Timothy R. Franson in Support of Defendant Eli Lilly and Company's Motion Requesting Protection of Regulatory Communications Not Subject to Public Disclosure ("Franson Affidavit") at ¶ 9.

[6] *Id.*

[7] *Id.* at ¶ 13.

- Plaintiff's Ex. No. 10111: Note to the Reviewers.
- Plaintiff's Ex. No. 10153: Aug. 28, 2007 letter from T. Laughren to R. Wojcieszek (duplicate).
- Plaintiff's Ex. No. 10153: Sept. 4, 2007 FDA Briefing Document (duplicate).

Among the factors considered for confidentiality protection under Fed. R. Civ. P. 26(c)(7) are: (1) the extent to which information is known to those outside the business; (2) the extent to which the information is known to those inside the business; (3) the measures taken to guard the secrecy of the information; and (4) the value of the information to the business and its competitors.[8] The documents at issue here meet this standard.

A. The Extent to Which the Information Is Known Outside Lilly.

The regulatory documents identified by the State are not known outside Lilly, except among a small subset of FDA employees. Both Lilly and the FDA protect this information from public disclosure, in order to facilitate the regulatory compliance process.[9]

[8] *Sullivan Mktg. v. Valassis Comm.*, 1994 U.S. Dist. LEXIS 5824, at *4 (S.D.N.Y. 1994); *see Wilcock v. Equidev Capital L.L.C.*, 2001 U.S. Dist. LEXIS 11744, at *2 (S.D.N.Y. 2001). Courts in the Ninth Circuit have focused primarily on the potential for irreparable harm to the party seeking a protective order. *See Phillips*, 307 F.3d at 1210-11 (focusing on harm if no protective order is entered); *Nutratech, Inc. v. Syntech (SSPF) Intern., Inc.*, 242 F.R.D. 552, 555 (C.D.Cal. 2007) (entering protective order to protect against competitive harm); *In re Worlds of Wonder Sec. Litig.*, 147 F.R.D. 214, 216 (N.D.Cal. 1992) (entering a protective order covering "closely-guarded" documents because "their disclosure to competitors probably would be harmful").

[9] Franson Affidavit at ¶¶ 9, 11-12.

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B. The Extent to Which the Information Is Known To Those Inside Lilly.

The documents at issue here are not widely disseminated within Lilly, but instead are restricted to those employees with responsibility for regulatory affairs. Accordingly, Lilly employees, in general, do not have access to these documents.[10]

C. Measures Taken To Guard the Secrecy of the Information.

Given the restrictions of dissemination outlined above, Lilly and the FDA both take steps to insure that their regulatory interactions, documents and information remain confidential. Lilly recognizes the competitive threats within the pharmaceutical industry and has implemented elaborate safety precautions to prevent its confidential information from falling into competitors' hands. Within Lilly, additional measures are taken to guard the secrecy of these documents. In addition to the extraordinary measures Lilly takes to guard its computer systems from external disclosures and its physical plant facilities with security personnel, all Lilly employees are bound by The Red Book – Code of Business Conduct and by Global Lilly Policies, each of which delineates confidentiality measures for all Lilly Information Assets.[11]

[10] *Id.* at ¶¶ 10-11.

[11] *Id.*

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Among the ways the FDA protects these documents is though an exemption to FOIA requests.[12] Under section 552(b)(4) of FOIA ("Exemption 4"), documents will not be released to the public if: (1) the information for which exemption is sought is "commercial or financial" in character; (2) the information is obtained from a person;[13] and (3) the information is "privileged or confidential." Federal law prohibits the FDA from disclosing trade secrets.[14] Indeed, the FDA's disclosure of trade secrets is an actionable tort.[15]

In debating Exemption 4, Congress contemplated that information that customarily would not be made public should not lose its confidential nature simply because the information was provided to the government.[16] Congress was specifically concerned about the need to protect submitters from the competitive disadvantage attendant to public disclosure of confidential information.[17] Exemption 4 is meant to "'(1) encourag[e] cooperation by those who are not obliged to provide information to the government and

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[12] *Id.* at ¶ 13.

[13] "Person" encompasses corporations.

[14] *See Jerome Stevens Pharm., Inc. v. FDA*, 402 F.3d 1249, 1252 (D.C. Cir. 2005) (citing, *inter alia*, 21 U.S.C. § 331(j), and 5 U.S.C. § 552(b)(4)).

[15] *Id.* at 1255.

[16] *New York Public Interest Research Group v. EPA,* 249 F. Supp. 2d 327, 332 (S.D.N.Y. 2003).

[17] *See id.*

(2) protect[] the rights of those who must.'"[18] Because these documents are exempted from FOIA, they are exchanged with an expectation and understanding that they will not be disseminated to the public.

D. Value of the Information to Lilly and Its Competitors.

The data contained in these documents were *recently submitted* to the FDA, and concern a *currently marketed product*, making the data attractive for use by competing pharmaceutical companies. The pharmaceutical industry operates in an intensely competitive market generating revenues in the hundreds of billions of dollars per year. The atypical antipsychotic market is fiercely competitive, and Lilly must compete with pharmaceutical companies such as AstraZeneca, Bristol-Myers Squibb, Janssen, Merck, Novartis, and Pfizer, as well as with companies manufacturing generic medications, and potential competitors who may be deciding whether to enter these markets. It is a standard practice in the pharmaceutical industry to engage in competitive intelligence and monitor competitor intelligence data. Maintaining the confidentiality of these documents is vital to Lilly's continued survival and success. Correspondingly, disclosure of these documents would be devastating for Lilly, and could result in significant, irreparable harm.

[18] *Nadler v. Fed. Deposit Ins. Corp.*, 92 F.3d 93, 96 (2d Cir. 1996) (quoting *National Parks & Conservation Ass'n v. Morton*, 498 F.2d 765, 770 (D.C.Cir. 1974) (alterations in *Nadler*)).

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At the outset, the clinical data discussed in such documents are owned by Lilly, and were obtained and analyzed by Lilly at considerable time and expense. The data itself are proprietary in nature, having definable value to Lilly – value that could be transferred to Lilly's competitors if disclosed. Disclosure of this material would provide a competitor with insight into Lilly's internal workings, including Lilly's clinical trial strategies and protocols, as well as its deliberative and implementation processes. Accordingly, disclosure of the regulatory documents and information at issue would cause irreparable commercial hardship to Lilly while also providing a benefit to its competitors, yet no concomitant value to the public.[19]

That these regulatory communications are of such recent vintage further increases the harm if they are publicly disclosed. Companies with products that compete with Symbyax and Zyprexa could use these documents to gain insight as to the types of trials Lilly has sought and seeks to support, and exploit this information with responsive studies and marketing presentations to Lilly's customers.[20] Just as Lilly does not have access to its

[19] Franson Affidavit at ¶¶ 15-17.

[20] *Id.* at ¶ 17.

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competitors' communications with regulatory agencies, to avoid irreparable harm in the commercial marketplace, Lilly's confidential communications must be similarly protected.[21]

III. THE PUBLIC RIGHT OF ACCESS DOES NOT TRUMP LILLY'S INTERESTS IN MAINTAINING THE CONFIDENTIALITY OF ITS 2007 REGULATORY DOCUMENTS.

Simply because a confidential discovery document has been filed with the Court does not mean it loses its confidentiality. "Applying a strong presumption of access to documents a court has already decided should be shielded from the public would surely undermine, and possibly eviscerate, the broad power of the district court to fashion protective orders."[22] Instead, when evaluating the confidentiality of documents at trial, courts employ a "compelling reasons" standard to balance the public's interest in accessing the court with a litigant's interest in protecting confidential commercial information.[23] Under this standard, a

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[21] Under these same principles, Lilly's February 20, 2007, response to the FDA is confidential because it contains trade secret information and confidential commercial information. Soon after *The New York Times* published a series of articles relating to Zyprexa, the FDA sent Lilly a letter inquiring into the allegations in them. On February 20, 2007, Lilly submitted a three-part response to the FDA. The first part of this response is based upon, and structured around, *The New York Times* articles. (*The New York Times'* allegations were derivative of a biased subset of confidential Lilly documents, disclosed in violation of a court order). In preparing part one of this response to the FDA, Lilly offered views regarding *The New York Times* allegations, as part of a frank exchange of confidential information with the FDA to facilitate due diligence and the compliance process. Similarly, the second part contains literature requested by the FDA, and the third part contains data requested by the FDA. Although the circumstances behind the generation of this response were unique, this was a regulatory submission which must be afforded the same protections as typical regulatory submissions to preserve full and frank communications, and to prevent disclosure of any confidential information contained within.

[22] *Phillips*, 307 F.3d at 1213.

[23] *In re Gabapentin Patent Litig.*, 312 F. Supp. 2d. 653, 664 (D.N.J. 2004).

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"court must weigh relevant factors, base its decision on a compelling reason, and articulate the factual basis for its ruling . . . without relying on hypothesis or conjecture."[24] "Relevant factors include the public interest in understanding the judicial process and whether disclosure of the material could result in improper use of the material for scandalous or libelous purposes or infringement upon trade secrets."[25] "A well-settled exception to the right of access is the protection of a party's interest in confidential commercial information, such as a trade secret, where there is a sufficient threat of irreparable harm."[26] "[C]ourts may deny access to judicial records … where they are sources of business information that might harm a litigant's competitive standing."[27] The documents for which Lilly seeks protection contain current and confidential trade secret information intended solely for the use of the FDA in its deliberative process. Given the irreparable harm that would result from their disclosure, there are compelling reasons to keep them confidential.

IV. CONCLUSION

For the foregoing reasons, Lilly requests that the Court protect from disclosure at trial the identified confidential regulatory documents and information that would not otherwise be subject to public disclosure.

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[24] *Pintos v. Pacific Creditors Assoc.*, 504 F.3d 792, 802 (9th Cir. 2007) (alteration in original, internal quotation marks and footnote omitted).

[25] *Id.* at 802 n.9 (internal quotation marks omitted).

[26] *In re Gabapentin Patent Litig.*, 312 F. Supp. 2d. at 664 (internal quotation marks omitted).

[27] *Republic of the Philippines v. Westinghouse Elec. Corp.*, 949 F.2d 653, 662 (3d Cir. 1991) (internal quotation marks omitted).

DATED this 28th day of February, 2008.

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John F. Brenner, admitted *pro hac vice*
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I certify that on February 28, 2008, a copy of the foregoing was served by hand on:

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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

STATE OF ALASKA,	)	
Plaintiff,	)	
v.	)	Case No. 3AN-06-5630 CIV
ELI LILLY AND COMPANY,	)	
Defendant.	)	

AFFIDAVIT OF TIMOTHY R. FRANSON IN SUPPORT OF DEFENDANT ELI LILLY AND COMPANY'S MOTION REQUESTING PROTECTION OF REGULATORY COMMUNICATIONS NOT SUBJECT TO PUBLIC DISCLOSURE

I, TIMOTHY R. FRANSON, being duly sworn, state as follows:

1. I am currently employed by Eli Lilly and Company ("Lilly") as Vice President, Global Regulatory Affairs.

2. Since 1996, I have had regulatory management responsibility in the United States for all products within the neuroscience therapeutic area. I have worked closely with the regulatory scientists who have primary responsibility for Zyprexa®.

3. During my tenure, I have participated in meetings and discussions with the Food and Drug Administration ("FDA") regarding changes to the United States label for Zyprexa in 2003 and 2007.

4. On January 12, 2007, the FDA sent Lilly a letter requesting certain information in response to articles published in *The New York Times*. On February 20, 2007, Lilly submitted to the FDA the solicited response, in three parts. Part one of this response, structured in direct reply to allegations in *The Times* articles, offers Lilly's views regarding the allegations. The second part contains literature requested by the FDA, and the third part contains data requested by the FDA.

5. In March 2007, in the context of an approvable letter for a new indication for Symbyax® (combination of olanzapine and fluoxetine), the FDA requested certain analyses of Zyprexa clinical trial data with the intent of updating the United States label. The FDA made a similar request in April 2007, in an approvable letter for a new indication for Zyprexa.

6. In August and September 2007, Lilly submitted the requested analyses to the FDA.

7. During this time, Lilly and the FDA also exchanged communications regarding draft labeling. Lilly revised the Zyprexa label on October 5, 2007.

8. Pharmaceutical companies and regulatory bodies regularly exchange confidential information to facilitate the drug approval and compliance process in an efficient and fair manner. These protections encourage full and frank communications, and both parties maintain these communications in confidence.

9. Regulatory submissions and communications between Lilly and the FDA are private and confidential, not subject to public disclosure. They contain confidential proprietary information, confidential commercial information, confidential trade secret information, and other confidential information. These submissions and communications are exchanged between Lilly and the FDA with an expectation and understanding that they will not be disclosed or disseminated.

10. Such regulatory submissions and communications are not widely disseminated within Lilly, but instead are restricted to those employees with responsibility for regulatory affairs. Lilly employees, in general, do not have access to these documents.

11. Within Lilly, measures are taken to guard the secrecy of these documents. In addition to the measures Lilly takes to guard its computer systems from external disclosures and its physical plant facilities with security personnel, Lilly employees are bound by The Red Book – Code of Business Conduct, and by Global Lilly Policies, each of which delineates confidentiality measures for Lilly Information Assets.

12. Such regulatory submissions and communications are not publicly available, nor have they been disclosed to the public.

13. These types of documents would not be subject to disclosure under the Freedom of Information Act ("FOIA"), even if requested.

14. Documents such as the New Drug Applications for Zyprexa and for Symbyax, which typically contain such submissions and communications, also are not publicly available, nor have they been disclosed to the public. Such documents contain a cover sheet typically reflecting the following statement:

> THIS DOCUMENT CONTAINS TRADE SECRETS, OR COMMERCIAL OR FINANCIAL INFORMATION, PRIVILEGED OR CONFIDENTIAL, DELIVERED IN CONFIDENCE AND RELIANCE THAT SUCH INFORMATION WILL NOT BE MADE AVAILABLE TO THE PUBLIC WITHOUT EXPRESS WRITTEN CONSENT OF ELI LILLY AND COMPANY.

15. Clinical data discussed in such submissions and communications is owned by Lilly. Lilly dedicates a substantial amount of resources to clinical trials and data analysis. The data is proprietary because it has definable value to Lilly, and that value could be transferred to Lilly's competitors if disclosed. With access to such information, competitors could gain

considerable insight into Lilly's strategies, plans, processes, goals, and actions. This type of information is useful as a guide for competitors' own drug development and research efforts.

16. Dissemination of the data and of these strategies could cause commercial hardship to Lilly and would benefit its competitors in the marketplace.

17. In particular, the 2007 submissions and communications are so current that companies with products in competition with Zyprexa and Symbyax could use this information to gain unfair insight to their benefit, as well as to exploit this information to harm Lilly in the marketplace today.

Timothy R. Franson

Timothy R. Franson

SWORN TO AND SUBSCRIBED
BEFORE ME, NOTARY, this
27th day of February, 2008
Lana L Dishman
Notary Public

Lana Dishman
My Commission Expires:
February 8, 2015
Resident of Johnson County

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, vs. ELI LILLY AND COMPANY, Defendant.	Case No. 3AN-06-5630 CIV

NOTICE OF FILING PLAINTIFF'S COUNTER DESIGNATIONS TO DEFENDANT'S DEPOSITION DESIGNATIONS AND EXHIBITS UNDER SEAL

On this date the State of Alaska is filing a pleading titled "Plaintiff's Counter Designations to Defendant's Deposition Designations for Trial." Because one or more exhibits filed with this pleading may be confidential documents under the Court's April 6, 2007 oral ruling, the State of Alaska is submitting this pleading and the attached exhibits under seal.

DATED this 28 day of January, 2008.

See Judge Pindners 6/13/08 order, page 21, #18 Documents unsealed Lurde 8/11/08

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Certificate of Service
I hereby certify that a true and correct copy of
Notice of Filing Plaintiff's Counter Designations To Defendant's Deposition Designations for Trial
was served by messenger on:

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Barry Boise, via email (boiseb@pepperlaw.com)
Pepper Hamilton

By Peggy J. Crowe
Date 1/28/08

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Pages 5673B-5741

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, v. ELI LILLY AND COMPANY, Defendant.	)	Case No. 3AN-06-05630 CI

PLAINTIFF'S COUNTER DESIGNATIONS TO DEFENDANT'S DEPOSITION DESIGNATIONS FOR TRIAL

Plaintiff, through undersigned counsel, hereby files its Counter-Designations to Defendant Eli Lilly and Company's Designations of Deposition Testimony to be offered at trial as follows:

Exhibit 1; Deposition of Charles Beasley, Jr. M.D (Vol. 1)

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159:4	159:23

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Exhibit 2; Deposition of Charles Beasley, Jr. M.D (Vol. 2)

START (PAGE:LINE)	END (PAGE:LINE)
590:23	592:20
593:9	594:5
595:20	596:9
601:6	601:8
602:8	602:11
603:2	603:15
605:9	608:12
610:6	612:21
616:17	617:6
619:8	622:10
639:7	639:12
640:3	640:16
643:19	645:5
647:7	649:19
651:6	652:4
653:13	654:8
654:19	655:22
657:7	658:9
659:8	660:13
663:12	665:2
665:6	665:20
666:10	667:14
668:7	669:13
671:14	674:13
679:5	683:3
685:5	685:23
687:17	689:6
690:15	690:13
710:8	713:13
734:21	739:21
740:14	740:19

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744:19	745:3
746:17	747:7
780:24	781:18

Exhibit 3; Deposition of Lucy Curtiss, M.D.

START (PAGE:LINE)	END (PAGE:LINE)
5:18	5:21
6:8	6:11
26:4	26:9
28:17	28:19
34:21	35:12
36:24	37:5
38:6	38:23
42:3	41:8
41:25	42:12
46:25	47:13
47:18	47:23
48:1	48:8
48:11	48:17

Exhibit 4; Deposition of David Campana (Vol. II)

START (PAGE:LINE)	END (PAGE:LINE)
192:15	193:8
216:6	217:7
222:19	222:24
223:14	224:2
228:22	229:3
229:7	229:13
231:10	234:11

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248:3	249:9
250:21	250:23
259:12	259:13
272:13	274:3
275:13	278:11
279:15	279:17
280:5	280:12
308:23	309:20
312::21	313:3
314:5	314:7
314:12	314:15
315:16	316:8
341:16	342:11

Exhibit 5; Deposition of Joel Gilbertson

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15:22	17:7
24:17	24:21
25:10	25:25
26:19	27:5
28:21	29:6
76:14	77:8
77:10	77:25
78:3	78:5

Exhibit 6; Deposition of Duane Hopson, M.D.

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46:14	48:13
59:3	59:13

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62:1	62:13
78:7	79:14
91:4	91:12
99:24	100:20
106:15	107:19

Exhibit 7; Deposition of Karleen Jackson

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5:23	6:9
7:15	8:2
10:8	10:12
10:18	10:23
11:16	11:20
12:5	12:8
14:7	14:22
18:3	18:17
32:10	33:1
34:23	35:2

Exhibit 8; Deposition of Gary Tollefson, M.D.

START (PAGE:LINE)	END (PAGE:LINE)
43:11	43:12
43:15	44:16
44:17	44:19
44:24	45:5
45:7	48:9
55:24	56:3
56:6	56:9
107:9	107:11

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117:10	117:16
118:5	118:8
183:7	183:8
298:10	298:15
298:22	299:7
299:10	301:9
301:12	301:16
301:20	301:22
302:1	302:6
303:9	303:14
383:15	383:16
388:11	394:12

Plaintiff reserves the right to introduce any of the deposition testimony set forth in Defendant's deposition designations. Plaintiff further reserves the right to affirmatively designate any deposition testimony not yet taken in this or any other matter. Plaintiff further reserves the right to introduce additional deposition testimony not included above, if deemed necessary for the rebuttal of testimony from witnesses called by defendant or exhibits introduced by defendant at the trial of this action.

DATED this 28 day of January, 2008.

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Certificate of Service

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Beasley, Charles M.D. (July 26,2006)
159:4-23
Issues: 03 Plaintiff's Counter Designations

159: 4 that they were somehow linked, would you
5 agree that if an individual has both weight
6 gain and is -- has genetic vulnerability then
7 they would be at increased risk for
8 hyperglycemia?
9 MR. SEE: Object to the form.
10 A. I don't know precisely. I
11 believe that the data suggests that the more
12 risk factors you have the higher potential
13 there is for the development of diabetes,
14 whether these are simply additive or they
15 reinforce each other we don't know.
16 Q. Okay. Clearly, you wouldn't
17 want a person to have both weight gain and
18 genetic vulnerability, at least with respect
19 to their risk for diabetes or hyperglycemia,
20 correct?
21 MR. SEE: Object to the form.
22 A. No. I mean, you don't want
23 weight gain or genetic vulnerability.

Beasley, Charles M.D.(July 27, 2006)
590:23-592:20
Issues: 03 Plaintiff's Counter Designations

590:23 QUESTIONS BY MR. ALLEN:
24 Q. Dr. Beasley, Scott Allen, how
591: 1 are you?
2 A. Good.
3 Q. When you testified to me
4 earlier today and yesterday was your
5 testimony truthful and accurate?
6 A. Yes, it was.
7 Q. And when you wrote your
8 e-mails concerning the clinical trials to the
9 people throughout Eli Lilly, were your
10 e-mails truthful and accurate?
11 A. To the best of my knowledge
12 those data were correct at the time I wrote
13 them.
14 Q. Right. So if a jury looks at
15 your e-mails when you say things like
16 "olanzapine is the worst offender," the jury
17 can know that Dr. Beasley truly believes that
18 Zyprexa is the worst offender concerning
19 weight gain in the second generation
20 antipsychotic class?
21 A. No, you have, I believe,
22 slightly mischaracterized what I said. I
23 believe I said second, because I would
24 include clozapine as an atypical
592: 1 antipsychotic.
2 Q. But if your e-mail says, if
3 it says, "olanzapine is the worst offender,"
4 the jury can know that you're telling the
5 truth in your e-mails?
6 A. I believe that e-mail made
7 reference to clozapine.
8 Q. Okay. So we can count on
9 your e-mails, right?
10 A. And again, my understanding
11 of the data at the time.
12 Q. If your e-mails say things
13 like "it would be ludicrous to conclude that
14 weight gain associated with Zyprexa does not
15 put one at increased risk of cardiovascular
16 disease" the jury can count on that to be
17 true, correct?
18 A. Again, with the understanding
19 that if you did empirical analysis that
20 showed otherwise part of the e-mail, yes.

Beasley, Charles M.D.(July 27, 2006)
593:9-594:5
Issues: 03 Plaintiff's Counter Designations

593: 9 Q. Okay. Now we recall, I think
10 it was early on, and I don't know the exhibit
11 number but the jury will have seen it by the
12 time they hear your testimony, that
13 Dr. Breier, I guess he'd be called your boss,
14 one of your bosses, what would he be called?
15 A. No. He was, actually, always
16 a contemporary, a peer of mine.
17 Q. Your peer and co-equal, and
18 as you said had the ear of senior management,
19 right?
20 A. Yes, he had, yes.
21 Q. Thank you. I lost my train
22 of thought but I'm going to get it back. Oh,
23 I know, if Dr. Breier says something akin to
24 this, it's in an exhibit if you want to find
594: 1 it, I'll put it on the screen, let's see if
2 you recall it, "we need to abandon,"
3 abandon -- what's the word "abandon" mean to
4 you?
5 A. That would mean give up.

Beasley, Charles M.D.(July 27, 2006)

595:20-596:9
Issues: 03 Plaintiff's Counter Designations

595:20 Q. And so if Dr. Breier sends an
21 e-mail that says we need to abandon the
22 spinning mentality, you recall that?
23 A. Yes.
24 Q. Dr. Breier as your co-equal
596: 1 certainly knows what's going on at Eli Lilly,
2 doesn't he?
3 MR. SEE: Object to the form.
4 A. And again, I have not
5 discussed that e-mail with Dr. Breier, and as
6 you so rightly characterized he discussed and
7 put in that e-mail a reference to mentality,
8 not to behavior, that was taking place, and I
9 think that's very important.

Beasley, Charles M.D.(July 27, 2006)

601:6-8
Issues: 03 Plaintiff's Counter Designations

601: 6 Q. Mr. See is your counsel,
7 correct?
8 A. That's correct.

Beasley, Charles M.D.(July 27, 2006)

602:8-11
Issues: 03 Plaintiff's Counter Designations

602: 8 Q. Okay. He just asked you
9 questions about clinical trials. Do you
10 recall that?
11 A. Yes, I do.

Beasley, Charles M.D.(July 27, 2006)

603:2-15
Issues: 03 Plaintiff's Counter Designations

603: 2 Q. He talked to you about
3 whether or not it's important during a trial
4 to determine if an event is statistically
5 significant; do you recall that?
6 MR. SEE: Object to the form.
7 A. He, I believe he, actually,
8 asked me to illustrate how we would deal with
9 the data in clinical trials. And I said that
10 one of the things we would do with those data
11 would be to subject them to certain
12 statistical analyses.
13 Q. And you do that in order to
14 see if they have statistical significance?
15 A. That's correct.

Beasley, Charles M.D.(July 27, 2006)

605:9-608:12
Issues: 03 Plaintiff's Counter Designations

605: 9 You testified yesterday under
10 oath that .05 was, approximately, the gold
11 standard in determining statistical
12 significance?
13 A. That's the generally
14 agreed-upon standard.
15 Q. It's the scientific standard?
16 A. That's correct.
17 Q. It is the one that is used by
18 epidemiologists?
19 A. That's correct.
20 Q. All right. And in order to
21 have statistical significance using the gold
22 standard to help one determine a statistical
23 association it has to be .05 P value or less?
24 A. Or less. That is -- there
606: 1 are some exceptions to that but, in general,
2 that is the case.
3 Q. And that's the standard Eli

Lilly uses in its clinical trials?
A. That's correct.
Q. Okay. Now did I hear you tell Mr. See or did Mr. See -- were you trying to indicate that Zyprexa is associated with hypoglycemia?
A. Could we look at -- I'm telling you what the data were reported to us and what the, yes, in this particular trial 7 percent of people, I think it was seven, approximately, 7 percent had, by anytime glucoses, an event that would be called hypoglycemia.
Q. Yes. That's what you told Mr. See?
A. That's correct.
Q. And were you spinning when you all, when you gave your answer, were you spinning the data?
A. Not at all. I'm providing the numbers as they are written here.
Q. Is there something that Mr. See and you could have done to better tell the jury the significance of that 7 percent finding in the clinical trials?
A. I think the most important aspect of that is that it is in excess of what we saw with the hyperglycemia cases. I did not indicate that it proved anything. I said what this is is evidence that we need to look at a larger number of analysis to come to a conclusion.
Q. Well, isn't it a fact that when you have your clinical trials and you look at this data, you were referring to this data on Page 11, weren't you? Isn't that the data on Page 11 you were referring to?
A. Yes, it is.
Q. And that 7 percent figure you gave to Mr. See in your answer to this jury is right here, 7.7, actually, on the hypoglycemia?
A. That's correct.
Q. But that's a meaningless statistic, isn't it?
A. I told you, no, it is not. I told you how we would use that statistic.
Q. What's the P value? Remember, here's the column of P value. You all have it. What's the P value overall of this hypoglycemia you and Mr. See discussed? What's the P value?
A. Compared to haloperidol it is .254.
Q. .254. It doesn't reach statistical significance, does it, sir?
A. No, it does not.

Beasley, Charles M.D.(July 27, 2006)
610:6-612:21
Issues: 03 Plaintiff's Counter Designations

610: 6 Q. And just so the record is now
7 full and complete, this finding on
8 hypoglycemia was not statistically
9 significant using the gold epidemiologic
10 standard, correct?
11 MR. SEE: Object to the form.
12 A. It was not statistically
13 significant.
14 Q. Right. But the
15 hyperglycemia, the elevated blood glucose in
16 the largest clinical trial was statistically
17 significant, wasn't it?
18 A. We have spoken about that on
19 a number of occasions and, yes, that was the
20 fact.
21 Q. So when we look at the data
22 and don't spin the data, the data says
23 hyperglycemia is statistically significant in
24 the largest trial, and hypoglycemia doesn't
611: 1 even approach that, does it, sir?
2 MR. SEE: Object to the form.
3 A. And I cannot answer that
4 because you have characterized that as
5 spinning. I have presented you with the
6 reasons that the seven was discussed.
7 Q. Yes, sir.
8 MR. ALLEN: I object as
9 nonresponsive.
10 QUESTIONS BY MR. ALLEN:
11 Q. What does it mean when you
12 need to come clean? Come clean.
13 A. Discuss openly.
14 Q. Be fair. Is that another --
15 come clean, be fair?
16 A. I think that would be a
17 reasonable characterization.
18 Q. And once you went down to
19 Atlanta in October of 2000, didn't the
20 endocrinologists with whom you spoke and
21 Lilly made a presentation -- I think you said
22 Dr. Cavazzoni made a presentation, right?
23 A. I believe she did, yes.
24 Q. Wasn't it the impression of
612: 1 those in attendance that it was about time
2 for Lilly to come clean on the issue of
3 hyperglycemia and its relationship to
4 Zyprexa?
5 MR. SEE: Object to the form.
6 A. That's not -- we've looked at

a lot of e-mails, that's not my recollection. And I think my best recollection of those data at the time would be captured in my e-mail responding to Dr. Baker.

Q. But you're not the only person at Eli Lilly that writes e-mails and you're not the only doctor. Are you trying to cast some doubt upon somebody else's e-mail?

MR. SEE: Object to the form.

A. All I'm saying is what I can recall in my impression.

Q. Well, can you get out Exhibit 1453? It's there. And if you want me to help you find it I will.

Beasley, Charles M.D.(July 27, 2006)

616:17-617:6

Issues: 03 Plaintiff's Counter Designations

616:17 Q. Okay. Well, this is subject: Meeting with endocronologic -- I keep on massacre-ing that word -- consultants. It says: "Robert, clearly this group of endocrinologists who spoke up, and I would rate those who did speak up as the leaders of the pack."

Let me stop there. We also saw the endocrinologists in the another e-mail referred to as Who's Who in endocrinology, right?

A. I don't recall that but we agreed these are very prominent endocrinologists.

Beasley, Charles M.D.(July 27, 2006)

619:8-622:10

Issues: 03 Plaintiff's Counter Designations

619: 8 Q. "As the leaders of the pack are very concerned with the approach Lilly is taking towards the issue that Zyprexa leads to diabetes. I can only hope that you and all of the team who attended the NADAB --" Can you tell us what that is?

A. That would have been an abbreviation for the group, the North American Diabetes Advisory Board, I believe.

Q. Right. "Meeting are gaining the ear of senior leadership and articulating this finding. Although the board's recommendation is, probably, not the way

Lilly, typically, does business, I do believe they made a very strong point that unless we come clean on this, it could get much more serious than we might anticipate."
Did I read that correctly?
620:
A. Yes, you did.
Q. And at that meeting of these well recognized endocrinologists, Dr. Cavazzoni, the expert, as you earlier said on hyperglycemia, made a presentation of Lilly data, did they not?
A. The data that had been developed to that time it was our intent to share that with them and get their recommendations.
Q. Right. And as opposed to what Mr. See asked you on direct-examination, didn't the endocrinologists who were present, these leaders of the pack, tell you that it was time for Eli Lilly to come clean on the issue of hyperglycemia?
A. Again, this is not in any way consistent with my recollection. They advised additional analyses -- they advised additional analyses, they wanted to collaborate with us. I do not believe that at that time we discussed with them a general approach to information sharing. We simply
621: shared with them the analyses that we had done and they suggested additional analyses.
Q. Right. You shared with them your analyses and they told you it's time for you all to come clean.
A. I don't recall that and you'd really need to discuss that with Mr. Brodie.
Q. He, at least writes in an e-mail to Dr. Robert Baker that that occurred, right?
A. That is certainly his characterization. It is not in quotes, and I'm not sure about the basis.
Q. What about your e-mails, you put all your e-mails in quotes?
A. No, but --
Q. And so, but you write them and you're speaking the truth when you write them, aren't you?
A. Yes, I am.
Q. Thank you. Exhibit 10. Let me see if I can. This is an exhibit, your lawyer put it into evidence with you. It's double-sided. How many pages is this?
622: A. Physically, I think it's probably around 800 or so.
Q. Right. I hadn't had time to read it since your lawyer introduced it into evidence. I haven't had time to go over it

all, but I have a question about it. Is that the type of data and analyses that you would have discussed with the endocrinologists in Atlanta?

A. Yes, it was.

Beasley, Charles M.D.(July 27, 2006)

639:7-12

Issues: 03 Plaintiff's Counter Designations

639:

Q. It says, "Welcome to the primary care resource guide. This guide will function as your resource for our launch of the primary care message."

Do you see that?

A. Yes.

Beasley, Charles M.D.(July 27, 2006)

640:3-16

Issues: 03 Plaintiff's Counter Designations

640:

Q. Down at the bottom here, and it's highlighted for you. It says "proven safety." You know there's a sales force that goes out and details to doctors and goes to their offices and tells them things. You know that, don't you?

A. Yes, I do.

Q. And the sales force was instructed "because many primary care physicians may not be familiar with the safety profiles of the newer psychotropic medications we must emphasize the safety of Zyprexa" and it goes on. Do you see that?

A. Yes, I do.

Beasley, Charles M.D.(July 27, 2006)

643:19-645:5

Issues: 03 Plaintiff's Counter Designations

643:19

Q. The next page, Page 12 in the Zyprexa Implementation Guide is the question "Do I need to do any blood monitoring with Zyprexa?" Did I say that --

A. That's correct.

Q. And the answer from Lilly is what?

644:

A. "No."

Q. Do I need to do any blood monitoring with Zyprexa. Isn't that what it

says?
A. That's correct.
Q. It doesn't say do I need to do blood monitoring for white blood cell count, it says "any," right?
A. That's correct.
Q. Okay. And it's right above the next question. I have heard that Zyprexa causes diabetes.
Do you see that?
A. Yes, I do.
Q. By why don't we just go ahead and approach this question. I was going to approach it later on another topic. The answer that Eli Lilly gives is "Has this been your clinical experience question mark." "In a large 5,022 retrospective analysis the incidence of treatment emergent glucose elevations with Zyprexa was comparable to placebo, 3.1 versus 2.5 percent. Further, the incidence of developing diabetes while on Zyprexa is not statistically different from the population at large."
Did I read that correctly?
A. You read that correctly.

Beasley, Charles M.D.(July 27, 2006)

647:7-649:19
Issues: 03 Plaintiff's Counter Designations

Q. Wasn't Eli Lilly, specifically, told by the FDA in October 2000 quit saying, quit saying that glucose elevations were comparable to placebo? Hadn't the FDA told you all to stop doing that?
A. I think what the FDA told us was to remove that language with those specific numbers from the package insert.
Q. And the advisory committee in October of 2000, when you took that statement down to Atlanta told you to stop doing that and come clean, didn't they?
MR. SEE: Object to the form.
A. Again, I don't recall that statement.
Q. Okay. Let me find the exhibit where the FDA in October of 2000 -- I forgot the number but I'll find it. Here it is. It's 195, I'll give you, you all have a copy. I'll give this to the good doctor. Remember you're supposed to be abandoning the spinning mentality, you recall that?
MR. SEE: Object to the form.

Q. Right?
A. That was a statement that I recall being made by Dr. Breier.
Q. Do you agree with it?
A. Again --
Q. Do you agree that that's a good philosophy to abandon the spinning?
MR. SEE: Object to the form.
A. I do not understand that Dr. Breier is speaking to behaviors, I understand that he is speaking to mentality. His view was that was a mentality, that was or it may have been that that was his view that that was a mentality that was existent at Lilly, and I think that would be good advice if he believed that.
Q. Right. Back to the implementation guide. It says "glucose elevations was comparable to placebo." In October of 2000 -- do you have 195 in front of you, Exhibit 195?
A. Yes, I do.
Q. And that's from the Food and Drug Administration. Remember Mr. See referred to you "does the Food and Drug Administration regulate you" or some question along that line?
A. Yes.
Q. And you said, "yes, they do?"
A. I think that was with respect to, probably, the package insert. That they control the package insert.
Q. Was that all they control, according to you?
A. That was, I think, what we were speaking to at the time. They certainly oversee much more than that.

Beasley, Charles M.D.(July 27, 2006)

651:6-652:4
Issues: 03 Plaintiff's Counter Designations

Q. Didn't the FDA in October 2000 tell you "The scripted data that is provided expresses a certain level of implied safety with respect to treatment-emergent hyperglycemia. This reassuring language is not appropriate for submission" and it goes on?
A. What this says it was, it was not appropriate for submission under a unilateral decision to submit and change without their prior review.
Q. And they told you to take

this language out?
A. That's correct, out of the package insert.
Q. And they use the term, not Scott Allen, that when you compare, when you try to say that the blood glucose elevations with Zyprexa are equivalent to a placebo that's reassuring language to a doctor, isn't it?
A. They viewed those numbers in this fashion, yes.

Beasley, Charles M.D.(July 27, 2006)
653:13-654:8
Issues: 03 Plaintiff's Counter Designations

Q. And so when the package insert places language in there indicating that blood glucose elevations with Zyprexa were equivalent to a placebo, the FDA said stop using this reassuring language in your package insert, didn't they?
MR. SEE: Object to the form.
A. They said take it out of the package insert, yes, sir.
Q. Right. And in fact, I think it's your, it's Attachment E, your Attachment E, we've talked about it several times. Do you remember Attachment E?
A. I believe I do.
Q. It's 990?
A. I think this was the original draft of the original suggestion to package labeling change.
Q. Right. And in February of 2000, before Zyprexa primary care launch --

Beasley, Charles M.D.(July 27, 2006)
654:19-655:22
Issues: 03 Plaintiff's Counter Designations

Q. You, specifically, indicated that random glucose levels with Zyprexa compared to a placebo, there was a statistically significant difference, correct?
A. I don't recall whether that finding at that time was statistically significantly different. There were certainly, the numbers were reported, I don't think it makes reference to whether they were statistically significant.

Q. Okay.
A. And that was not for inclusion at the time in the suggested package labeling.
Q. No, it was not, was it. But it indicated that the incidence of hyperglycemia in Zyprexa patients was, approximately, three and-a-half times greater than that of placebo in a clinical trial?
A. In a set of clinical trials.
Q. Right. Now let's good. Let's get to the issue of clinical trials which started with your counsel on your exam. You sat down and you said, you drew us a diagram about clinical trials, do you recall that?
A. Yes, I do.

Beasley, Charles M.D.(July 27, 2006)
657:7-658:9
Issues: 03 Plaintiff's Counter Designations

657: 7 Q. And a couple of things you
8 said, I think one of the things you said is
9 something like this, and you tell me, we do
10 our testing pursuant to CIOMS, I think,
11 guidelines?
12 A. That was with reference to
13 the number of patients that would be studied
14 prior to making an application.
15 Q. And I apologize, sir, because
16 I heard that term yesterday, too. How do you
17 spell that?
18 A. It is an acronym, capital C,
19 capital I, capital O, capital M, capital S.
20 I believe it is French and I don't know the
21 French words.
22 Q. Parlez vu francais?
23 A. But we all refer to it as
24 CIOMS. And it's an international
658: 1 organization that provides guidance to
2 international regulators.
3 Q. Right. And I think your
4 lawyer said in a question to you and you said
5 you agreed it is a well respected and
6 internationally recognized set of guidelines.
7 Do you recall that general question?
8 A. That this organization is
9 well respected.

Beasley, Charles M.D.(July 27, 2006)
659:8-660:13
Issues: 03 Plaintiff's Counter Designations

659: 8 Q. And the reason that struck me
9 is we use the term CIOMS also yesterday in
10 regard to the fact that by February of 2000
11 their guidelines were such that diabetes and
12 hyperglycemia were supposed to be in the
13 labeling as common or frequent; do you recall
14 that?
15 MR. SEE: Object to the form.
16 A. No, I do not, because CIOMS,
17 again, is a, as far as I know, is an entity
18 that develops guidelines. So I'm not sure
19 exactly what we're speaking about.
20 Q. Attachment E, Exhibit 990. I
21 thought you said yesterday that by February
22 of 2000 when you prepared the proposed label
23 change you said the CIOMS guidelines were
24 such that hyperglycemia was a common and
660: 1 frequent adverse --
2 A. Now I understand what you're
3 speaking about. Based on the number of our
4 finding in our analyses that the incidence of
5 these glucose elevations, to either greater
6 than 160 or greater than 200, were in excess
7 of certainly over 2 percent, over 3 percent,
8 that that would fall in this range between
9 1 percent and 10 percent.
10 Q. And you said under CIOMS
11 guidelines these blood glucose elevations
12 would be common or frequent?
13 A. Yes.

Beasley, Charles M.D.(July 27, 2006)
663:12-665:2
Issues: 03 Plaintiff's Counter Designations

663:12 Q. Okay, you told Mr. See on
13 direct-examination that there's these well
14 recognized ways to do clinical studies and
15 Eli Lilly does their clinical studies in
16 these good ways, right?
17 A. That's correct.
18 Q. And you talked about the
19 fact, and we talked about it earlier,
20 findings have to be statistically significant
21 and it's best if they're compared to mean,
22 and things of that nature?
23 A. That's correct.
24 Q. All right. And you describe
664: 1 in your diagram, just give us some kind of an
2 illustration of what clinical trials look
3 like?
4 A. That's correct.
5 Q. And then I just wanted to see

what your findings were in the Lilly documents about the clinical trials that were done, okay?

A. That's correct.

Q. All right. And I want to look first, and I prepared a new exhibit. I hand wrote out an exhibit, too, on clinical trials. We're going to mark it, it will be, it's 15, and the Court reporter will add Beasley. It will be Beasley 15.

(Whereupon, Deposition Exhibit(s) 15 duly received, marked and made a part of the record.)

A. Okay.

Q. You have Exhibit 990 in front of you, Attachment E?

A. Oh, yes.

Q. And it's what we talked about earlier. It says recent review of random glucose.

Beasley, Charles M.D.(July 27, 2006)

665:6-20

Issues: 03 Plaintiff's Counter Designations

Q. Recent review of random glucose levels of patients in olanzapine clinical trials. I'll stop there.

Clinical trials, those are the type of trials you described with your lawyer, right?

A. That's correct.

Q. And you followed all the appropriate guidelines and standards?

A. That's correct.

Q. Revealed that the incidence, the incidence, I think we've used that term a lot but we haven't talked about it. And incident means what?

A. Percentage of patients.

Beasley, Charles M.D.(July 27, 2006)

666:10-667:14

Issues: 03 Plaintiff's Counter Designations

Q. Incidence is those numbers of new cases in a population that occur; is that correct?

A. Within a certain time frame.

Q. Right.

Right. So let's go back.

That the incidence of treatment emergent hyperglycemia in olanzapine group was 3.6 percent and it was higher than the placebo group 1.05 percent, correct?

A. That's correct.

Q. So and I'm going to show you my new exhibit in regard to clinical trials which you discussed with your lawyer, Exhibit 15. We're going to put Beasley in that, the Court reporter will add Beasley later. Is in February of 2000, Exhibit 990, and I've summarized it.

Treatment emergent hyperglycemia in Zyprexa group 3.6 percent was higher than that in the placebo group. And I underlined placebo, do you see that?

A. That's correct.

Q. And the placebo group is what you told your lawyer on direct-examination is one of the best ways to get a controlled trial as you have there in your diagram, Beasley No. 5?

A. That's correct.

Beasley, Charles M.D.(July 27, 2006)

668:7-669:13

Issues: 03 Plaintiff's Counter Designations

Q. All right. The true quote from the document 990 is quote, dot dot dot, "treatment emergent hyperglycemia in Zyprexa 3.6 was higher than that in the placebo," parens, "1.05 percent." That's a direct quote from Exhibit 990, is it not?

A. Yes, it is.

Q. All right. Another clinical trial and your findings would be Exhibit 5565. By the way I'll agree on the last Exhibit 990 that the highlighting and the marks are mine.

And on 5565 the highlighting and the marks are mine. You're again, this is you, February of 2001 about a year after 990, you've seen this document before, it's re olanzapine and hyperglycemia, right?

A. That's correct.

Q. And I want to go down, these are my highlightings and my markings, "our continuous analysis show that olanzapine does result in statistically significant," that's that P value of .05, right?

A. That would be correct.

Q. "Mean increases in random glucoses relative to placebo and

haloperidol." Did I read that correctly?
A. That's correct.
Q. And that's getting data from a clinical trial?
A. That's correct.

Beasley, Charles M.D.(July 27, 2006)

671:14-674:13
Issues: 03 Plaintiff's Counter Designations

671:14 you said this 5565 and the findings of these
15 continuous analyses come from more than one
16 clinical trial; is that right?
17 A. These, all of these analyses
18 that we're referring to come from the pooling
19 or the putting together --
20 Q. Right. A pooled analysis?
21 A. -- of clinical trials.
22 Q. A pooled analysis?
23 A. A pooled analysis.
24 Q. That means you're taking all
672: 1 these clinical trials that were done just
2 like you told your lawyer they're going to be
3 done, you're taking actual data and pooling
4 it and you're looking at all these fine
5 clinical trials and you came to the
6 conclusion that our continuous analyses
7 indicate we're having blood glucose
8 elevations, right?
9 A. Again, I have not
10 characterized it as a conclusion. I have
11 characterized the specific findings of the
12 analyses.
13 Q. And we just for the record,
14 we discussed, and just so we're right here
15 together, hyperglycemia is prediabetes and it
16 adds a risk factor for diabetes, right?
17 A. It is a precondition and
18 would be a risk factor.
19 Q. And it's well-recognized by
20 the American Diabetes Association as
21 something you need to identify as quickly as
22 possible to hopefully prevent all the medical
23 consequences that are bad that can occur,
24 correct?
673: 1 A. That's correct.
2 Q. All right. Let's go to March
3 of 2001. You've seen this document. This
4 is, let me see what number it is, sir. 6128.
5 Again, I will stipulate for the record to
6 Mr. See and Barry, that this is my writing
7 and my highlighting.
8 You're looking at some
9 clinical trial data in this e-mail, are you

not?
A. That's correct.
Q. And it says: "One thing we can say definitively" and that's just a way of saying for certain, right?
A. That's correct.
Q. One thing we can say definitively is that olanzapine causes weight gain and for, approximately, 50 percent of patients in trials who remained on the drug for greater than six months the amount of gain was greater than 10 pounds. Some patients in clinical trials gained as much as 80-plus pounds, correct?
A. That's correct.
Q. And so the clinical trial data as reflected here in Beasley 15, indicated -- and again that was a pooled analysis, I think, wasn't it?
A. That's correct. That's making reference to the majority of that data to that that we had available at the time of NDA.
Q. Okay. Clinical trials, clearly and definitively and without a doubt show that weight gain is statistically significantly associated with Zyprexa?
A. Yes, absolutely.

Beasley, Charles M.D.(July 27, 2006)
679:5-683:3
Issues: 03 Plaintiff's Counter Designations

Q. And by the way, you also made it clear today, and I don't think you discussed it with your lawyer, if I'm not mistaken you said that by 1999 in Europe that hyperglycemia and diabetes was in the equivalent of the warning section?
A. Yes, it was.
Q. So by 1999, the patients and doctors over in Europe were being warned about hyperglycemia and diabetes?
A. There was a warning slash precautions in that label written in Europe.
MR. ALLEN: Yes, and I'm trying to get out, I think it was your, what exhibit number? It's Beasley No. 6. I don't think, Beasley No. 6, your lawyer and you introduced this.
QUESTIONS BY MR. ALLEN:
Q. You said this is the package insert that was initially put out, I think is

what you said, on Zyprexa?
A. Again, without benefit of seeing it we need to look at the date.
Q. Well, you and your lawyer introduced it. Here, I'll give it to you, I thought your lawyer asked you and you said you agree. Here it is, sir, and I'll give it to you and I think it's on the back page. I think you told your lawyer it was '96.
A. 10/29/96. I just did not remember the exhibit number and what that exhibit, specifically, was.
Q. Okay. Put this back up on the screen, please. I've actually -- this is my highlighting. Where is a warning in this package insert in 1996 on hyperglycemia and diabetes?
A. There is not one.
Q. Okay. And where is the warning in the United States package insert like Europe's in 1999 on the hyperglycemia and diabetes?
A. There is not one.
Q. Where is that black box warning on Zyprexa in 2002 like Japan had concerning hyperglycemia, diabetes, diabetic ketoacidosis?
A. There is not one.
Q. Is there any particular reason that you at Eli Lilly felt that the doctors in the United States should be treated differently than the doctors in Japan and Europe?
MR. SEE: Object to the form.
A. From our perspective and my perspective we were, in fact, labeling the molecule appropriately. There are clearly differences in the labeling. Different countries evaluate materials differently and have different interests in their package insert.
Q. Lilly's interest is the same throughout the world, isn't it?
A. Yes.
Q. You want to give the doctors in the United States the same information and in the same manner you give doctors over in France, don't you?
MR. SEE: Object to the form.
A. Absolutely.
Q. Your lawyer objected but you said "absolutely", right, sir?
A. Yes.
Q. You want to give doctors in Japan the same information you give doctors in the United States and vice-versa?
MR. SEE: Object to form.

A. Yes.
Q. Your answer was what?
A. Yes.
Q. Okay. Let's go back on the screen on this '96 package insert. This is the actual print size of a package insert, isn't it? This is actual print size, right?
A. I think it's, approximately, the print size. Given that it's a Xerox copy it's hard for me to know it's the precise print size but, yes, I think it is.
Q. I have this projector here. I can magnify stuff times 12 but we can focus out without any magnification. Let's go first page, second page, third page, last page; is that right?
A. That's correct.

Beasley, Charles M.D.(July 27, 2006)

685:5-23
Issues: 03 Plaintiff's Counter Designations

it. You said not to your knowledge is Zyprexa associated with or does it cause cystitis, female lactation, tinnitus, eczema, seborrhea, laryngitis, facial paralysis, rheumatoid arthritis, leukocytosis, thrombocytopenia?
MR. SEE: Object to the form.
Q. Right?
A. I think that those things have been reported in temporal association with the drug but I have no knowledge that those things are caused by the drug.
Q. Or statistically significantly associated?
A. That's correct.
Q. Okay. Well, all of those are in the adverse reaction section of the 1996 package insert. Did you know that?
A. Yes, I had --

Beasley, Charles M.D.(July 27, 2006)

687:17-689:6
Issues: 03 Plaintiff's Counter Designations

Q. Now you told me to your knowledge none of those conditions are statistically significantly associated with or caused by Zyprexa?
A. That's correct.
Q. But yet it's sitting there in

the adverse reaction section?
A. That's correct.
Q. The same place you put, you, being Eli Lilly, diabetes?
A. That's correct.
Q. And it's displayed with no more prominence than eczema, seborrhea, tinnitus, facial paralysis, bursitis, rheumatoid arthritis, leukocytosis and thrombocytopenia, right?
A. That's correct.
Q. So if a doctor was looking at this conglomeration of listings of all types of medical conditions in the adverse reaction section, he or she could not separate the wheat from the shaft on female lactation and cystitis and diabetes, could they?
MR. SEE: Object to the form.
A. I can't speak to what any other physician than I would do with a package insert.
Q. Well, we know what you would do because you don't prescribe medications, you just told us that, right?
A. I can tell you what I would do with a package insert. I mean, that's all I can speak to.
Q. You just told me within the last 15 minutes that you to not prescribe medications.
A. That I don't prescribe medications on a routine basis.

Beasley, Charles M.D.(July 27, 2006)
690:15-691:3
Issues: 03 Plaintiff's Counter Designations

Q. You were not trying to warn doctors about eczema and Zyprexa, were you?
MR. SEE: Objection to the form. Asked and answered.
A. We were informing them of these events. These events had not been placed in a warning.
Q. Right. So you were not warning them about eczema, were you, sir?
MR. SEE: Objection to the form. Asked and answered.
A. We were informing them and we had not placed them in a warning.

Beasley, Charles M.D.(July 27, 2006)
710:8-713:13

Issues: 03 Plaintiff's Counter Designations

710: 8 Q. Sir, you're looking at the
9 Consensus Development Conference on
10 Antipsychotic Drugs and Obesity and Diabetes,
11 correct?
12 A. That's correct.
13 Q. And we're not going to take
14 up your time unless you want me to, and what
15 this was was a meeting over several days and
16 a review of the world literature that took
17 place by experts, isn't that true?
18 A. Of available world literature
19 as I understand it.
20 Q. And Lilly got to have a say.
21 Their voice was heard, wasn't it?
22 A. I think that we had people in
23 attendance at the meeting. I was not there.
24 Q. Well, you didn't just have
711: 1 people, you had presenters. You had
2 presenters at this conference, didn't you?
3 A. I believe so.
4 Q. Right. And it's right here.
5 Patrizia Cavazzoni, your expert, got to
6 speak?
7 A. I believe so.
8 Q. Right. And you said Dr. John
9 Buse, that was one of your Thought Leaders
10 and Speakers Bureau Members, wasn't it?
11 A. He was.
12 Q. That's a guy that Lilly paid
13 money to, right?
14 A. I assume that we paid money
15 to him. I don't know that we paid money to
16 him.
17 Q. And there was, actually,
18 members of the panel on this consensus
19 statement who had received Lilly money,
20 right?
21 A. I would believe that to be
22 the case.
23 Q. And we can go through all the
24 presenters but you have met with, we talked
712: 1 about some of these people in here. You know
2 a lot of these presenters, don't you. You
3 mentioned Dr. Allison today, David Allison?
4 A. That's correct.
5 Q. He's a well-respected doctor,
6 right?
7 A. He is a Ph.d., he's not a
8 physician.
9 Q. Right. But he's
10 well-respected?
11 A. Yes.
12 Q. He's an expert?
13 A. On the issue of weight gain

particularly.
Q. Yes. He's a well-recognized internationally respected expert in that field?
A. In the field of weight gain to my understanding, yes.
Q. You referenced him today on several occasions?
A. Absolutely.
Q. And you told us, and your e-mail said, Patrizia Cavazzoni is you all's expert on the issue of hyperglycemia. You told me that today.
MR. SEE: Objection to the form.
A. She is our expert with respect to directing the entirety of our work beginning in 2000 on this topic.
Q. And you also said that John Buse was one of the members, I think, I think you said, and correct me if I'm wrong, you recall Dr. Buse being at that Atlanta meeting in October 2000?
A. Yes, he was.

Beasley, Charles M.D.(July 27, 2006)

734:21-739:21
Issues: 03 Plaintiff's Counter Designations

MR. ALLEN: I'm going to introduce Exhibit 16 and Exhibit 2368, they're the same thing. Now -- it's a consensus statement.
THE WITNESS: These are the same type documents.
MR. ALLEN: Yes, sir. You can compare. They're the consensus statement.
QUESTIONS BY MR. ALLEN:
Q. Your last answer said in order to get the best analysis, we'd like a consensus reached after, you said, experts review the data. Isn't that what you said?
MR. SEE: Object to the form.
A. I said after experts review the entirety of available data, not just that available in the public domain.
Q. And by the way, in the consensus statement Eli Lilly, nobody put any -- well, let's go on. Let's go to the consensus page.
Question, "What is the relationship between the use of these drugs

and the incidence of obesity or diabetes?"
Skipping down, "There is considerable
evidence, particularly in patients with
schizophrenia that treatment with SGAs can
cause a rapid increase in body weight in the
first few months of therapy that may not
reach a plateau even after one year of
treatment." Did I read that correctly?
A. That's correct.
Q. "There is, however,
considerable" -- what's the word
"considerable" mean to you? We've seen it
twice in this paragraph?
A. Not small.
Q. That means large, important,
would you agree?
A. Yes.
Q. "There is" -- let me just
substitute it. "There is, however,
considerable variability in weight gain among
the various SGAs," and it refers you to table
two, right?
A. That's correct.
Q. Table two, SGAs and Metabolic
Abnormalities, do you see that?
A. That's correct.
Q. The consensus panel -- what
were the worst offenders in regard to weight
gain?
A. There are in this table,
clozapine has three plus marks, meaning an
increased effect; olanzapine also has three
plus marks; risperidone has two; quetiapine
has two; and the two other compounds have a
plus-minus.
Q. All right. And so my
question to you was, back to my question:
According to the consensus panel who are --
what drugs are the worst offenders for weight
gain?
MR. SEE: Objection to the
form.
A. I understand this to be that
this group considered clozapine and
olanzapine to be associated with more weight
gain than risperidone and quetiapine or
aripriprizole or ziprasidone.
Q. So the worst offenders are
clozapine and Zyprexa?
MR. SEE: Objection to the
form.
Q. Correct?
A. The -- my understanding is
that it was the view of this panel that these
two drugs caused more weight gain than the
others.
Q. What are the only two drugs

who have, according to this consensus statement, an increased effect for the risk of diabetes?

A. Clozapine and olanzapine have a one plus.

Q. And that would be Zyprexa?

A. That's correct.

Q. Okay. And which ones have the positive for a worsening lipid profile?

A. That would be, also, clozapine and olanzapine.

Q. And a lipid profile is things like cholesterol, triglycerides, things of that nature?

A. That's correct.

Q. And you already told us you agree it would be ludicrous to contend, it would be crazy to contend, that an increase in weight would not put you at risk for getting additional cardiovascular side effects?

MR. SEE: Object to the form.

A. My characterization of that was with respect to extreme weight gain.

Q. A summary is done by the panel. Doesn't it? Here at the last page, you see the summary?

A. Yes.

Q. By the way, you said you wanted to be objective. Did you recall that?

A. Yes.

Q. But yet you've told us that you cannot recall if you've ever even read the entire consensus panel statement before; is that right?

MR. SEE: Object to the form.

A. I cannot recall reading this entire -- I may well have, but I do not recall the specific reading.

Beasley, Charles M.D.(July 27, 2006)
740:14-19
Issues: 03 Plaintiff's Counter Designations

Q. All right. Did you read it in preparation for your testimony today?

A. No, I did not.

Q. Did you read it in preparation for your testimony yesterday?

A. No, I did not.

Beasley, Charles M.D.(July 27, 2006)
744:19-745:3

Issues: 03 Plaintiff's Counter Designations

744:19 Q. Now, do you recall discussing
744:20 with your counsel, Mr. See, some articles
744:21 which I'm not -- I'll put up here, some clamp
744:22 studies?
744:23 A. Yes, I do.
744:24 Q. Okay. And then there was a
745: 1 comment. This, really, this other one was a
745: 2 comment, in the clamp study, right?
745: 3 A. That's correct.

Beasley, Charles M.D.(July 27, 2006)

746:17-747:7

Issues: 03 Plaintiff's Counter Designations

746:17 Q. When you discussed these
746:18 articles briefly with your attorney on
746:19 direct-examination was there any particular
746:20 reason that you all -- that you left out or
746:21 failed to mention the consensus statement
746:22 that has been published?
746:23 MR. SEE: Object to the form.
746:24 Q. Is there any particular
747: 1 reason you didn't mention this when you were
747: 2 discussing medical articles with your
747: 3 counsel?
747: 4 MR. SEE: Object to the form.
747: 5 A. I was not asked about this
747: 6 article. I was asked about research that we
747: 7 had done to investigate mechanism.

Beasley, Charles M.D.(July 27, 2006)

780:24-781:18

Issues: 03 Plaintiff's Counter Designations

780:24 If Eli Lilly, your employer,
781: 1 asked you to come to a trial and testify in
781: 2 New York City or California or Texas, you
781: 3 would come, wouldn't you?
781: 4 MR. SEE: Object to the form.
781: 5 A. I would seek advice of
781: 6 counsel and based on that make a
781: 7 determination as to whether I would come or
781: 8 not.
781: 9 Q. You have -- let me, then, I
781:10 guess I have to ask a following question.
781:11 You've traveled to Japan for Eli Lilly?
781:12 A. That's correct.
781:13 Q. All over the world for Eli
781:14 Lilly?

A. That's correct.
Q. You went to Atlanta for Eli Lilly?
A. That's correct.

Curtiss, Lucy M.D. (December 13, 2007)
5:18-21
Issues: 03 Plaintiff's Counter Designations

5:18 Are you aware -- were you aware of
19 this lawsuit before you found out you were going
20 to have your deposition taken?
21 A. Yes.

Curtiss, Lucy M.D. (December 13, 2007)
6:8-11
Issues: 03 Plaintiff's Counter Designations

6: 8 Q. What is it that you do know about the
9 case?
10 A. That it has to do with Zyprexa, and
11 disclosure of risks related to Zyprexa.

Curtiss, Lucy M.D. (December 13, 2007)
26:4-9
Issues: 03 Plaintiff's Counter Designations

26: 4 Q. Any other factors that would militate in
5 favor of using perphenazine besides patient
6 preference?
7 A. Well, it has anti-psychotic effect. You
8 know, I'm looking for effectiveness of a
9 medication, and acceptability to a patient.

Curtiss, Lucy M.D. (December 13, 2007)
28:17-19
Issues: 03 Plaintiff's Counter Designations

28:17 Q. Any other times it's affected your
18 practice?
19 A. Overall, I'd say not.

Curtiss, Lucy M.D. (December 13, 2007)
34:21-35:12
Issues: 03 Plaintiff's Counter Designations

34:21 Q. When did your concern about metabolic
22 side effects change?
23 A. Again, I can't tell you what year, but
24 it has been within the last few years.
25 Q. Do you recall a classwide label change

35: 1 in 2003 with regard to the second-generation
2 anti-psychotics?
3 A. I don't. I'm sorry.
4 Q. Do you recall any label changes for
5 either Zyprexa or the class of medications? And
6 I'm not asking you for a date, but just the --
7 the event or the fact of it occurring.
8 A. Well, I know that it has definitely
9 become more of a focus. In my practice what
10 stands out more is the black box warnings about
11 patients with vascular dementia and use of
12 anti-psychotics.

Curtiss, Lucy M.D. (December 13, 2007)
36:24-37:5
Issues: 03 Plaintiff's Counter Designations

36:24 Q. Have you read the results of the CATIE
25 trials?
37: 1 A. Yes, I have.
2 Q. Do you keep any kind of folders in your
3 office where you collect literature on topics of
4 interest?
5 A. I keep as little paper as possible.

Curtiss, Lucy M.D. (December 13, 2007)
38:6-23
Issues: 03 Plaintiff's Counter Designations

38: 6 Q. When did that practice change of having
7 a block and not having a block of time?
8 A. Probably when I became medical director.
9 Q. Which was a few years ago?
10 A. Which was a few years ago.
11 I am also more cautious, being on
12 the P & T Committee.
13 Q. Because?
14 A. Because I am being visited by reps
15 that -- that detail agents that I would never
16 prescribe ophthalmologic agents and all kinds of
17 other things. And I'm -- I'm also very clear
18 that I don't -- I am turned off by sales.
19 Q. What do you mean by that?
20 A. That if a rep comes in -- I did one time
21 have a rep say, "I want you to promise to
22 prescribe this for your next X number of
23 patients." I didn't meet with him again.

Curtiss, Lucy M.D. (December 13, 2007)
41:3-8

Issues: 03 Plaintiff's Counter Designations

41: 3 Q. Can you recall any instances where
4 you've been -- where you've met with a sales
5 representative from a pharmaceutical company and
6 you believed you've been misled by that
7 representative about his or her product?
8 A. Possibly.

Curtiss, Lucy M.D. (December 13, 2007)

41:25-42:12
Issues: 03 Plaintiff's Counter Designations

41:25 Q. Do speakers from pharmaceutical
42: 1 companies ever come to your practice here?
2 A. Yes.
3 Q. What companies bring in speakers?
4 A. A number of companies do. I ask that
5 the trainings be coordinated by our nursing
6 manager; and I don't personally attend them.
7 Q. Have you ever attended them?
8 A. Not for years.
9 Q. Why don't you go?
10 A. I'm too busy, and I am -- again,
11 skeptical that I don't trust that the information
12 truly is unbiased.

Curtiss, Lucy M.D. (December 13, 2007)

46:25-47:13
Issues: 03 Plaintiff's Counter Designations

46:25 Q. (BY MR. ROGOFF) Dr. Curtiss, how many
47: 1 patients do you see now on a weekly basis now
2 that you're medical director?
3 A. Good grief. Oh, it varies tremendously.
4 50? And that's just really a rough estimate.
5 Q. How many did you see before you became
6 medical director, rough estimate?
7 MS. MANDALA: Per week?
8 A. Per week? Probably not a whole lot
9 more.
10 Q. (BY MR. ROGOFF) So you're working
11 harder?
12 A. I am working harder and faster. Very
13 fast.

Curtiss, Lucy M.D. (December 13, 2007)

47:18-23
Issues: 03 Plaintiff's Counter Designations

47:18 Q. Have you -- have any of your patients,
19 while using any of the psychiatric medications,
20 developed diabetes?
21 A. Yes.
22 Q. Were some of them on Zyprexa?
23 A. Yes.

Curtiss, Lucy M.D. (December 13, 2007)

48:1-8
Issues: 03 Plaintiff's Counter Designations

48: 1 Q. For those who are taking anti-psychotic
2 medications, do you regularly monitor any of
3 their -- their blood levels -- the glucose
4 levels?
5 A. I try to.
6 Q. How long have you been doing that for
7 your patients?
8 A. Oh, it's been a few years.

Curtiss, Lucy M.D. (December 13, 2007)

48:11-17
Issues: 03 Plaintiff's Counter Designations

48:11 Q. For which patients do you test glucose
12 levels?
13 A. I check for anyone who is on -- well, I
14 try to get all my patients to have at least
15 yearly physical health care. For people that are
16 on anti-psychotics, I try, all of them, to get
17 them to do it.

Campana, David - Vol. II (September 19, 2007)
192:15-193:8
Issues: 03 Plaintiff's Counter Designations

192:15 The good example of that is when Vioxx was
16 available, you had to take Ibuprofen or you had to take
17 Naprosyn before you could get a prescription of Vioxx
18 filled.
19 Q. This was before, obviously, Vioxx was taken off
20 the market?
21 A. Correct.
22 Q. Do you remember the date of that, estimate when
23 Vioxx went off the market? I'm just trying to orient
24 ourselves.
25 A. It was September of '04 or '03.
193: 1 Q. Was the step edit in place for Vioxx in Alaska --
2 was the step edit in place the entire time Vioxx was on
3 the market?
4 A. Actually, we did not implement it. We had the
5 programming ready to go and then did not implement it.
6 Q. When did Alaska start the process of, you know,
7 developing the step edit?
8 A. In 2003.

Campana, David - Vol. II (September 19, 2007)
216:6-217:7
Issues: 03 Plaintiff's Counter Designations

216: 6 Q. How did the idea of having a PDL start in Alaska?
7 A. Well, it was actually an idea that came out of
8 Florida and Michigan. They were the first two states
9 that had developed the preferred drug list. Another
10 state that had even done it longer than those was
11 California has done it indefinitely.
12 But Florida started, and then Michigan also
13 started, and it came out from that.
14 Q. Who suggested the idea in Alaska?
15 A. Well, in reading court cases, because Florida had
16 been sued by pharma and it was an idea that we had
17 talked about in our department.
18 And in 2003, my supervisor said, "Let's do it."
19 Q. Who is your supervisor?
20 A. At that time, my supervisor was Terry Keklak.
21 Q. Is the PDL something you had been promoting prior
22 to that?
23 A. I thought it was a good idea. Actually, I
24 thought when I looked at the California model back in
25 the early nineties it was a good idea to do it at that
217: 1 time.
2 However, without having enough staff to do it, it
3 was virtually impossible to try to do it.
4 Q. By this point, you had enough staff?
5 A. Well, you never have enough staff. I have,

working with the contractor, I have enough staff at least to do the job that I think is adequate.

Campana, David - Vol. II (September 19, 2007)

222:19-24

Issues: 03 Plaintiff's Counter Designations

Q. So if it's been voted out as a class effect, then you basically know whichever one, three or six of the drugs in the class have agreed to that, those will be the ones who are preferred?
A. Correct.
Q. So that's one conclusion that the P&T committee

Campana, David - Vol. II (September 19, 2007)

223:14-224:2

Issues: 03 Plaintiff's Counter Designations

Q. So they can vote on a class effect. What else can they vote on?
A. They could vote that none of the drugs should be preferred or they could vote that one of the drugs should be preferred in addition to any supplemental rebates that are available.
Q. So if that occurs, what they voted out, is that one drug, even if everything else is the same, and it's going to be -- its status on the PDL is going to be contingent on the supplemental rebate, this particular drug or two drugs have qualities, clinical qualities that warrant it being on the PDL, even if they don't give a supplemental rebate?
A. Correct.

Campana, David - Vol. II (September 19, 2007)

228:22-229:3

Issues: 03 Plaintiff's Counter Designations

Q. Is it possible for First Health to have a class of drugs where some manufacturers have agreed to supplemental rebates, but the state determines not to put that class up for review anyway?
A. That could happen.
Q. Has that happened?
A. Not to my knowledge.

Campana, David - Vol. II (September 19, 2007)

229:7-13

Issues: 03 Plaintiff's Counter Designations

229: 7 class of drugs that have been reviewed by other states.
8 Q. Do you know what states?
9 A. I know Oregon has reviewed it. Washington has
10 reviewed it. I know those two for sure.
11 Q. Why haven't anti-psychotics been reviewed for the
12 Alaska PDL?
13 A. Because we just have not wanted to do that yet.

Campana, David - Vol. II (September 19, 2007)

231:10-234:11
Issues: 03 Plaintiff's Counter Designations

231:10 Q. How often do you have a discussion about what
11 drugs should be reviewed for the PDL?
12 A. Well, we actually did that following the last P&T
13 meeting. We meet -- the last meeting was in May, and
14 then we put a schedule together for this year.
15 We start in September and meet through --
16 actually, we're going to meet through April this next
17 year.
18 Q. So right after the May P&T committee meeting, the
19 two of you sit down and have a discussion about what
20 drugs we should review next year?
21 A. Right.
22 Q. How long a meeting is that?
23 A. I don't remember.
24 Q. Estimate?
25 A. A couple of hours.
232: 1 Q. And is that couple-hour meeting, is it sort of a
2 once-a-year thing where you discuss what drugs are going
3 to be reviewed or are there ongoing discussions
4 throughout the year?
5 A. There is -- you know, we would go over the
6 schedule, look at the schedule and then make sure we
7 have got all the classes from last year to rereview.
8 We try to rereview all drugs yearly. And there
9 may be -- her memory is jogged or my memory is jogged
10 and we'll pick up another class to add to the schedule.
11 Q. So the decision whether to review or not to
12 review anti-psychotics, that was made by you and
13 Mr. Babb in the first instance and then you and
14 Ms. Sater?
15 A. Correct.
16 Q. Did you actually have discussions about whether
17 or not to review anti-psychotics?
18 A. Yes.
19 Q. When have you had those discussions?
20 A. At the spring meeting when Ms. Sater and I had
21 met. We also mentioned it at the pharmacy and
22 therapeutics meeting.
23 We indicated that we would be reviewing the
24 anti-depressants and the sedative hypnotics, and someone
25 mentioned, "Are you going to review the atypicals," and

233: 1 the answer -- and I forget whether it was myself or
2 someone else or someone on the committee -- was "No, but
3 do you want to."
4 And this was one of the psychiatrists on the
5 committee that we were answering that way. And the
6 answer was, "Oh, no."
7 Q. So you said, "No, we're not planning on it, but
8 do you want to," and the psychiatrist who had asked the
9 question said, "No"?
10 A. Right.
11 Q. Do you know who that psychiatrist was?
12 A. Lucy Curtis.
13 Q. This is -- the conversation you just referred to
14 was from last May?
15 A. Right.
16 Q. And after the meeting, did you actually have a
17 discussion with Ms. Sater about whether to put the
18 anti-psychotics up for review?
19 A. She mentioned that we could review those during
20 the next year.
21 Q. Ms. Sater said that?
22 A. Yes.
23 Q. What did you say?
24 A. I said, "Let's not do it yet."
25 Q. Why?
234: 1 A. There is some political pressure not to do it.
2 And I think that will turn around as we go forward.
3 There was political pressure at one time not to
4 do the anti-depressants, and as we went forward, showed
5 that the PDL is not that intrusive, it's easy to work
6 with, the psychiatric group came along and said, "Oh
7 sounds like a good idea. Why don't you do it?"
8 Q. But you told Ms. Sater, "Let's not do it yet,"
9 because you felt there was some political pressure not
10 to do it?
11 A. Correct.

Campana, David - Vol. II (September 19, 2007)

248:3-249:9

Issues: 03 Plaintiff's Counter Designations

248: 3 Q. That's the letter you referred to?
4 A. That's the letter.
5 Q. Again, you don't remember sitting here today
6 whether it was Zyprexa specific or a class specific?
7 A. Correct.
8 Q. The FDA letter you were referring to, what letter
9 is that?
10 A. The letter on CBX that the FDA sent to Eli Lilly
11 requesting that they improve the labelling on the
12 causation of diabetes.
13 Q. When did you receive -- do you remember the date
14 of that letter?
15 A. It was March 28th.

Q. Of --
A. Of -- well, actually, there wasn't an actual date from the FDA, but there was a date on the letter of March 28th.
Q. 2007?
A. 2007.
Q. When did you receive that letter?
A. It was in my notebook again, and so I had received it as from counsel.
Q. And you said -- do you know when you received it?
A. I don't remember exactly when I had received it.
Q. But you said that's now motivating another intervention?
A. That's correct.
Q. What intervention?
A. That will be an intervention to look at Zyprexa and to also remind prescribers that it can cause diabetes and to be on the watch out for metabolic changes.

Campana, David - Vol. II (September 19, 2007)
250:21-23
Issues: 03 Plaintiff's Counter Designations

Q. How would you go about finding that?
A. Look on Pub Med or one of the resources, medical resources.

Campana, David - Vol. II (September 19, 2007)
259:12-13
Issues: 03 Plaintiff's Counter Designations

Q. And you have experienced that pressure?
A. I have experienced that pressure.

Campana, David - Vol. II (September 19, 2007)
272:13-274:3
Issues: 03 Plaintiff's Counter Designations

Q. I have gathered from your testimony today that the state has filed lawsuits against other prescription drug manufacturers?
A. It's my understanding that we have joined lawsuits filed against other drug manufacturers.
Q. What other drug manufacturers, and if you can identify it by medication as well?
A. Well, as far as the other manufacturers, the first case I worked on was Mylan. That was a national suit that was done through the AG's office where Mylan had conspired to raise prices of generic drugs.

Q. I'm actually glad -- let's put aside price issues and just talk about lawsuits that the state has filed because of, you know, safety issues or improper promotion kind of issues.

A. There are two other cases I know of. I don't know all the particulars about the cases. The OxyContin case where improper marketing was done by the manufacturer, and that case has been recently settled.

Then there was the Neurontin case where I believe it was a qui tam issue and done by the AG's office due to the improper labelling and marketing of the drug.

Q. In either of those cases, has there been any lawsuit filed against the manufacturer of Vioxx?

A. I can't answer that. I don't know.

Q. In either of the cases you identified, OxyContin and Neurontin, did you play any role in deciding whether to file a lawsuit or join a lawsuit?

A. No.

Q. So one reason you said you hadn't reviewed Zyprexa for the PDL after drawing your conclusions about the safety issues was the over-burdened mental health community, and we had discussed it.

You again refer to political issues, and I want to make sure we're on the same page. What do you mean by that exactly?

A. The political issues were carryover from a previous administration. And as far as the current administration, I don't know if that's still valid. I believe it to be a fact. However, I haven't pursued it any further to determine that.

Campana, David - Vol. II (September 19, 2007)

275:13-278:11

Issues: 03 Plaintiff's Counter Designations

Q. So you are saying under that regime, the Murkowski, Gilbertson, Jackson Peeples regime, you felt political pressure about whether to put mental health drugs on the PDL?

A. Correct.

Q. And you described internal memos at the department about recommending drugs for PDL; is that correct?

A. Correct. And I had two personal discussions with people at the Division of Behavioral Health, Christy Willer, who was director then at behavioral health, and the deputy commissioner, Bill Hogan.

And he -- let's see. Bill Hogan, Dwayne Peeples and I and Christy Willer met about putting the mental health drugs at that time, which were the four that I had mentioned, the anti-depressants and the anti-convulsants, et cetera, on the preferred drug list.

At that time, they were buying into it and said, "Well, you know, we'll think about it. We'll take it to

the commissioner."

And shortly after that, then the commissioner said, "Okay, you can move forward with the mental health drugs."

Q. And when you were presenting that, were you presenting that about specific mental health drugs?

A. Specific mental health drugs, the stimulants, the anti-depressants, the sedative hypnotics. Let's see. Anti-depressants, anti-convulsants, stimulants and ADHD.

Q. There were memos from you recommending that?

A. There were at least one memo from me to Dwayne Peeples to Bill Hogan recommending that we move forward with the preferred -- those drugs on the preferred drug list.

Q. Were there any -- was there any documentation from those above you in the food chain so to speak responding to that before a decision was made that you could do it?

A. I don't remember, you know, as far as having any direct thing, other than e-mail. And I used to query my director occasionally, "Can we put on the mental health drugs yet? Can we do that yet?"

And at one point he said, "Okay, go for it. We have permission and authority granted all the way up."

Q. Was there any communications, whether by e-mail or verbally, prior to the decision to go ahead and do it, were there any e-mails or other communications pushing back saying no?

A. Yes.

Q. Where did those come from?

A. From Joel Gilbertson and through Dwayne Peeples.

Q. How was that communicated to you?

A. That was by e-mail and verbal.

Q. In terms of the e-mails that you are referring to, have you retained those e-mails?

A. I don't know. I had to clean out my e-mail this year because we went on a new system, and I don't know how much I have retained.

Q. In the communications -- can we refer to them as sort of negative communications just for --

A. Sure.

Q. Was there any rationale provided for why you couldn't go forward?

A. No.

Q. Just we're not doing it right now, that kind of thing?

A. We're not going to do it right now.

Q. Eventually, though it was allowed?

A. Eventually, we were able to prevail and say that, you know, the preferred drug list is up and running, we have good buy-in with the prescribers and we have compliance over 80 percent.

This is what it's going to do for these drugs and it will, you know, basically be okay to do this. And it just took a while to get buy-in to do that.

Campana, David - Vol. II (September 19, 2007)

279:15-17
Issues: 03 Plaintiff's Counter Designations

279:15 Q. Did you ever make the same case in your agency or
16 above for putting the anti-psychotics on the PDL?
17 A. No, I haven't, but I will.

Campana, David - Vol. II (September 19, 2007)

280:5-12
Issues: 03 Plaintiff's Counter Designations

280: 5 What are the reasons that you have now decided to
6 recommend a PDL for the anti-psychotics?
7 A. I think we have a good product with our preferred
8 drug list and there is no reason at this point not to
9 ask for it.
10 We have -- you know, there is going to be
11 political pressure. There is always going to be some
12 political pressure.

Campana, David - Vol. II (September 19, 2007)

308:23-309:20
Issues: 03 Plaintiff's Counter Designations

308:23 Q. Is it a utilization review limited to
24 anti-psychotic medications?
25 A. It's limited to anti-psychotics and opioids. And
309: 1 in, say, in the anti-psychotics, that includes the
2 anti-depressants, the stimulants, the anti-epileptic or
3 anti-convulsants and anti-depressants.
4 Q. So it's not just --
5 A. It's not your atypical or typical. It's the
6 atypical and typical and other classes of mental health
7 drugs.
8 Q. How long has Alaska been participating in this
9 BPMS program?
10 A. Let's see. We started in, I believe it was 2005,
11 and continued it 2005 through 2006. Then the contract
12 for it had expired earlier this year and we did another
13 contract for another two years.
14 Q. I'm sorry. So it started what year again?
15 A. 2005.
16 Q. It started in 2005?
17 A. Started in 2005 in Alaska.
18 Q. So really you have been participating
19 continuously since 2005 under two separate contracts?
20 A. Correct.

Campana, David - Vol. II (September 19, 2007)

312:21-313:3

Issues: 03 Plaintiff's Counter Designations

312:21 Q. You said Lilly was hesitant to fund the grant at
22 all. How do you know that?
23 A. I had discussions with Mr. Walters on that. And
24 there was information coming from other states that Eli
25 Lilly was balking at providing that grant, and the
313: 1 information also came from CNS.
2 Q. Do you know why they were balking?
3 A. I don't know why.

Campana, David - Vol. II (September 19, 2007)

314:5-7

Issues: 03 Plaintiff's Counter Designations

314: 5 Q. Does the program reveal off-label prescribing?
6 A. It really doesn't come up against off-labeled
7 prescribing.

Campana, David - Vol. II (September 19, 2007)

314:12-15

Issues: 03 Plaintiff's Counter Designations

314:12 Q. Does the program in any way look for side
13 effects?
14 A. No, it doesn't. There is no diagnosis
15 information used at this point.

Campana, David - Vol. II (September 19, 2007)

315:16-316:8

Issues: 03 Plaintiff's Counter Designations

315:16 Q. How is your relationship with Kevin Walters?
17 A. Pretty good.
18 Q. Do you ever talk to him about the lawsuit?
19 A. No.
20 Q. Did you -- you have never ever talked to him
21 about the conclusions you reached that the product that
22 his company is selling causes diabetes?
23 A. No.
24 Q. Why not?
25 A. I don't know.
316: 1 Q. You told me a little while ago that you had
2 concluded that Eli Lilly had misrepresented Zyprexa in
3 its package insert?
4 A. Correct.
5 Q. Did you ever tell him that?

A. No.
Q. Why not?
A. I just don't go out and pick fights.

Campana, David - Vol. II (September 19, 2007)

341:16-342:11
Issues: 03 Plaintiff's Counter Designations

341:16 Q. Mr. Campana, you said that you sort of reached
17 the conclusion at lunch that maybe you ought to
18 recommend or at least consider recommending
19 anti-psychotics for the PDL.
20 Is there anything that you learned at this
21 deposition that caused you to come to that conclusion?
22 A. Well, it seems like Eli Lilly and yourself are
23 questioning us why we didn't do that, why, if our
24 process is a good process to review drugs, that we don't
25 review drugs.
342: 1 So maybe we need to revisit that and look at that
2 process again, and look at all of the processes as far
3 as if we need to do some other action on the atypical
4 and psychotropic drugs.
5 Q. So this was a conclusion that you didn't come
6 into this deposition -- a position you didn't come into
7 this deposition holding, but during the course of this
8 deposition, you have come to the conclusion that, based
9 on the questions that I have asked you, that perhaps you
10 should review the atypical anti-psychotics?
11 A. Correct.

Gilbertson, Joel (December 6, 2007)
15:22-17:7
Issues: 03 Plaintiff's Counter Designations

15:22 The functional responsibilities of
23 the Department include overseeing all public
24 health powers, so operating public health
25 laboratories, overseeing the medical examiner's
16: 1 office, public health functions, running public
2 health clinics, disease surveillance,
3 bioterrorism preparedness, those types of
4 functions. Overseeing the Juvenile Justice
5 System for the State of Alaska, so operating
6 juvenile detention facilities, overseeing
7 juvenile probation services.
8 Overseeing the Medicaid program and
9 its tentacles into other programs, of course.
10 Overseeing the child protection system, so foster
11 care, investigating reports of harm, general
12 social work, targeted case management.
13 Overseeing senior and disability services, so
14 that would include running the Pioneer Home
15 system, which is a collection of assisted living
16 facilities in the State of Alaska.
17 Overseeing the Developmental
18 Disability Waiver program, the Senior Waiver
19 program, the Personal Care Attendant program.
20 Would also include overseeing all behavioral
21 health programs for the State of Alaska, so that
22 includes running the State Psychiatric Institute,
23 and managing behavioral health grants, which are
24 grants that go out to local community mental
25 health providers for delivering clinic-based
17: 1 outpatient services.
2 And then there's a collection of
3 regulatory functions, Certificate of Need,
4 licensure certification. I'm probably missing
5 some, but that's sort of a -- it's your broad
6 health and social service functions for a State
7 agency.

Gilbertson, Joel (December 6, 2007)
24:17-21
Issues: 03 Plaintiff's Counter Designations

24:17 Q Did you do anything as Commissioner to
18 keep yourself apprised about the medications
19 being reimbursed by the State of Alaska?
20 A At the individual drug level, no.
21 Simply not enough time in the day.

Gilbertson, Joel (December 6, 2007)

25:10-25
Issues: 03 Plaintiff's Counter Designations

25:10 Q Did you in your role as Commissioner
11 interact with representatives from pharmaceutical
12 companies?
13 A Yes.
14 Q Okay. And for what purposes?
15 A I didn't seek them out, but they seemed
16 to want to visit frequently to lobby the
17 Department on various issues.
18 Q Was Eli Lilly one of the companies
19 that --
20 A Eli Lilly hired lobbyists and Eli Lilly
21 did lobby the Alaska state government during my
22 years in office.
23 Q Okay. Did they personally interact with
24 you?
25 A Yes, yeah.

Gilbertson, Joel (December 6, 2007)

26:19-27:5
Issues: 03 Plaintiff's Counter Designations

26:19 Q What did they lobby you about?
20 A They lobbied me in 2003 to not implement
21 a preferred drug list, and then during -- when I
22 say "me," I mean the State, not me personally.
23 And then they lobbied the State in 2003 and 2004
24 to have their drugs -- or mental health drugs
25 carved out from the States's preferred drug list.
27: 1 And I'm sure there were a collection of other
2 issues, I just don't recall them.
3 Q What did they say to you when they
4 lobbied not to implement a PDL?
5 A Nothing logical.

Gilbertson, Joel (December 6, 2007)

28:21-29:6
Issues: 03 Plaintiff's Counter Designations

28:21 Q And whether Eli Lilly individually or
22 this group collectively, do you recall any
23 discussion about particular products?
24 A Not as a group, no.
25 Q Okay.
29: 1 A It became clear later in the legislative
2 session in 2003 that Eli Lilly's lobbyists, while
3 not lobbying me personally, they did lobby in the
4 legislature for legislation that would carve out
5 mental health drugs from the preferred drug list,

and that was done by Eli Lilly's lobbyists.

Gilbertson, Joel (December 6, 2007)
76:14-77:8
Issues: 03 Plaintiff's Counter Designations

Q (BY MR. SNIFFEN) Mr. Gilbertson, Ed Sniffen. I'm an Assistant Attorney General with the State. We've talked earlier pertaining to this deposition. Just a couple of follow-up questions to some questions posed to you by Mr. Rothschild.

He'd asked you if you had hoped to know or become aware of certain issues during your tenure as Commissioner relating to Zyprexa, for example, whether it was used for off-label purposes.

Do you recall that question?

A I do.

Q He also asked you if you had hoped to become aware of any safety issues with Zyprexa.

Do you recall that?

A I do.

Q Does the fact that you were not aware of those things mean to you that they did not happen or that you just don't recall?

Gilbertson, Joel (December 6, 2007)
77:10-25
Issues: 03 Plaintiff's Counter Designations

A It means I don't recall. I think it's fair to say that, you know, there's a good portion of the Department, particularly that which is at the program level, at the clinician level, at the skill professional level where those decisions are made, and those experts manage it. There's a certain level of detail that you get involved in at the Commissioner's office, and that I was not aware of it doesn't mean much in terms of did it happen or not.

Q (BY MR. SNIFFEN) So, is it fair to say, then, that there would have been times when some of those issues may have come to the Department's attention through its program administrators or other employees and they would not have been brought to your attention?

Gilbertson, Joel (December 6, 2007)
78:3-5

Issues: 03 Plaintiff's Counter Designations

78: 3 A Certainly that could happen, yes.
4 MR. SNIFFEN: Thank you. I have
5 nothing further.

Hopson, Duane M.D.(December 11, 2007)
46:14-48:13
Issues: 03 Plaintiff's Counter Designations

46:14 Q Do pharmaceutical company sales reps
15 ever attend these meetings?
16 A Yes.
17 Q How often?
18 A Well, typically, those are the
19 individuals responsible for setting them up,
20 so -- and the drug rep usually accompanies them.
21 So, typical scenario, they're -- most of the drug
22 reps are not located in Alaska. They're in the
23 Lower 48. So a typical rep will bring a
24 particular speaker up and they'll make the rounds
25 to the different hospitals and give a lecture.
47: 1 Q How often does that occur?
2 A I would say it averages once a month.
3 Q Since you're having -- and you're having
4 staff meetings every week?
5 A Yes.
6 Q So once a month at a staff meeting, on
7 average, you see an outside speaker who's brought
8 in by a sales rep?
9 A This is -- it's done on a separate day.
10 It doesn't take the place of medical staff.
11 Q Do outside speakers ever come to medical
12 staff meetings?
13 A There was a time when they did. When I
14 first came there, a medical staff meeting was
15 used for that purpose, but we decided that it was
16 kind of crowding that, so we moved outside
17 speakers to a different day of the week.
18 Q Does the staff -- during the regular
19 staff meetings, do sales reps ever come to those
20 meetings?
21 A Not any longer, no.
22 Q Now, when you have separate meetings
23 with speakers -- let me start all over.
24 Do you have separate meetings where
25 there are just sales reps present and not outside
48: 1 speakers?
2 A Very rarely. Very rarely.
3 Q When would -- why would they occur?
4 A It seems like there was an instance of a
5 particular company was releasing a new product
6 and they didn't have a speaker, but they wanted
7 to get the word out, pass out some information,
8 so they would just do it on their -- they did it
9 on their own.
10 Q But most of the time when you have an
11 extra meeting with someone from outside, it's a
12 speaker brought in by a sales rep; is that right?
13 A Yes.

Hopson, Duane M.D.(December 11, 2007)
59:3-13
Issues: 03 Plaintiff's Counter Designations

59: 3 Q Did they discuss those individual
4 prescribing decisions in your staff meetings?
5 A Not on a regular or detailed basis, no.
6 Q Do you remember it ever coming up?
7 A You know, just general discussion,
8 again, that there is this risk. It's open
9 formulary, be mindful of it. And it was around
10 that time that Dr. Love, you know, really began
11 monitoring BMI, weight, lipids.
12 Q Dr. Love is your family care physician?
13 A Yes, family practice, yes.

Hopson, Duane M.D.(December 11, 2007)
62:1-13
Issues: 03 Plaintiff's Counter Designations

62: 1 Q What kind of articles do you keep?
2 A Oh, perhaps one that I think is going to
3 be something that I might want to reference back
4 to. Maybe the CATIE trial. I think I've got a
5 copy of that. You know, things like that.
6 Q Do you keep any promotional literature
7 that company representatives bring to you?
8 A Not for the long haul.
9 Q Have you kept -- beside CATIE or the
10 CATIE study, have you kept any of the literature
11 that you've read over the years about Zyprexa?
12 A I don't believe I have anything right
13 now.

Hopson, Duane M.D.(December 11, 2007)
78:7-79:14
Issues: 03 Plaintiff's Counter Designations

78: 7 Q Now, you said -- did I understand you
8 that the way you obtain consent has changed over
9 the years because your knowledge has changed?
10 A Right.
11 Q But with the knowledge that you had
12 early on about weight gain and blood sugar
13 changes that were associated with Zyprexa, you
14 were passing that information along to patients
15 right from the start; is that right?
16 A The weight gain was from the start,
17 because almost immediately we recognized that it
18 caused weight gain. You know, and we were told

weight gain in varying degrees depending upon patient, type, that sort of thing.
Q Told by whom?
A Pharmaceutical reps.
Q Did your prescribing habits change as a result of the 2003 label change in Zyprexa?
A I would say yes.
Q Even though you were aware before the label change of the information in the label?
A Yes, I think that it did.
Q And how did it change?
A Well, I think after the label change, it -- not only me, but I think other people that made us even more cognizant. It made the things that we had perhaps suspected, you know, as side effects or potential side effects with Zyprexa, were actually, you know, real. They were being admitted to, being told to us, whatever, and so we -- I, in particular, you know, took that into consideration when you're considering a medication.

Hopson, Duane M.D.(December 11, 2007)
91:4-12
Issues: 03 Plaintiff's Counter Designations

Q Do you anticipate that there will be restrictions placed by the State?
A I think that that, you know, is a possibility.
Q Has it been discussed at any P&T meetings?
A Not that I'm aware of. I was not present for the most recent P&T committee. I was out of town, and so I don't know for that one.

Hopson, Duane M.D.(December 11, 2007)
99:24-100:20
Issues: 03 Plaintiff's Counter Designations

Q Does the CNS program provide to the BPMS committee information concerning how many people in the state are being treated with atypical antipsychotics and typical antipsychotics?
A Yes, I believe that's one of the indicators, are the typicals in addition to the atypicals.
Q Does it break down among the atypicals which medications are being used in what quantities?
A No, not the reports that I see.
Q Do you recall what the ratio is of the

use of typical antipsychotics to atypical antipsychotics within the State Medicaid program?
A The use of atypicals is significantly higher than the typicals. I don't know a dollar amount.
Q In terms of the number of patients, do you know what the significant difference is?
A Again, weighted towards the typical -- more patients receive the atypicals than the typicals.

Hopson, Duane M.D.(December 11, 2007)
106:15-107:19
Issues: 03 Plaintiff's Counter Designations

A Roughly --
MR. STEELE: Can I ask a question?
MR. ROGOFF: Please.
MR. STEELE: I mean, I assume you're not asking him to vouch for their numbers. What you're just asking him to do is to read the exhibit, right --
MR. ROGOFF: Yes.
MR. STEELE: -- because he has no way of knowing whether it's right or wrong.
MR. ROGOFF: Correct.
A Roughly 6.6 million.
Q (BY MR. ROGOFF) Dollars?
A From the projected. And I do recall during the steering -- during the stakeholders committee meeting, because there were some providers there that did have question about this as to how, you know, how confident the CNS people were that the -- the projection was true. You know, would it actually have ended up costing as much?
Q Did -- I'm sorry.
A Their response was that they felt that they had enough data points to -- but there was a lot of time there -- you know, I do recall there was some discussion about that, that there was a significant amount of time had lapsed there and there might have been some other influences there, but --
Q Okay. Thank you.

Jackson, Karleen (December 12, 2007)
5:23-6:9
Issues: 03 Plaintiff's Counter Designations

5:23 Q. What's been put in front of you is
24 Exhibit 1 for your deposition. Can you identify
25 that document?
6: 1 A. It would appear to be a lawsuit, the
2 State of Alaska versus Eli Lilly.
3 Q. Have you ever seen that document before?
4 A. No, sir, I have not.
5 Q. And you're sure of that?
6 A. It's possible that it may have come
7 through my office, but that -- I would not
8 necessarily remember it, and I have not read it
9 in detail.

Jackson, Karleen (December 12, 2007)
7:15-8:2
Issues: 03 Plaintiff's Counter Designations

7:15 Q. What are the major components or
16 divisions of your department?
17 A. We're what's referred to by other state
18 agencies as a super agency. So we include
19 everything from children's services, which is
20 Child Protection, Division of Juvenile Justice,
21 Behavioral Health, which is mental health and
22 substance abuse. Boy, this is going to be a
23 test. Division of Senior and Disability
24 Services; our Alaska Pioneer Home System; Public
25 Health. I'm missing a couple here. Let me think
8: 1 for a minute. What am I missing.
2 Q. It's not a memory test?

Jackson, Karleen (December 12, 2007)
10:8-12
Issues: 03 Plaintiff's Counter Designations

10: 8 Q. Do you know what the State's expenses
9 were in the last fiscal year for pharmaceuticals
10 in the Medicaid program?
11 A. I'm sorry, I don't. I have wonderful
12 budget people that do, but I don't.

Jackson, Karleen (December 12, 2007)
10:18-23
Issues: 03 Plaintiff's Counter Designations

10:18 Q. Where did you go to college?
19 A. I got my undergraduate degree here in
20 Anchorage at the Alaska Pacific University; and
21 then went through The Fielding Institute and got
22 a master's and a Ph.D. through The Fielding
23 Institute.

Jackson, Karleen (December 12, 2007)
11:16-20
Issues: 03 Plaintiff's Counter Designations

11:16 Q. Were you working while you were getting
17 your degrees from Fielding?
18 A. Yes.
19 Q. Where were you working?
20 A. At Catholic Social Services.

Jackson, Karleen (December 12, 2007)
12:5-8
Issues: 03 Plaintiff's Counter Designations

12: 5 Q. The first job was working in a shelter?
6 A. Correct.
7 Q. Doing what?
8 A. Working as, basically, a case manager.

Jackson, Karleen (December 12, 2007)
14:7-22
Issues: 03 Plaintiff's Counter Designations

14: 7 Q. When you were a case manager or a
8 supervisor, did you deal with any of your
9 clients' mental health providers?
10 A. Absolutely, yes.
11 Q. Did you learn about mental health
12 medications?
13 A. To some degree, yes. But, again, my --
14 my work was not about being an expert about
15 mental health medication, but who to refer people
16 to.
17 Q. And were you helping to coordinate care
18 for your clients?
19 A. Not in the mental health model of
20 coordination of care, but more around the -- the
21 helping folks develop a plan for how they could
22 exit homelessness and stay housed.

Jackson, Karleen (December 12, 2007)

18:13-17
Issues: 03 Plaintiff's Counter Designations

18:13 Q. What role did you have at all -- if at
14 all, in administering Medicaid funds for the
15 behavioral health component of your job?
16 A. I really did not have a role in -- in
17 that way.

Jackson, Karleen (December 12, 2007)

32:10-33:1
Issues: 03 Plaintiff's Counter Designations

32:10 Q. Have you ever met with any
11 representatives of Eli Lilly & Company?
12 A. Often in my former role as deputy
13 commissioner and my role as commissioner we get
14 lobbyists that come to Juneau or want to meet
15 with the commissioner or the commissioner's
16 representative, so I have met with
17 representatives of the major pharmaceutical
18 companies.
19 Q. Let's talk about your time as deputy
20 commissioner. Do you recall meeting with Eli
21 Lilly & Company representatives?
22 A. I am sure that I did, but I can't tell
23 you who, when, or where. I mean, I can tell you
24 where; Juneau. But not specifically who or when.
25 And we get a parade of people through during the
33: 1 legislative session that are lobbying.

Jackson, Karleen (December 12, 2007)

34:23-35:2
Issues: 03 Plaintiff's Counter Designations

34:23 Q. Do you think you have in your office any
24 documents that Eli Lilly & Company
25 representatives provided to you?
35: 1 A. It's possible that we have some things
2 on file that they may have left behind, yes.

Tollefson, Gary M.D. (November 6, 2006)
43:11-12
Issues: 03 Plaintiff's Counter Designations

43:11 Q. And what types of people were
12 these healthy volunteers?

Tollefson, Gary M.D. (November 6, 2006)
43:15-44:16
Issues: 03 Plaintiff's Counter Designations

43:15 A. I'm not sure that I
16 understand what type of people. These would
17 be normal individuals that would opt to
18 volunteer to participate and contribute to
19 medical education and research.
20 Q. And how long would they be
21 involved in studies?
22 A. Again, that's entirely
23 dependent on the protocol of the particular
24 study that had been approved by the local
44: 1 institutional review committee.
2 Q. Just sort of ballpark. Do
3 you have a range? Is it like an hour, days,
4 weeks, months?
5 A. It could be as short as a day
6 or could extend for several weeks. Again, if
7 we're referring to the Phase 1 studies.
8 Q. Okay. And, sir, isn't it
9 true that back in the 1990s Lilly used
10 homeless people as test subjects in those
11 studies?
12 A. I'm not sure of the
13 socioeconomics of subjects. I don't think
14 that Lilly in any way discriminated against
15 anyone that wanted to participate, whether
16 they had a home or whether they didn't.

Tollefson, Gary M.D. (November 6, 2006)
44:17-19
Issues: 03 Plaintiff's Counter Designations

44:17 MR. SUGGS: Let me hand you
18 what I'm going to mark as Tollefson
19 Exhibit 2.

Tollefson, Gary M.D. (November 6, 2006)
44:24-45:5
Issues: 03 Plaintiff's Counter Designations

MR. SUGGS: For the record this is a copy of the Wall Street Journal Online dated November 14, 1996. The article has a title "Lilly's 'Quick Cash' to Habitues of Shelters Vanishes Quickly."

Tollefson, Gary M.D. (November 6, 2006)

45:7-48:9

Issues: 03 Plaintiff's Counter Designations

Q. Do you remember this article coming out in the Wall Street Journal back in 1996?

A. I vaguely recall.

Q. Okay. If you look over to the side it says, "Food and Drug Administration chastised Lilly in 1994 for using alcoholics in a drug study." Do you see that?

A. I'm sorry, I don't.

Q. It's over in the little box to the right. In the small print over there. There's a one beside it?

A. Looks like a footnote.

Q. Yes. Do you recall Food and Drug chastising Lilly in 1994 for using alcoholics in a drug study?

A. I don't recall that.

Q. If I could direct your attention to the bottom of the first page there's a section of the article has a heading "Day Rates," do you see where that is?

A. I do.

Q. And the paragraphs below that state, "For the pharmaceuticals industry persuading ablebodied people to sample untried and potentially dangerous drugs is a tough sell. To woo their human subjects most companies have to advertise heavily and shell out $125 or so a day, occasionally as much as $250. SmithKline Beecham PLC, even pays referral bonuses. By contrast Lilly advertises less frequently, and at $85 a day pays what competitors believe is the lowest per diem in the business.

Alone among its peers, Lilly has become a potent magnet for homeless people. For more than two decades Lilly's testing clinic has drawn from the ranks of the homeless, often alcoholic, men who drift in and out of Indianapolis's church-run

inner-city missions. Some mission directors privately express misgivings about this but say they are reluctant to speak up because they receive funding from a foundation built on Lilly stock even though the foundation is independent of the company and its clinic.

Word of mouth about testing at Lilly, a company best known for the blockbuster drug Prozac, has gradually spread through the soup kitchens, prisons, and shelters from coast to coast. Today so many homeless men come to Indianapolis seeking admittance to Lilly's research clinic that Mathias Vaga, medical director of the local homeless initiative program, credits the clinic with creating a shadow economy. One veteran nurse at the Lilly Clinic says that the majority of its subjects are homeless alcoholics."

Do you see that language, sir? Does that refresh your recollection about this article coming out back in 1996?

A. Again, as I indicated earlier, I recall the article.

Q. Okay. And in fact, homeless people were used as subjects in some of the Zyprexa studies; isn't that correct?

A. I would just repeat what I said earlier. I don't believe that the clinic made any effort to discriminate against whether someone did or did not have a home.

Tollefson, Gary M.D. (November 6, 2006)
55:24-56:3
Issues: 03 Plaintiff's Counter Designations

55:24 Q. Would you expect to see a
56: 1 higher incidence of hyperglycemia in a
2 population in their mid-30s or in a
3 population in their mid-50s?

Tollefson, Gary M.D. (November 6, 2006)
56:6-9
Issues: 03 Plaintiff's Counter Designations

56: 6 A. I think the risk of
7 developing Type 2 diabetes as a
8 representative of hyperglycemia would be
9 higher in that older patient cohort.

Tollefson, Gary M.D. (November 6, 2006)
107:9-11
Issues: 03 Plaintiff's Counter Designations

107: 9 MR. SUGGS: We'll leave that
10 subject for the expert witnesses.
11 THE WITNESS: Very good.

Tollefson, Gary M.D. (November 6, 2006)
117:10-16
Issues: 03 Plaintiff's Counter Designations

117:10 Q. Okay. So in that '99/2000
11 time period, you would have been three steps
12 or, actually two steps below the top level of
13 the company, correct?
14 A. I was a member of the senior
15 management team with -- yeah, that's a fair
16 characterization.

Tollefson, Gary M.D. (November 6, 2006)
118:5-8
Issues: 03 Plaintiff's Counter Designations

118: 5 Q. Okay. So again, would you
6 have been regarded as senior management in
7 that period?
8 A. Yes.

Tollefson, Gary M.D. (November 6, 2006)
183:7-8
Issues: 03 Plaintiff's Counter Designations

183: 7 MR. LEHNER: Object to the
8 form. Asked and answered.

Tollefson, Gary M.D. (November 6, 2006)
298:10-15
Issues: 03 Plaintiff's Counter Designations

298:10 Q. Thank you, sir. Let's talk
11 about -- the facet I'd like to focus on is are
12 risks or adverse events associated with
13 treatment. That's one of the facets you just
14 identified, wasn't it?
15 A. Yes.

Tollefson, Gary M.D. (November 6, 2006)
298:22-299:7
Issues: 03 Plaintiff's Counter Designations

298:22 Q. My question to you is -- let
23 me just get right to Zyprexa. In
24 identifying, I asked you to give this jury
299: 1 your definition of risk. You gave us some
2 facets and one of the facets was adverse
3 events associated with treatment, correct?
4 A. Um-hum. Correct.
5 Q. Would it be appropriate for
6 Eli Lilly to try to minimize adverse events
7 associated with Zyprexa, yes or no?

Tollefson, Gary M.D. (November 6, 2006)
299:10-301:9
Issues: 03 Plaintiff's Counter Designations

299:10 A. I'm not sure what you mean by
11 "minimize."
12 Q. Is that your best answer to
13 that question?
14 A. I was just asking if you
15 would like to elaborate what you meant by
16 minimize because I'm not sure what you meant.
17 Q. Is that your best answer to
18 my question?
19 A. Again, I think the data is
20 the data. And you share the data, once it's
21 been validated, and you don't maximize or
22 minimize. The data is the data. The data
23 tells the story. That's my view. But I'm
24 not sure what you meant by "minimize."
300: 1 Q. You just used the term
2 "minimize," how do you use the term
3 "minimize?"
4 A. If I were using it --
5 Q. I'm sure you've used it your
6 entire life.
7 A. Probably something different
8 than maximize. Something less than maximize.
9 Q. You know what maximize means.
10 I've seen documents with your name on it
11 talking about maximization of profit, right?
12 You know what that means, don't you?
13 MR. LEHNER: Objection to
14 form.
15 A. I do.
16 Q. To maximize something means
17 to make it -- to highlight it, to get it as
18 great as possible. Is that a fair definition

of maximize?
A. That is a definition, yes.
Q. Okay. Minimize. What do you mean when you talk about minimizing something, you, Dr. Tollefson?
A. Not overstating it.
Q. So to minimize doesn't mean to downplay it to you? To downplay it, make it less significant?
A. That could be an extreme of it.
Q. Yes. Would it be appropriate for Eli Lilly to minimize, downplay, make less significant, an adverse event associated with Zyprexa?

Tollefson, Gary M.D. (November 6, 2006)
301:12-16
Issues: 03 Plaintiff's Counter Designations

A. I think if someone is unsure whether there is a causal relationship, there is a detriment to either over or maximizing or minimizing in the absence of knowing whether there's causality.

Tollefson, Gary M.D. (November 6, 2006)
301:20-22
Issues: 03 Plaintiff's Counter Designations

Q. My only question to you was should Eli Lilly try to minimize the adverse events associated with Zyprexa?

Tollefson, Gary M.D. (November 6, 2006)
302:1-303:6
Issues: 03 Plaintiff's Counter Designations

A. No.
Q. Should Eli Lilly try to neutralize the adverse events associated with Zyprexa?
A. No. I think they should put them in the proper context.
Q. But they should not try to neutralize them, should they, sir?
A. Again, I'm not sure of your definition of neutralize.
Q. What does neutralize mean to you? Make something neutral. I'm sure

you've used it all your life, you're a smart and educated man. When you neutralize something, what do you do?

A. Take away a positive or a negative valence.

Q. Right. You take away, you try to -- don't want to have a positive or negative feeling. You try to neutralize the feeling. You have no opinion, right?

A. Or you might have opinions that are offsetting and you end up with a neutral outcome.

Q. Right. And a neutral outcome means what, sir?

A. Neither positive or negative.

Q. Right. Should Eli Lilly attempt to neutralize the adverse events associated with Zyprexa treatment?

Tollefson, Gary M.D. (November 6, 2006)

303:9-14

Issues: 03 Plaintiff's Counter Designations

A. They should present the events as they understand the data to be.

Q. Should they attempt to neutralize the events associated with Zyprexa treatment?

A. No.

Tollefson, Gary M.D. (November 6, 2006)

383:15-16

Issues: 03 Plaintiff's Counter Designations

MR. SUGGS: Objection to form.

Tollefson, Gary M.D. (November 6, 2006)

388:11-394:12

Issues: 03 Plaintiff's Counter Designations

As of 2000, how many drug therapies for treatment of schizophrenia were available besides Zyprexa?

THE WITNESS: In the United States?

MR. ALLEN: Yes.

A. I would only be able to guess, but 12, 16 --

Q. Okay.

A. -- something like that.
Q. Are you familiar with a study that was done by a Dr. Rosenheck that was published in the "New England Journal of Medicine" in, I'm looking for the date. This is a document I have on my computer, I don't have a paper copy.
I take it back, it was not published in the "New England Journal of Medicine" it was published in the "Journal of the American Medical Association" in 2003.
A. I think I might know what you're referring to.
Q. I'm referring to a study by Dr. James Rosenheck. You know Dr. Rosenheck, don't you?
A. I do know him, know of him.
Q. He was a consultant for Lilly, was he not?
A. He may have been.
Q. In fact, Lilly helped fund that study, did it not?
A. I believe so.
Q. Okay. And do you recall that the conclusion of his article was, "Olanzapine does not demonstrate advantages compared with haloperidol in combination with prophylactic benztropine in compliance symptoms, extrapyramidal symptoms, or overall quality of life, and its benefits in reducing akathisia and improving cognition must be balanced with problems of weight gain and higher cost."
A. That was his conclusion in that study.
Q. And in that study that was funded in part by Lilly, correct?
A. That's correct.
Q. Okay. And do you recall that there was also a study published in the "New England Journal of Medicine" just last month, I believe, in October 2006, by a Dr. Schneider and others entitled Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease?
A. Yes. That was a CATIE study in Alzheimer's. Sort of equivalent to the CATIE schizophrenia study where olanzapine was the best performing agent, as I recall.
Q. Do you recall that that study concluded that there were no significant differences among treatments with regard to the time to discontinuation of treatment for any reason?
A. I recall that the study -- that was the primary outcome of the study, and that patients on drug therapy tended to

discontinue therapy fairly early in the course of treatment. I do think they did a secondary efficacy analysis, though, where olanzapine was the best performing agent.

Q. Do you recall that there was another recent study published in October 2006 in the Archives of General Psychiatry by a Dr. Peter Jones, among others?

A. Yes.

Q. And was that study funded by a drug company or was it conducted -- was it sponsored by the British government?

A. The latter, I believe.

Q. Okay. It was sponsored by the British government?

A. Yes.

Q. Do you recall it concluded that, quote, "In people with schizophrenia whose medication is changed for clinical reasons there is no disadvantage across one year in terms of quality of life, symptoms, or associated costs of care, in using first generation antipsychotics rather than nonclozapine second generation antipsychotics, and that neither inadequate powered or patterns of drug discontinuation accounted for the result?"

A. Yeah. I think it's important to just realize that that was a sample of patients that had been either nonresponsive to second generation drugs and/or intolerant to second generation drugs. So these are people that didn't benefit by that class of drugs now being treated with another one from the same class or what is you called a second generation drug, but is not available in this country, and it's a fairly unique molecule called amisulpride, and in that nonresponding group my understanding was he did not find significant differences in the 200 and some patients that he looked at.

Q. It's fair to say that in recent years there have been several studies funded, either by Lilly or by governmental entities, which have concluded that Zyprexa is no more effective than first generation antipsychotics, correct?

A. I think there are studies that say that it is, there are some studies that are equivocal, and there are a few studies that you cited that may call into question whether it is. And it depends a lot on the population and the design of the study.

Q. And, sir, regardless of whether a drug is efficacious or not, a

physician, in making the decision to prescribe the drug has to consider both the benefits of the drug and the potential risks, correct?

A. That's correct.

Q. The physician has to be fully apprised of the risks by the drug company, correct?

A. I would hope that's not their only source of information but I would agree they should be fully apprised.

394: Q. And Lilly had an obligation to convey the information that it had about both the risks and the benefits to physicians so that they could consider that information before they decided whether they were going to use Zyprexa or some alternative treatment for patients with the very serious illness of schizophrenia, right?

MR. LEHNER: Object to form.

A. I agree they had the obligation to share validated data with clinicians.

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, vs. ELI LILLY AND COMPANY, Defendant.	)	Case No. 3AN-06-5630 CIV

NOTICE OF FILING PLAINTIFF'S OBJECTIONS TO DEFENDANT'S PAGE/LINE DESIGNATIONS AND EXHIBITS UNDER SEAL

On this date the State of Alaska is filing a pleading titled "Plaintiff's Objections to Defendant's Page/Line Designations." Because one or more exhibits filed with this pleading may be confidential documents under the Court's April 6, 2007 oral ruling, the State of Alaska is submitting this pleading and the attached exhibits under seal.

DATED this 28 day of January, 2008.

See Judge Rindner's 6/13/08 order, page 22, #19 documents unsealed Lwade 8/11/08

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I hereby certify that a true and correct copy of **Notice of Filing Plaintiff's Objections to Defendant's Page/Line Designations and Exhibits Under Seal** were served by messenger on:

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PAGES 1 THRU 1102

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff,	)	
v.	)	Case No. 3AN-06-05630 CI
ELI LILLY AND COMPANY, Defendant.	)	

PLAINTIFF'S OBJECTIONS TO DEFENDANT'S PAGE/LINE DESIGNATIONS

Plaintiff respectfully submits its specific objections to Defendant's designations of deposition testimony on the grounds set forth below:

Exhibit 1; Deposition of Charles Beasley, Jr. M.D (Vol. II)

START (PAGE:LINE)	END (PAGE:LINE)	OBJECTION
565:8	567:9	Beyond scope of direct
567:13	569:11	Beyond scope of direct
572:22	578:1	Lack of foundation; improper expert testimony
578:5	578:6	Lack of foundation; improper expert testimony

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578:18	582:20	Lack of foundation; improper expert testimony
583:4	583:16	Lack of foundation; improper expert testimony
722:8	712:11	Not relevant

Exhibit 2; Deposition of David Campana (Vol. II)

START (PAGE:LINE)	END (PAGE:LINE)	OBJECTION
255:15	255:24	Asked and answered
267:10	267:13	Speculation

Exhibit 3; Deposition of Joel Gilbertson

START (PAGE:LINE)	END (PAGE:LINE)	OBJECTION
62:4	62:7	Speculation
64:10	65:20	Speculation
68:1	68:12	Speculation

Exhibit 4; Deposition of Duane Hopson, M.D.

START (PAGE:LINE)	END (PAGE:LINE)	OBJECTION
11:16	11:25	Outside scope of knowledge
30:15	30:22	Asked and answered; repetitive
51:8	52:13	Speculation; outside scope of knowledge

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Exhibit 5; Deposition of Robin Pitts Wojcieszek.

START (PAGE:LINE)	END (PAGE:LINE)	OBJECTION
10:5	11:3	Unnecessary for fairness
12:1	12:14	Unnecessary for fairness
171:1	171:5	Leading; lack of foundation
177:12	177:14	Leading
177:16	177:16	Leading

DATED this 28 day of January, 2008.

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Beasley, Charles M.D.(July 27, 2006)
565:8-567:9
Issues: 02 Defendant Designation
Comment: Objection: Beyond Scope of Direct

565: 8 Q. Now after that, Dr. Beasley,
9 did Lilly receive -- well, you were asked
10 some questions early in your deposition about
11 an inquiry from the drug regulatory agency in
12 South Africa, do you recall that?
13 A. Yes, I did.
14 Q. And did Lilly receive an
15 inquiry from the drug regulatory agency in
16 South Africa asking for some information?
17 A. I believe that we did.
18 Q. And what did Lilly do in
19 response to that inquiry?
20 A. Well, the pharmacovigilance
21 department would have prepared a report on
22 the, the spontaneous adverse events to date
23 that had been observed.
24 MR. SEE: Let me hand you
566: 1 what we've marked as Beasley
2 Exhibit 8.
3 (Whereupon, Deposition
4 Exhibit(s) 8 duly received,
5 marked and made a part of the
6 record.)
7 QUESTIONS BY MR. SEE:
8 Q. And ask if you can tell us
9 what that is?
10 A. It's marked Appendix Seven
11 Review Of Blood Sugar Alterations. The date
12 is October 1997. I believe that because it's
13 marked Appendix Seven it was part of a larger
14 document. Let me look at the --
15 So this appears to be a, the
16 analysis that would have been put together
17 for South Africa. Given that it's marked as
18 an appendix I believe that it would have
19 been, this specific document would have been
20 an inclusion, probably, in a larger
21 regulatory report to the U.S. and/or Europe
22 or other regulatory agencies.
23 Q. Okay. Now at the time Lilly
24 provided or pulled together the information
567: 1 in response to the inquiry from the South
2 African regulatory agency was it possible to
3 draw any conclusion from spontaneous reports
4 whether Zyprexa was causally related to
5 hyperglycemia?
6 A. No, based exclusively on this
7 data we would not draw any sort of firm
8 conclusion about causality. But let me just
9 review the summary.

Beasley, Charles M.D.(July 27, 2006)
567:13-569:11
Issues: 02 Defendant Designation
Comment: Objection: Beyond Scope of Direct

A. And what we indicate given the exposure we, it was considered that the number of events reported was, actually, quite small, and that post-marketing spontaneous adverse events reports of alterations in blood glucose are consistent with the safety profile observed in the clinical trials.

Q. All right. And did Lilly subsequently receive a request from the drug regulatory agency in Europe with respect to spontaneous reports of hyperglycemia regarding Zyprexa?

A. Yes, we did.

Q. All right. And what did Lilly do in response to that request?

A. That would, again, have been a review of the spontaneous adverse events performed by the pharmacovigilance and epidemiology group.

MR. SEE: Let me hand you what we've marked as Beasley Exhibit No. 9 and ask if you can tell us what that is.

(Whereupon, Deposition Exhibit(s) 9 duly received, marked and made a part of the record.)

A. It's titled A Review Of All Spontaneous Cases Of Hyperglycemia Reported In The Lilly Safety Database, Clintrace, that was the name of the computer system, In The First 21 Months Of Marketing Of Commercially Available Olanzapine. And it would be through data through 30 June of '98.

And, okay. I wasn't sure, specifically, what, it says in the introduction: This task was undertaken to fulfill the commitment made to CPMP in the PSUR covering the period December 1997 to March 1998. So --

Q. And what is the CPMP?

A. That is the scientific branch of the European medicines regulatory agency. So this was a report prepared to specifically address the question of analysis and review of the spontaneous adverse events for Europe.

Beasley, Charles M.D.(July 27, 2006)
572:22-578:1
Issues: 02 Defendant Designation
Comment: Objection: Lack of Foundation; Improper Expert Testimony

572:22 Q. All right, thank you,
23 Dr. Beasley. Now, in addition to Lilly's
24 review of the spontaneous reported data, and
573: 1 Lilly's review and analysis of the controlled
2 clinical trials with Zyprexa, were there
3 other different types of studies that looked
4 at the specific question whether Zyprexa was
5 exerting some direct effect to cause
6 hyperglycemia?
7 A. There were a large number of
8 studies and activities going on both
9 clinically and preclinically under this group
10 that Dr. Breier had organized. I'm most
11 familiar with two studies that were conducted
12 in humans referred to as clamp studies.
13 Q. First, tell us, you said
14 there were two studies referred to as clamp
15 studies?
16 A. That's correct.
17 Q. Tell us first what was it
18 that the two clamp studies were directed at
19 looking at?
20 A. Okay. Type two diabetes is
21 thought to be caused by two types of what we
22 call pathophysiology together, or
23 abnormalities in the body, is what
24 pathophysiology means.
574: 1 One is the, the failure of
2 what we call the insulin receptor. And this
3 is a molecule on cells in the body that
4 insulin, which insulin, which is a hormone,
5 interacts with to allow glucose to move into
6 the cells.
7 So you've got to have this
8 receptor working right in order for glucose
9 to move into the cells so that you lower
10 blood glucose levels and the cells are able
11 to use glucose's energy.
12 Q. Are you familiar with the
13 term, Dr. Beasley, insulin sensitivity?
14 A. Yes.
15 Q. Tell me what that means?
16 A. That would be a measure of
17 how well these insulin receptors work.
18 Q. All right.
19 A. The other thing that seems to
20 be necessary for the development of type two
21 diabetes, clinical type two diabetes would be
22 the failure of the pancreas, which is an
23 organ that sits in the abdominal cavity close
24 to the stomach, to put out sufficient amounts

of insulin.

The pancreas is signaled to release insulin when glucose is high in the blood. It releases this insulin, goes to insulin receptors, and this allows glucose to be transported into cells. So the thinking is to be frankly or actual clinical type two diabetes you have to have failure of the insulin receptor, decreased insulin sensitivity, and a decrease in the pancreas' ability to make enough insulin to compensate for poor insulin sensitivity.

Q. All right. Let me ask you first about, actually the second thing you mentioned, that is the failure of the pancreas to actually produce insulin or to produce enough insulin. Was there one of the clamp studies directed at that question?

A. Yes, there was. And again, why did we, we take on these studies? The thinking behind this was that it was important to us to do a study that would look at whether or not olanzapine was causing the effects in the body that would lead to type two diabetes. So that was the purpose in doing the studies.

Q. All right. Now first I want to ask you to describe the clamp study that was directed at the question whether Zyprexa exerted some adverse effect that would cause the pancreas not to produce insulin or not to produce enough insulin.

First, tell us what was that study called and how did you perform it?

A. That's a hyperglycemic clamp study.

Q. And please tell us in layperson's language how that's done?

A. First of all, you have your parallel treatment groups, as we talked about this morning. You have in this case it was placebo, another antipsychotic, and olanzapine. And before patients, or, actually these were what we call normal volunteers, these were healthy subjects. They were tested.

And the way they were tested was by this thing that's called a hyperglycemic clamp. They have an intravenous line inserted into their arm. They are then given glucose, actually --

Q. Glucose is what?

A. Is sugar. Large amounts of glucose, blood sugar, into this line into their body. And then the pancreas has the opportunity to react to this. And what is measured is the amount of insulin that the

Exhibit 1, Page 4 of 10
SOA Obj to Designations
Case No. 3AN-06-05630 CI

body produces in response to this extra glucose. Then the patients, or the subjects are treated.

Q. When you say "treated", what do you mean?

A. They receive double blind either placebo or olanzapine or this other medication. In this case they received it for two weeks and then they were retested.

I think it was probably worth stating that, that this, this type of sophisticated study was -- I did not design this study.

Q. Who did design it?

A. This would have been designed by our --

Beasley, Charles M.D.(July 27, 2006)
578:5-6
Issues: 02 Defendant Designation
Comment: Objection: Lack of Foundation; Improper Expert Testimony

A. -- by our endocrinology colleagues.

Beasley, Charles M.D.(July 27, 2006)
578:18-582:20
Issues: 02 Defendant Designation
Comment: Objection: Lack of Foundation; Improper Expert Testimony

Q. All right, Dr. Beasley, before we changed the tape I was asking you about the hyperglycemic clamp study. And now let me just ask, were the results of the study performed by Lilly looking at whether Zyprexa exerted an adverse effect on the pancreas to produce insulin, were the results of that study published?

A. They were published in a peer reviewed journal.

MR. SEE: Let me hand you what's been marked as Beasley Deposition Exhibit 11.

THE WITNESS: Actually, it's not. You need to add the Beasley.

MR. SEE: Let me add the Beasley on it, sorry.

Let me now hand you what's been marked as Beasley Deposition 11. And can you tell us what that is, please?

(Whereupon, Deposition

Exhibit(s) 11 duly received, marked and made a part of the record.)

A. This would be the academic publication regarding the results of the study we just discussed.

Q. All right. Now, Dr. Beasley, tell us what did the results show of the study done by Lilly to see whether Zyprexa exerted an adverse influence on the pancreas such that the pancreas produced a little or insufficient insulin?

A. The results are summarized in the last paragraph of the abstract. "We found no evidence that treatment of healthy volunteers with olanzapine or the other drug," left that one out, "decreased the insulin secretory response to a prolonged hyperglycemic challenge. The results of this study do not support the hypothesis that olanzapine or the other drug directly impair pancreatic beta cell function."

Q. All right. Dr. Beasley, let me ask you, this hyperglycemic clamp study methodology, is that a recognized methodology to look at the question whether the pancreas is affected to produce insufficient or no insulin?

A. That's my understanding from my endocrine colleagues.

Q. Now, Dr. Beasley, turning to the second prong of these clamp studies, did Lilly perform a study looking at the question of whether Zyprexa produced insulin insensitivity?

A. Yes. That was what was referred to as the euglycemic clamp study.

Q. All right, the euglycemic clamp study. Can you tell us again in layperson's language, what was the euglycemic clamp study looking at?

A. Well, this looks at insulin receptor sensitivity. And here in contrast to the last study you first give a lot of insulin and you also give some glucose. And you determine, essentially, how much glucose you can give, a fixed amount of insulin, and how well the body uses that amount of glucose.

(Whereupon, Deposition Exhibit(s) 12 duly received, marked and made a part of the record.)

QUESTIONS BY MR. SEE:

Q. Let me hand you what we've marked as Beasley Exhibit 12 and ask first were the results of the euglycemic clamp

582: 1 study performed by Lilly published?
2 A. Yes, they were.
3 Q. All right. Now let me ask
4 you to look at Beasley Exhibit 12 and ask you
5 to tell us what that is?
6 A. This would be the academic
7 publication of the study that we just
8 discussed.
9 Q. Can you tell us, Dr. Beasley,
10 what were the results of the euglycemic clamp
11 study performed by Lilly to look at the
12 question whether Zyprexa affected insulin
13 sensitivity?
14 A. That's probably, again, best
15 summarized in the abstract, in the last part
16 of the abstract. "In summary, this study did
17 not demonstrate significant changes in
18 insulin sensitivity in healthy subjects after
19 three weeks of treatment with olanzapine or a
20 different drug."

Beasley, Charles M.D.(July 27, 2006)
578:18-582:20
Issues: 02 Defendant Designation
Comment: Objection: Lack of Foundation; Improper Expert Testimony

578:18 Q. All right, Dr. Beasley,
19 before we changed the tape I was asking you
20 about the hyperglycemic clamp study. And now
21 let me just ask, were the results of the
22 study performed by Lilly looking at whether
23 Zyprexa exerted an adverse effect on the
24 pancreas to produce insulin, were the results
579: 1 of that study published?
2 A. They were published in a peer
3 reviewed journal.
4 MR. SEE: Let me hand you
5 what's been marked as Beasley
6 Deposition Exhibit 11.
7 THE WITNESS: Actually, it's
8 not. You need to add the Beasley.
9 MR. SEE: Let me add the
10 Beasley on it, sorry.
11 Let me now hand you what's
12 been marked as Beasley Deposition
13 11. And can you tell us what that
14 is, please?
15 (Whereupon, Deposition
16 Exhibit(s) 11 duly received,
17 marked and made a part of the
18 record.)
19 A. This would be the academic
20 publication regarding the results of the
21 study we just discussed.

Q. All right. Now, Dr. Beasley, tell us what did the results show of the study done by Lilly to see whether Zyprexa exerted an adverse influence on the pancreas such that the pancreas produced a little or insufficient insulin?

A. The results are summarized in the last paragraph of the abstract. "We found no evidence that treatment of healthy volunteers with olanzapine or the other drug," left that one out, "decreased the insulin secretory response to a prolonged hyperglycemic challenge. The results of this study do not support the hypothesis that olanzapine or the other drug directly impair pancreatic beta cell function."

Q. All right. Dr. Beasley, let me ask you, this hyperglycemic clamp study methodology, is that a recognized methodology to look at the question whether the pancreas is affected to produce insufficient or no insulin?

A. That's my understanding from my endocrine colleagues.

Q. Now, Dr. Beasley, turning to the second prong of these clamp studies, did Lilly perform a study looking at the question of whether Zyprexa produced insulin insensitivity?

A. Yes. That was what was referred to as the euglycemic clamp study.

Q. All right, the euglycemic clamp study. Can you tell us again in layperson's language, what was the euglycemic clamp study looking at?

A. Well, this looks at insulin receptor sensitivity. And here in contrast to the last study you first give a lot of insulin and you also give some glucose. And you determine, essentially, how much glucose you can give, a fixed amount of insulin, and how well the body uses that amount of glucose.

(Whereupon, Deposition Exhibit(s) 12 duly received, marked and made a part of the record.)

QUESTIONS BY MR. SEE:

Q. Let me hand you what we've marked as Beasley Exhibit 12 and ask first were the results of the euglycemic clamp study performed by Lilly published?

A. Yes, they were.

Q. All right. Now let me ask you to look at Beasley Exhibit 12 and ask you to tell us what that is?

A. This would be the academic

publication of the study that we just discussed.

Q. Can you tell us, Dr. Beasley, what were the results of the euglycemic clamp study performed by Lilly to look at the question whether Zyprexa affected insulin sensitivity?

A. That's probably, again, best summarized in the abstract, in the last part of the abstract. "In summary, this study did not demonstrate significant changes in insulin sensitivity in healthy subjects after three weeks of treatment with olanzapine or a different drug."

Beasley, Charles M.D.(July 27, 2006)
583:4-16
Issues: 02 Defendant Designation
Comment: Objection: Lack of Foundation; Improper Expert Testimony

Q. Now, Dr. Beasley, given the results of the two clamp studies performed by Lilly, based upon the results of those studies, what conclusions, if any, did Lilly draw regarding whether Zyprexa demonstrated a causal and a mechanistic effect on producing type two diabetes?

A. Well, these studies certainly did not support the hypothesis that olanzapine was causing either type of pathophysiology that would cause diabetes. It was not causing the things that would cause diabetes in these two studies.

Beasley, Charles M.D.(July 27, 2006)
722:8-723:11
Issues: 02 Defendant Designation
Comment: Objection: Not Relevant

Q. And by the way, you told Mr. See something on direct-examination that one of the things we like to do in studies is to blind them so in order to prevent -- what's the word?

A. Bias.

Q. Bias.

A. On reporting by the investigator or the patient.

Q. And how does blinding prevent bias?

A. That prevents both the, both the investigator and the patient from knowing

the medication they're on and because of knowing the medication they're on making assumptions or coming to beliefs about what they're experiencing and then reporting it.

Q. Right. If you blind the study, if the individual does not know, the doctor doesn't know, such as a researcher, right?

A. Correct.

Q. And the patient doesn't know which medication they're taking, you're more likely to get an objective as opposed to a subjective biased analysis, correct?

A. That's correct. That is the intent of blinding.

Exhibit 1, Page 10 of 10
SOA Obj to Designations
Case No. 3AN-06-05630 CI

Campana, David - Vol. II (September 19, 2007)
255:15-24
Issues: 02 Defendant Designation
Comment: Objection: Asked and Answered

255:15 Q. So why not have that step edit process?
16 A. I don't want to do it.
17 Q. This is your job. You have testified that part
18 of your job is to protect the safety of Alaska Medicaid
19 recipients. You have identified a safety mechanism.
20 I'm going to ask you these same questions for
21 some of the other procedures you have at your disposal
22 for protecting the safety of Alaska Medicaid recipients.
23 You have told me you don't want to do it, but I'm
24 not getting a clear answer for why.

Campana, David - Vol. II (September 19, 2007)
267:10-13
Issues: 02 Defendant Designation
Comment: Objection: speculation

267:10 Q. And the P&T committee might have come to the
11 conclusion that the safety issues warranted Zyprexa
12 being non-preferred, correct?
13 A. Correct.

Gilbertson, Joel (December 6, 2007)
62:4-7
Issues: 02 Defendant Designation
Comment: Objection; Speculation

62: 4 Q Are you aware of any -- sitting here
5 today, do you believe that Eli Lilly omitted,
6 failed to tell the State anything that they
7 should have?

Gilbertson, Joel (December 6, 2007)
64:10-65:20
Issues: 02 Defendant Designation
Comment: Objection: speculation

64:10 Q If it turned out to be the case during
11 your tenure as Commissioner that the State --
12 anybody employed by the State had come to the
13 conclusion that a pharmaceutical company was
14 misrepresenting the characteristics of a
15 prescription drug reimbursed by Medicaid, if the
16 State actually became aware of that, is that
17 something you would expect you as Commissioner
18 would be made aware of?
19 A I would hope I would be made aware of
20 it. I don't know if I could expect it. I mean,
21 at the end of the day, buried in that question
22 is: Would I be aware of it? And I can't tell
23 you that everyone would have made sure that I was
24 aware of it. I would hope I would have been
25 aware of it.
65: 1 Q Why is that?
2 A Because I don't know what the process
3 would have been for the State to make that
4 evaluation. I can tell you that I would hope I
5 would have been made aware of it, but I don't
6 know.
7 Q Right. And I'm asking: Why would you
8 hope to be? Would it be the case that you would
9 figure that was important to your role as
10 Commissioner?
11 A Well, I think for an agency head who
12 oversees a health agency for the State, there's
13 very little bit of -- very little information
14 regarding health care in Alaska I wouldn't want
15 to be aware of.
16 Q And potentially, depending on what the
17 issue is, you might want to take action about it?
18 A I certainly would want to have
19 deliberations around the merits or the
20 authorities for that.

Gilbertson, Joel (December 6, 2007)
68:1-12
Issues: 02 Defendant Designation
Comment: Objection: speculation

68: 1 Q The fact of -- the alleged fact of
2 misrepresentations about Zyprexa -- given the
3 firewalling arrangement you've just described,
4 would you have expected that information to have
5 percolated up to you under the arrangement you
6 were working under?
7 A I don't know if I would have expected
8 it. I mean, I don't know.
9 Q Would you, to use your phrase, hoped you
10 would still find out about that?
11 A I would hope, yeah. I wanted to know
12 everything in office. Who wouldn't, right?

Hopson, Duane M.D.(December 11, 2007)
11:16-25
Issues: 02 Defendant Designation
Comment: Objection: Outside scope of knowledge

11:16 Q How were their -- how was the treatment
17 paid?
18 A My understanding was that, of course, if
19 they had a commercial payor, you know, the
20 hospital would bill that. If they had Medicaid,
21 they would bill that. If not, there is a
22 State-funded program for indigent. The DET
23 program is what it's called, diagnostic and
24 evaluation and treatment, and that would pick up
25 the other.

Hopson, Duane M.D.(December 11, 2007)
30:15-22
Issues: 02 Defendant Designation
Comment: Asked and answered - repetitive

30:15 Q That would mean -- that's from the head
16 of the Department of HSS on down; am I correct
17 that not one of those people has ever suggested
18 that you not involuntarily medicate anyone with
19 Zyprexa?
20 A No.
21 Q I'm correct?
22 A You're correct.

Hopson, Duane M.D.(December 11, 2007)
51:8-52:13
Issues: 02 Defendant Designation
Comment: Objection: speculation; outside scope of knowledge

51: 8 Q Are you aware of any instances where
9 either -- at one of these meetings where a
10 Lilly-sponsored speaker made any
11 misrepresentations about Zyprexa?
12 A You know, specific misrepresentation,
13 it's difficult to say. You know, I think each
14 speaker has their own sense of the effectiveness
15 or safety or whatever their story, whatever
16 they're talking about. They have their own
17 commitment to what they're talking about. And
18 so, you know, I think out of that, you know, you
19 could say, well, they didn't really talk about
20 this particular concern very much. So whether
21 that's purposeful misrepresentation or not, it's
22 difficult to say, because everybody has their own
23 commitment to their beliefs, I guess.

Q If you felt that somebody was leaving something out that was important with regard to safety or effectiveness, have you attempted to correct that or bring it to the speaker's attention?

A There have been opportunities when questions would be asked of the speaker, particularly if it was something that was just kind of glaring and maybe one of my doctors -- I've had turn-over of doctors, as I've said. Some are more outspoken than others; some more committed to their beliefs. And they, you know, they will ask a challenging question. That's not my experience, perhaps, or something like that. Get some feedback going.

Wojcieszek, Robin Pitts (December 11, 2007)
10:5-11:3
Issues: 02 Defendant Designation
Comment: Objection: Unnecessary for fairness

10: 5 Q Okay. Between 1993 when you received your
6 bachelor's degree and -- did you say 2002?
7 A Correct.
8 Q What did you do?
9 A I worked -- after school I worked in retail
10 pharmacy at CVS Pharmacy and then was also -- I
11 worked as a project manager at FDA in the division
12 of neuropharmacological drug products and then
13 transitioned to a job in regulatory affairs at
14 Parke-Davis in 1996 and then went through the
15 merger with Pfizer and then in 2002 came to Lilly.
16 So all my experience has been in regulatory
17 affairs.
18 Q Okay. How long were you at FDA?
19 A I was there from '94 to '96.
20 Q Prior to that time, it was strictly a retail --
21 A Correct.
22 Q -- pharmacist?
23 A Correct.
24 Q And did you have any job responsibilities regarding
25 Zyprexa?
11: 1 A Prior to coming to Lilly, no.
2 Q Well, I didn't think that you would before.
3 A Yeah. No, no.

Wojcieszek, Robin Pitts (December 11, 2007)
12:1-14
Issues: 02 Defendant Designation
Comment: Objection: Unnecssary for fairness

12: 1 Q Okay. So would you have been the person
2 responsible for interacting with FDA regarding the
3 September 2003 label change?
4 A I was the -- we've had multiple regulatory
5 scientists supporting Zyprexa. So at that time
6 Michele Sharp was a colleague of mine, and both of
7 us worked on Zyprexa. And she took primary
8 responsibility of that labeling change.
9 Q Does she -- does she still work on Zyprexa?
10 A She -- she does work on some Zyprexa materials, but
11 she has moved on to another position within
12 regulatory affairs.
13 Q Do you have any responsibilities for Symbyax?
14 A Yes, I do.

Wojcieszek, Robin Pitts (December 11, 2007)
171:1-5

Issues: 02 Defendant Designation
Comment: Objection: Leading; Lack of Foundation

171: 1 Q And there would have been other analyses that would
2 have looked at the glucose levels as well?
3 A Yes.
4 Q Is that right?
5 A That's correct.

Wojcieszek, Robin Pitts (December 11, 2007)

177:12-14
Issues: 02 Defendant Designation
Comment: Objection: Leading

177:12 Q And is it your understanding that Lilly has abided
13 by its regulatory obligations to submit such data
14 to FDA?

Wojcieszek, Robin Pitts (December 11, 2007)

177:16-16
Issues: 02 Defendant Designation
Comment: Objection: Leading

177:16 A Yes.

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

RECEIVED
Chambers of
Judge Rindner
FEB 25 RECD
State of Alaska Superior Court
Third Judicial District
in Anchorage

STATE OF ALASKA, Plaintiff, vs. ELI LILLY AND COMPANY, Defendant.	Case No. 3AN-06-5630 CIV

NOTICE OF FILING UNDER SEAL

On this date the State of Alaska is filing a pleading titled "**State of Alaska's Request for Clarification of the Court's Order Excluding Evidence of the Defendant's Profits, Net Worth, and the Price of Zyprexa**." Because one or more exhibits filed with this pleading may be confidential documents under the Court's April 6, 2007 oral ruling, the State of Alaska is submitting this pleading and the attached exhibits under seal.

DATED this 25th day of February, 2008.

FELDMAN ORLANSKY & SANDERS
Counsel for Plaintiff

BY _____
Eric T. Sanders
AK Bar No. 7510085

See Judge Rindner's order 9/6/13/08, pages 13 & 14
#3 Documents unsealed
Lisa 8/11/08

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005763A

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
v.	)	
	)	
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	Case No. 3AN-06-05630 CI
	)	

STATE OF ALASKA'S REQUEST FOR CLARIFICATION OF THE COURT'S ORDER EXCLUDING EVIDENCE OF THE DEFENDANT'S PROFITS, NET WORTH, AND THE PRICE OF ZYPREXA

INTRODUCTION

On February 4, 2008, defendant Eli Lilly and Company filed a three-page motion in limine to exclude "at trial any evidence of Lilly's Zyprexa-based profits or general net worth and evidence relating to the price of Zyprexa." In short, Lilly argued that evidence of "Lilly's financial condition is irrelevant due to the Court's bifurcated trial plan in which issues of damages are not relevant unless a second trial phase is required." Although the State requested oral argument to clearly articulate what evidence it intended to present at trial, the Court signed Lilly's proposed order before hearing from the parties. Based upon the pleadings that were filed on this specific issue and the Court's order, the State seeks clarification about what evidence may be presented.

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005763B

The State requests clarification of the Court's recent order excluding evidence of the defendant's net worth, profits, and the price of Zyprexa. The State is not interested in offering argument or soliciting testimony about Lilly's profits or net worth, and agrees that the price of Zyprexa is not central to its case. But the State wants to confirm its understanding that the Court is not precluding the State from conveying (1) that Lilly as a corporation and its salespersons, like all corporations and sales forces, has been driven by a desire to make profit and (2) that the profit motive that drove Lilly and its sales force during time periods relevant to this case was particularly strong because Lilly learned in 2000 that its valuable patent on Prozac would unexpectedly expire in 2001, years ahead of the date that Lilly anticipated.

DISCUSSION

The Alaska Rules of Evidence provide that, subject to enumerated exceptions, "all relevant evidence is admissible."[1] Under the Rules, evidence that has "any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable" is relevant,[2] regardless of whether the evidence is

[1] ALASKA RULE OF EVIDENCE 402 *Relevant Evidence Admissible—Exceptions—Irrelevant Evidence Inadmissible.*

[2] ALASKA RULE OF EVIDENCE 401 *Definition of Relevant Evidence.*

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probative of a fact that is "ultimate, intermediate, . . . evidentiary,"[3] or merely "background in nature."[4]

In this case, the fact that Lilly was driven by the desire to make money, and that its incentive to find a new source of profit was elevated by the early expiration of its Prozac patent, is probative of whether Lilly would have failed to adequately investigate Zyprexa's side effects and of whether Lilly's salespersons would have over-promoted Zyprexa; and they are facts that cannot be sensibly redacted from the documentary evidence that supports the State's case.

---

[3] *See Commentary* to ALASKA RULE OF EVIDENCE 401 ("The fact to be proved may be ultimate, intermediate, or evidentiary; it matters not, so long as it is of consequence in the determination of the action.") *Cf. id.* ("The standard of probability under the Rule is "more . . . probable than it would be without the evidence." Any more stringent requirement is unworkable and unrealistic. As McCormick (2d ed.) § 185, at 436, says, "A brick is not a wall," or, as Falknor, Extrinsic Policies Affecting Admissibility, 10 Rutgers L. Rev. 574, 576 (1956), quotes Professor McBaine," . . . [I]t is not to be supposed that every witness can make a home run." Dealing with probability in the language of the Rule has the added virtue of avoiding confusion between questions of admissibility and questions of the sufficiency of the evidence.").

[4] *Cf. id.* ("Evidence which is essentially background in nature can scarcely be said to involve disputed matter, yet it is universally offered and admitted as an aid to understanding.").

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005765

I. Evidence That The Early Expiration of its Patent on Prozac Left Lilly With a Particularly Strong Desire to Make Profits Is Directly Probative Of The State's Claims.

Lilly's documents reveal that the marketing conduct at issue in this case was forged in response to the expiration of Lilly's Prozac pattern, and took on a form that can only be explained by reference to that event.

A. Lilly's Zyprexa Marketing Campaign Was Formed in Direct Response to the Loss of Its Prozac Patent.

From the beginning, Lilly viewed Zyprexa as important to the "financial health of the company."[5] But it was the sudden collapse of the Prozac market that made Zyprexa a truly indispensable component of Lilly's business.

The truth of that observation is encoded in a number Lilly's documents, and is revealed with special clarity in Lilly's year 2000 Annual Report. Under the heading "What happened with Prozac?" the Report first noted that Prozac's "three-year-early" patent loss would be an "enormous challenge" that would have to be met by "earnings growth" fueled by its sales force's ability to "sell" and "launch" Lilly's other products:

> We've significantly increased the size of our global sales force and will continue to do so in order to have the 'firepower' we need to successfully launch and sell the next wave of products from our pipeline.[6]

---

[5] Email from Dr. Alan Breier, Lilly's Zyprexa Product Team leader, Exhibit # 08262 (Nov. 9, 1999), attached as Exhibit A.

[6] Annual Report 2000, attached as Exhibit B.

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Under the heading "So, what now?" the Report then explicitly identified Zyprexa as the first product designated to replace the revenue loss from Prozac:

> Our newer products will stand as our front line against inevitable generic competition for Prozac. Introduced throughout the last half of the 1990's they'll be the key to our ability to produce earnings growth during that time and resume our strong performance thereafter.
>
> Zyprexa is a genuine blockbuster, surpassing the $2 billion sales mark in 2000 and becoming Lilly's number-one selling product in the fourth quarter . . . We're exploring broader uses for Zyprexa . . .

Elsewhere, the Report's emphasis on the economic implications of the company's loss of the Prozac patent, and the company's pressing need to replace lost Prozac sales with additional Zyprexa sales, was directly communicated to the sales force. Lilly's vice president for U.S. Sales and Marketing drove home the point in a slideshow that gave the sales force its marching orders:

> You make us Number 1!!!
>
> Made us "Number 1" in the PAST with Prozac-Depression
>
> Are NOW making us "Number 1" with Zyprexa-Schizophrenia, Bipolar Mania, Depression.[7]

[7] As reflected in "Jordan Exhibit #6" Bill Robinson, attached as Exhibit C.

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B. The Loss of Lilly's Prozac Patent Is Integral to a Proper Understanding of the Wrongful Conduct Alleged By the State In This Case.

The slide presented to the company's sales force by Lilly's vice president is but one example of the documentary evidence that establishes the Prozac-Zyprexa connection, and it provides a specific demonstration of the fact the two subjects cannot be sensibly separated: despite the fact that Zyprexa is not, and has never been, indicated for "depression," the slide reveals that, in order to keep Lilly "number 1," Lilly instructed its sales force unlawfully to market Zyprexa for use in an off-label disease category, a fact that is fully appreciable only when viewed as it was presented in it original context—in immediate juxtaposition to Lilly's loss of the patent on Prozac.

Evidence of Lilly's marketing Zyprexa to the "primary care physicians" (PCP) market also bears this out. Lilly similarly instructed its sales force to market Zyprexa to the primary care physicians, despite the fact that Zyprexa was not indicated for PCP use:

> Opportunities: [The Primary Care Physicians] customer group is huge (250,000 prescibers – 59,000 are key targets) . . . we can maximize return while building a strong clinical foundation. . .
>
> Challenges: . . . Zyprexa's primary indications – schizophrenia and bipolar are not viewed as PCP-treated conditions, so there's not a specific indication for Lilly reps to promote in the PCP segment.[8]

[8] Lilly's "Zyprexa-Primary Care Strategy and Implementation Overview" Exhibit #04121, attached as Exhibit D.

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Again, the absence of a lawful indication for PCP promotion did not stop Lilly. Instead, Lilly created a Zyprexa "Position" (entitled "mood, thought and behavior disorders") that was expressly designed to allow Lilly representatives to engage in illegal off-label promotion:

> Position: Zyprexa: The safe, proven solution in mood, thought and behavior disorders. . . "Mental disorders" is intentionally broad and vague, providing latitude to frame the discussion around symptoms and behaviors rather than specific indications.

Here, too, the influence of Lilly's loss of the Prozac patent was felt. Lilly "launched" its PCP campaign with a slide show that asked and answered telling questions:

> Why are we entering this market?
> Zyprexa's success is crucial to corporate performance; PCP's represent last major untapped segment.

The presentation projected $259.6 million in sales growth from the PCP campaign, and promised to financial incentives to top sellers. Less than one year later the author of Lilly's PCP strategy explained that the campaign was expressly designed to compensate for the company's loss of the Prozac patent:

> This is Year X for Eli Lilly, and the conventional wisdom is that companies just don't 'bounce back' from losing patent protection from their biggest product.
>
> We need to OWN this target, because [Lilly] needs our help.

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> I personally challenge each of you to drive toward a goal that will help turn Year X in to Year X-ceptional.[9]

C. Evidence About Lilly's Heightened Profit Is Also Necessary To Rebut Assertions That Lilly Will Offer About The Considerations That Motivated Its Conduct.

In a recent filing, Lilly asserts that it entered the PCP market to "help" bipolar patients. The State must be allowed to refute Lilly's claim of unqualified altruism. It was not altruism, but profit that drove Lilly to seize upon the "opportunity" to sell Zyprexa to primary care physicians. By July 2001, Lilly was admitting internally that it was "betting the farm on Zyprexa":

> The company is betting the farm on Zyprexa. . . [T]he ability of Eli Lilly to remain independent and emerge as the fastest growing pharma company of the decade depends solely on our ability to achieve world class commercialization of Zyprexa.[10]

It later described Zyprexa as the "heart and soul" and "engine" of the corporation,[11] and when word of Zyprexa's connection to diabetes first began impacting sales, Lilly's response was predictable: "increase detailing, customer contact and capture new business."

---

[9] In March, 2001 at Lilly's National Sales Meeting, Mike Bandick (The author of "PCP Strategy") speaks to the sales force about Zyprexa's VIVA purpose (MDL Plaintiffs' Exhibit No. 01079, attached as Exhibit E).

[10] In July 2001 the Zyprexa Product Team has a meeting (Torres #2) and describe in "Straight Talk" what Lilly had "at stake" (Torres Exhibit No. 2 attached as Exhibit F).

[11] *Id.*

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Lilly's documents and testimony in this case are replete with evidence connecting the expiration of Lilly's patent on Prozac to its promotion of Zyprexa. Ordering it excluded from trial would deny critical facts to the jury, and prevent it from making a proper assessment of Lilly's conduct.

CONCLUSION

Consistent with the Court's Order, the State will not offer argument or solicit testimony at trial about Lilly's profits or net worth, and it agrees that the price of Zyprexa is not central to its case. But the State interprets the Court's Order to enable it to present relevant evidence (1) that Lilly and its salespersons were driven by a desire to make profit and (2) that the profit motive that drove Lilly and its sales force during time periods relevant to this case increased because of the unexpectedly accelerated expiration of Lilly's patent on Prozac. The fact that Lilly was driven by the desire to make money, and that its incentive to find a new source of profit was elevated by the early expiration of its Prozac patent, is relevant and probative of whether Lilly would have failed to adequately investigate Zyprexa's side effects, and of whether Lilly's salespersons would have over-promoted Zyprexa.

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Dated this 25th day of February 2008.

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Certificate of Service
I hereby certify that a true and correct copy of **Request for Clarification of the Court's Order Re: Net Worth and (proposed) Order** was served by messenger on:

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Barry Boise, via email (boiseb@pepperlaw.com)
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By Peggy S Crowe
Date 2/25/08

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Lilly

Answers That Matter.

Talk

2000 Annual Report

Eli Lilly and Company 2000 Annual Report

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Zyprexa MDL 1596
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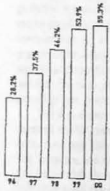
5913-001 / 1
005776
5913-001
Exhibit B, Page 1 of 52
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205080
Page 1

2000 Financial Highlights

Eli Lilly and Company and Subsidiaries (Dollars in millions, except per-share data) Year Ended December 31	2000	1999	Change %
Net sales	$10,862.2	$10,002.9	9
Research and development	2,018.5	1,783.6	13
Income from continuing operations	3,057.8	2,546.7	20
Net income	3,057.8	2,721.0	12
Earnings per share—basic	$ 2.83	$ 2.50	13
Earnings per share—diluted	2.79	2.46	13
Normalized[1]:			
Income from continuing operations	$ 2,904.6	$ 2,516.7	15
Income from continuing operations as a percent of normalized sales	26.5%	25.4%	
Earnings per share—diluted	$ 2.65	$ 2.28	16
Dividends paid per share	$ 1.04	$ .92	13
Capital expenditures	$ 677.9	$ 528.3	28
Economic Value Added (EVA®)	$ 1,776	$ 1,584	12

[1]Normalized income from continuing operations reflects the results of continuing operations adjusted for significant unusual items. In 2000, these items were the gain on the sale of Kinetra LLC and the net impact of year-2000-related sales made in the fourth quarter of 1999 that ordinarily would have been realized in the first quarter of 2000. In 1999, these items were a contribution to Eli Lilly and Company Foundation, the asset impairment and other site charges, the net impact of year-2000-related sales, income recognized from the sale of Lorabid® marketing rights, and proceeds from a patent infringement settlement. Normalized earnings per share reflects net income from continuing operations adjusted for these same items. See notes to the consolidated financial statements.



Return on Shareholders' Equity
(based on income from continuing operations before extraordinary item divided by average shareholders' equity)

Earnings growth and strong asset management, combined with measures to enhance shareholder value, such as the share repurchase program, resulted in a continued increase in return on shareholders' equity.

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
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Exhibit B, Page 2 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205081

To Our Shareholders

In keeping with our pledge to answer important questions, I want to address one that I am sure is on your minds.

For several years, we have been preparing for the expiration of the U.S. patents that have protected our exclusive rights to our top-selling product, Prozac®. Due to uncertainty over the exact timing of this event, we have referred to it as "Year X." In January 1999, a federal district court had affirmed our 2003 Prozac patent. Last August, we were very surprised when a federal appeals court reversed that ruling.

We strongly disagree with the ruling—and we are making every effort in the courts to secure our rights to the 2003 patent. At the same time, prudence dictates that we prepare and implement our plans with the assumption that Prozac will face generic competition in the United States in early August 2001.

Given this turn of events involving a product with U.S. sales of $2.2 billion, you may well ask whether Lilly can successfully navigate the next several years. My response is a strong "Yes." We fully recognize the magnitude of our challenge. And we are prepared not only to manage the short-term challenges of Year X but also to embark soon thereafter on a period of renewed growth. Here is why I am confident.

We continue to sharpen the implementation of our simple, clear-cut strategy that focuses on two areas: generating scientific innovations that meet patients' unmet medical needs and then helping as many patients as possible benefit from those innovations. As a result, our net sales increased 9 percent in 2000, to $10.9 billion. Adjusted for significant one-time items in 1999 and 2000, our net income rose 15 percent, to $2.9 billion, and our earnings per share grew 16 percent, to $2.65.

For a number of years, we have also implemented contingency plans that would help us overcome any Year X outcome we might face. For instance, we have invested aggressively in our products with the strongest growth potential. We have sped the development of high-potential molecules. And we have partnered with other companies to get access to additional molecules that further expand our opportunities.

In 2000, the investment community responded favorably to our progress. Our stock price rose 40 percent during the year. This gain was among the best in the pharmaceutical industry. Furthermore, it represented a major step in the right direction after our disappointing stock performance in 1999.

Strong product line fuels growth

Powering our growth in 2000 were six newer best-in-class products that accounted for 41 percent of our pharmaceutical sales and grew at a rate of 31 percent.

Zyprexa® exemplifies our growth opportunities. Initially introduced in 1996 as a treatment for schizophrenia, this molecule was approved in 2000 as a therapy for the manic phase of bipolar disease, a lifelong illness that affects as many as 34 million people worldwide. Late last year, Zyprexa was also approved for the long-term treatment of schizophrenia, making it the first product in its class to demonstrate such ongoing effectiveness. In 2000, our sales of Zyprexa were $2.3 billion, a 25 percent increase. During the fourth quarter, this neuroscience blockbuster surpassed Prozac as our top-selling product.

Two products surpassed the $500 million sales mark for the first time in 2000. Sales of Evista®, our novel product for the prevention and treatment of osteoporosis in postmenopausal women, were $522 million, an increase of 60 percent. Gemzar®, one of the world's top-selling anticancer agents, generated sales of $559 million, up 23 percent.

Sales of the human insulin analog, Humalog®, rose 56 percent, to $350 million. As more patients used Humalog, Humalog mixtures, and our pen-cartridge delivery systems, our total insulin sales grew 10 percent, to $1.5 billion. We also continued to expand our diabetes care presence through the copromotion of Actos®, an oral treatment for type 2 diabetes discovered by our partner, Takeda. Our revenue from Actos was $223 million during 2000—its first full year on the market.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 3
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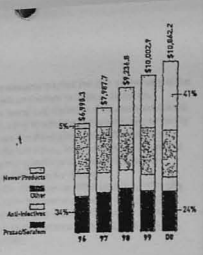
Exhibit B, Page 3 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205082
Page 3



Net Sales
($ millions)

Net sales during 2000 reflect the strong growth of Lilly's newer products and a consistent lessening of the company's reliance on the sales of Prozac. The company's newer products—Zyprexa, Evista, Actos, Humalog, Gemzar, and ReoPro—grew by a combined 31 percent over 1999, representing 41 percent of total net sales compared with 34 percent in 1999. Prozac sales accounted for 24 percent of total net sales in 2000, down from 34 percent in 1996.

The growth of those five products more than offset sales decreases for two other important products. The sales of our sixth newer product, the cardiovascular agent ReoPro® discovered by the Centocor unit of Johnson & Johnson, fell 7 percent, to $418 million. The worldwide sales of Prozac declined 2 percent, to $2.6 billion, largely due to the initial impact of generic competition in the United Kingdom.

Intense competition is a fact of life throughout the pharmaceutical industry. To meet that competition, we significantly elevated our marketing investments in 2000 with the goal of making our growth products available to more patients throughout the world. More specifically, we added some 2,000 sales representatives worldwide, an increase of more than 20 percent. We recruited scores of experienced marketing professionals to support our growing product line. And we pursued clinical studies supporting new indications and formulations for key products that will further expand our growth opportunities.

Outstanding pipeline adds further growth potential

Even as we capitalize on our current generation of products, we are speeding our next generation of new-product candidates to the global marketplace. As you will see later in this report, we could introduce as many as 10 more medicines by the end of 2004. Several of those candidates are potential first-in-class products that could address medical problems for which there are no current treatments. All are potential best-in-class products that could provide superior results for patients.

In the near term, we are immersed in our preparations for the launches of two unique biotech products. Clinical data indicate that drotrecogin alfa (activated), also known by the proposed trade name Zovant, may be the first therapy that effectively treats patients with sepsis, a condition that kills an estimated half million people worldwide annually. Fortéo™ is an innovative molecule that appears in clinical trials to rapidly rebuild bone diminished by osteoporosis. We filed regulatory submissions for Fortéo in late 2000 and for Zovant in early 2001. We expect to launch both in 2001.

Beyond Zovant and Fortéo, we hit the development targets last year for nearly all the molecules in our near-term pipeline. Two exceptions were the anticancer agent oxaliplatin, which was not approved by the FDA, and the antidepressant candidate R-fluoxetine, which did not meet its clinical-trial goals. We returned both potential products to partners.

While Lilly scientists have discovered most of the molecules in our pipeline, we continue to work with other companies to add more opportunities. For example, Cialis™ is a promising near-term drug candidate from ICOS Corporation for the treatment of male erectile dysfunction that Lilly and ICOS are working together to develop. During 2000, we announced agreements with three other companies—Ono, Sankyo, and Mitsubishi-Tokyo—that each added a molecule to our pipeline.

We currently have well over 100 scientific collaborations. Those cooperative efforts not only help us enhance our pipeline with additional drug candidates but also give us access to more biological targets for drug discovery and important new R&D technologies. Because collaborations are an essential part of our strategy, we created an Office of Alliance Management with the mission of helping Lilly become the pharmaceutical industry's best business partner. We are making good progress in that pursuit.

In 2000, we strengthened our internal research capabilities by recruiting nearly 700 scientists and expanding our "innovation engine," Lilly Research Laboratories, to 6,900 people at 11 sites worldwide. We also increased our global R&D investment by 13 percent, to $2 billion. This represented 19 percent of our sales.

Those actions are paying off. Last year was one of the best ever for Lilly Research Laboratories. Our scientists met or exceeded virtually all our rising research-productivity targets for identifying high-potential molecules and initiating early-stage clinical trials of drug candidates. A key factor in those productivity gains is the early impact of the biotech revolution about which we hear so much.

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Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 4
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5913-004
Exhibit B, Page 4 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205083
Page 4

Last October, the company marked the 30th anniversary of the listing of Lilly stock on the New York Stock Exchange. Chairman Sidney Taurel and the board of directors celebrated the occasion with a day of activities at the exchange, hosted by NYSE Chairman and Chief Executive Officer Richard Grasso. Capping the activities at 4 p.m., Taurel struck the ceremonial gavel at the exchange podium as the final bell sounded, signaling the close of trading for the day.

Prior to its initial listing on the NYSE on July 9, 1970, Lilly stock had been sold in the over-the-counter market. During those first days of trading on the New York exchange, the company's market capitalization was about $3 billion. Today, it's nearly $100 billion.

Technology revolutions create new opportunities

Over time, the biomedical revolution will transform all areas of pharmaceutical R&D. In the near term, however, we believe the greatest potential involves the use of new research tools to identify previously undiscovered genes that trigger the production of natural proteins in the body involved in major diseases. Those natural proteins, or modified versions, sometimes prove to be outstanding biotech drug candidates.

This trend plays directly into our strengths. We are established leaders in the discovery, development, and production of protein medicines. The upcoming launches of Fortéo and Zovant will expand our protein portfolio to seven products. And we have a number of additional protein candidates in various stages of development.

We are also using revolutionary new R&D capabilities to expedite our searches for so-called "small-molecule" medicines similar to Prozac and Zyprexa that constitute the majority of our drug candidates. Our scientists are committed to helping patients benefit from this unfolding biotech revolution as soon as possible.

Additionally, we are exploiting the power of the e-business revolution on behalf of patients. In 2000, we created a new organization, e.Lilly, that is generating, attracting, and testing scores of new approaches based on information technology. These concepts have the potential to accelerate improvement in virtually every aspect of our business, from the earliest stages of research to providing information for patients.

Ready for the future

In 2000, we enthusiastically welcomed two outstanding leaders to our board of directors. Sir Winfried "Win" Bischoff is chairman of Citigroup Europe and former chairman and CEO of Schroders, plc. George M. C. Fisher recently retired as chairman and CEO of Eastman Kodak Company and previously served as chairman and CEO of Motorola, Inc. Together, these men reinforce the leadership experience and global perspective of our board that will be great assets during this challenging period.

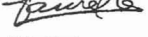
I also wish great success to Mitchell E. Daniels, Jr., who recently became director of the U.S. Office of Management and Budget for President George W. Bush. This cabinet-level appointment is a great honor for Mitch, who served most recently as our senior vice president for corporate strategy and policy. Among his many contributions to the company during the past 12 years, Mitch built an outstanding team in public affairs and communications and played a pivotal role in our preparations for Year X. We will long benefit from his legacy.

As I look ahead, our strategy is on target and our implementation is getting better and better. We are not only applying traditional R&D and sales-and-marketing capabilities but also capitalizing on the revolutions in biotechnology and information technology. Our ongoing progress throughout the company reflects the achievements and the aspirations of 35,700 Lilly colleagues in whom I take great pride.

Later this year, we will celebrate the 125th anniversary of Lilly's founding. Over these many years, our company has made history with medical breakthroughs—from the first insulin product and major antibiotic advances to Prozac and Zyprexa. So, we are very thankful for the Lilly family and Lilly retirees who created the heritage that we are working to extend into the twenty-first century.

As we face Year X, we intend to make history again with the greatest outpouring of innovation in Lilly history—beginning with Zovant and Fortéo. We plan to emerge from Year X a stronger company that is ready for a new growth era. We are prepared to write the next great chapters in the Lilly story.

For the board of directors,



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Sidney Taurel
Chairman of the Board, President, and Chief Executive Officer

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Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 5
005780
5913-005
Exhibit B, Page 5 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205084
Page 5

No company would relish losing the patent on its biggest product three years early. We certainly don't.

We were very surprised and disappointed by the judicial ruling that invalidated our 2003 U.S. patent on Prozac. We strongly disagree with the court's decision, and we are doing everything we can through the judicial process to reestablish our rights.

In the meantime, the U.S. Food and Drug Administration has granted us market exclusivity until August 2, 2001, under a federal statute encouraging pediatric studies of certain medicines.

We intend to focus on Prozac in the United States right up to the last day of its exclusivity. And we'll pursue related opportunities. One is our patented once-weekly formulation aimed at preventing the recurrence of depression. A second is Sarafem™, a newly introduced brand for women

What happened with Prozac?

who suffer from premenstrual dysphoric disorder, the severe mood and physical symptoms associated with their menstrual cycle that interfere with their daily activity and relationships.

We won't miss any opportunities for Prozac—or the rest of our business. For the last four years, we've been preparing to bridge the gap that would be created by generic competition for Prozac. We're ready.

We've invested aggressively in our next generation of innovative drugs and shortened their timelines to launch. We've accelerated development of additional indications and formulations for our newer products. And we've intensified our efforts to partner with other companies on their high-potential compounds in later stages of development.

We've significantly increased the size of our global sales force and will continue to do so in order to have the "firepower" we need to successfully launch and sell the next wave of products from our pipeline. We've also been sharpening our marketing and selling skills to help us realize the full potential of all our products worldwide.

In short, faced with the enormous challenge presented by the Prozac patent expiration, we've positioned ourselves to produce earnings growth through the immediate postexpiration period and resume fast growth following that.

Millions of people worldwide have benefited from Prozac. This remarkable product has revolutionized the way mental illness is viewed and treated. The success of Prozac has helped make possible the outstanding accomplishments of Lilly

research over the last decade and has provided us with the ability to pursue the breakthroughs we expect to introduce in this new decade. It's a wonderful story—for medical science, for patients, and for us. We are proud of Prozac.

And yet, as important as Prozac has been for patients and to our business, it's not the future. For patients, the future is the next generation of medicines with the ability to treat and cure difficult diseases in ways now only hoped for. For us, the future is our newer products already driving our growth and our pipeline of innovative products yet to come. Our focus is on the next Prozac—and the one after that.

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Zyprexa MDL Plaintiffs' Exhibit No.05913
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SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI

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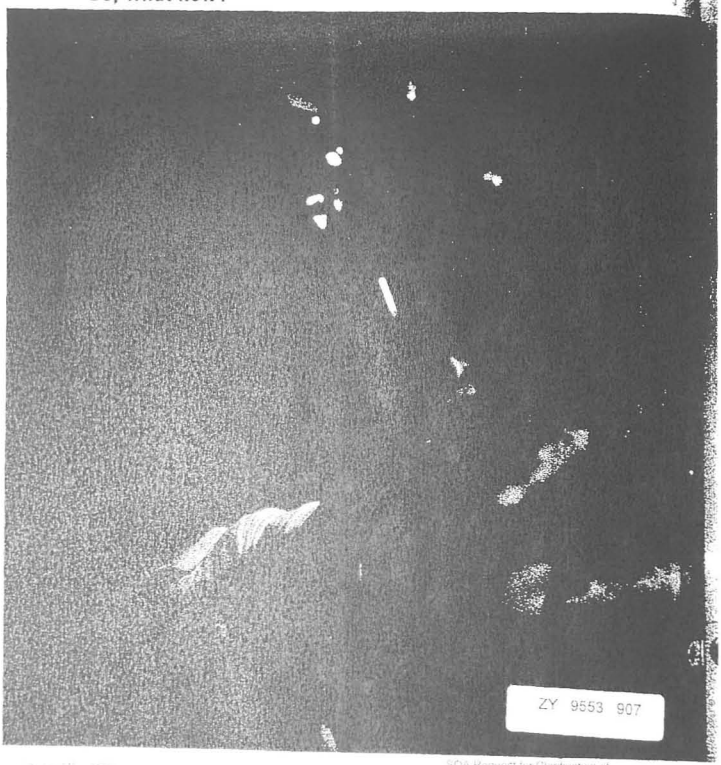
So, what now?



Zyprexa MDL Plaintiffs' Exhibit 05913
SOA Request for Clarification of the Court's Order re: Net Worth Case No. SAN 06 5630 CI
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Page 8

Gemzar Gemzar has been described as a "pipeline within a molecule." It's being used to treat the vast majority of pancreatic-cancer patients in both Europe and the United States, and it's become the standard of care for non-small-cell lung cancer in several countries. We're evaluating Gemzar in several types of solid tumors. Our goal is to make it a cornerstone of treatment for lung, pancreatic, bladder, breast, and ovarian cancers.

Our newer products will stand as our front line against inevitable generic competition for Prozac. Introduced throughout the last half of the 1990s, they'll be the key to our ability to produce earnings growth during that time and resume our strong performance thereafter.

Zyprexa Zyprexa is a genuine blockbuster, surpassing the $2 billion sales mark in 2000 and becoming Lilly's number-one-selling product in the fourth quarter. Just as Prozac changed the treatment of depression, Zyprexa has redefined the standard of care for schizophrenia, a devastating disease that ravages the mind and has been called the "cancer of mental illness."

Introduced as a therapy for schizophrenia in 1996, Zyprexa was approved in the U.S. last year for the additional indications of acute mania associated with bipolar disorder and the maintenance of treatment response in schizophrenia. We're exploring broader uses for Zyprexa in schizophrenia and other key segments of the antipsychotic market, including bipolar depression and the psychotic or behavioral disturbances that accompany dementia.

Evista Evista is a blockbuster in the making. The growth of our product for the prevention and treatment of osteoporosis in postmenopausal women continues to be outstanding. Evista has been shown to significantly reduce a woman's risk of clinical spinal fracture within one year of treatment and increase bone mineral density as early as six months.

We continue to investigate the potential of Evista beyond osteoporosis—including its potential effect on heart disease and the reduction of risk of breast cancer in postmenopausal women. Given the breadth of Evista's efficacy potential and its favorable tolerability, we believe it will ultimately set a new standard for women's health products.

Insulins In 1999, the world's first insulin company established itself as the world's leading insulin company, becoming number one worldwide in market share. This leadership was strengthened in 2000. We've achieved this success through the introduction of the Humalog family of insulins and the launch of world-class pen delivery devices. Patients are switching to our Humalog and Humalog mixture formulations and pen delivery devices from their earlier-generation insulin products and their vials and syringes.

Actos The quick uptake of Actos, the oral diabetes agent we launched with our copromotion partner Takeda in the United States during 1999, marked our successful expansion in diabetes care beyond insulins. Actos provides an excellent complement to our insulin business as an oral agent for type 2 diabetes, the most prevalent form of the disease. Our newest product, it is recognized as therapy for reducing insulin resistance, an underlying cause of type 2 diabetes.

New Submissions In addition, we expect 2001 launches for two new products currently under review by regulatory agencies. Drotrecogin alfa (activated), known by the proposed trade name Zovant, targets sepsis, a disease that kills approximately 1,400 people per day worldwide and for which there currently is no approved treatment. Results of a study indicated a nearly 20 percent reduction in the risk of death in patients who were given Zovant. And clinical trials of Forteo, our novel bone-formation agent for osteoporosis, have demonstrated that it strengthens overall skeletal architecture very rapidly. In addition, the trials showed it can significantly reduce fractures caused by thinning bones at both the spine and nonspine sites.

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
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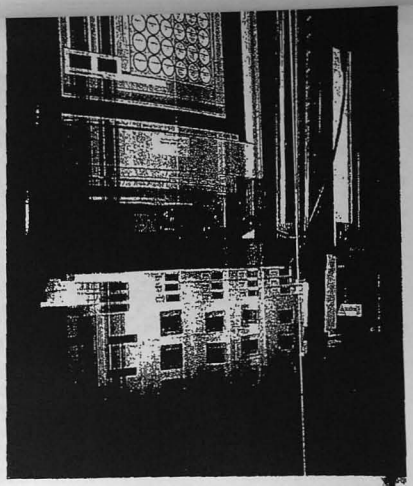
Exhibit B, Page 9 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205088
Page 9



"Drug hunters" in pharmaceutical research examine thousands of compounds annually, searching for molecules that may have activity against identified disease targets. The lead optimization biology laboratory researchers can process up to 2000 compounds in one day, a task that once took weeks. Chahrzad Montrose and Kevin Tichenor dissolve compounds and place them in various plate formats required for biological screening.

How good is our pipeline?

The opening years of this new century could well become the most productive period of innovation in Lilly's history.

From 2001 to 2004, we may launch as many as 10 new products for a wide range of serious, unmet medical needs. This is unprecedented for Lilly. It's nearly twice the number we introduced in the last half of the 1990s. All these novel, late-stage compounds support our focus on the development of either first-in-class or best-in-class products. And they all represent significant commercial opportunities. In fact, some analysts have said that the near-term Lilly pipeline is the richest in the pharmaceutical industry.

2001

Zovant—sepsis Zovant is our innovative, investigational biotech product for sepsis with associated acute organ dysfunction (severe sepsis), a disease caused by the body's overwhelming response to infection that can lead to organ failure and, ultimately, to death. More than 1.5 million people worldwide contract sepsis annually. A person dies from sepsis, on average, every minute.

Zovant has shown great promise against sepsis—so much so that an independent advisory board recommended last June that we stop enrolling patients in a late-stage clinical trial and submit Zovant for regulatory approval as soon as possible. We have submitted our regulatory package in support of Zovant to European and U.S. authorities. We hope to do something no pharmaceutical company has been able to do—bring to the market a specific treatment for this deadly disease.

Fortéo—osteoporosis Our recombinant parathyroid hormone Fortéo will target osteoporosis, the often "silent" disease that leads to the breakdown of bone, primarily in postmenopausal women. While other products for osteoporosis work by reducing the rate of bone loss, studies indicate that Fortéo puts bone back into its natural growth phase and stimulates the creation of healthy new bone.

Fortéo, if approved, has the potential to become a leading agent for the treatment of osteoporosis. We're also exploring how Fortéo and our osteoporosis product Evista might work together to strengthen bone. Fortéo is currently under review by the FDA.

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Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 10
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5913-010

Exhibit B, Page 10 of 52
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205089
Page 10

2002

Cialis—male erectile dysfunction We're collaborating with ICOS Corporation to study Cialis, an oral agent discovered by ICOS scientists, for male erectile dysfunction. The condition affects an estimated 70 million men and their partners worldwide.

In Phase II trials, more than 88 percent of men taking Cialis reported improved erections. Multiple studies to date have shown a promising side effect profile.

Atomoxetine—attention-deficit hyperactivity disorder Attention-deficit hyperactivity disorder (ADHD) is one of the most common mental disorders among children, affecting between 3 and 5 percent of school-aged children. It's primarily characterized by symptoms of inattentiveness, hyperactivity, and impulsive behavior. ADHD often continues into adolescence and adulthood. The most widely prescribed drugs for ADHD are psychostimulants. But these products can have undesirable side effects, such as insomnia, and often carry a stigma because of their classification as scheduled substances (narcotics).

Atomoxetine (formerly tomoxetine), our investigational drug for ADHD, is not a stimulant; it belongs to a different class of medications. It works by blocking a neurotransmitter that plays an important role in modulating brain systems that control attention and activity. Atomoxetine would be the first such agent approved for the treatment of ADHD.

Duloxetine—depression Depression is a leading cause of disability worldwide, robbing its sufferers of their ability to make decisions, work, or function at a basic level. The World Health Organization estimates that depression is present in 10 percent of all people seeking care at primary health care facilities globally.

Duloxetine is one of two compounds (the other is a combination of Zyprexa and Prozac) we're evaluating that address unmet needs in different segments of patients with depression. We're looking at duloxetine for the treatment of major depression. Duloxetine enhances levels of two important brain chemicals and has shown promise as a step forward in the treatment of depression.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
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5913-011
Exhibit B, Page 11 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205090
Page 11

Our pipeline: late-stage compounds

Anticipated launches for high-potential new products

2001	2002	2003	2004
Zovant Severe sepsis	Cialis Male erectile dysfunction	Alimta Mesothelioma, other cancers	Oritavancin Bacterial infections
Fortéo Osteoporosis	Atomoxetine Attention-deficit hyperactivity disorder	OFC Treatment-resistant depression	
	Duloxetine Depression	Duloxetine Stress urinary incontinence	
		Protein Kinase C beta inhibitor Diabetic retinopathy (in Europe)	

The search for new drugs is risky and uncertain. While we believe each of these molecules holds great promise, we know from experience that remaining scientific and regulatory hurdles may cause a late-stage compound to be delayed or even fail to reach the market at all.

2003

Alimta™—cancer In addition to inestimable costs in human suffering and loss, cancer generates enormous financial costs—an estimated $107 billion annually in the U.S. alone. Our novel multitargeted antifolate, Alimta, is one of a number of cancer drugs we have in various stages of development. It represents one of a variety of approaches we're taking in attacking cancer.

Alimta blocks at least three enzymes that are very important to cell replication. We think it may be possible for Alimta, by blocking any one of these enzymes, to disrupt a cancer cell's machinery and prevent it from replicating. It's also our goal with Alimta to develop a drug with a predictable, preventable, and manageable toxicity profile. Alimta has shown activity in mesothelioma, breast, non-small-cell lung, pancreatic, colon, and gastric cancers.

OFC—treatment-resistant depression We're studying a combination of olanzapine and fluoxetine (Zyprexa/Prozac) in treatment-resistant depression. Approximately one in every three depressed patients does not benefit from current therapies. Early clinical trial studies suggest that OFC may also address psychotic depression. Conventional antidepressants have produced a low response rate in such patients.

Duloxetine—stress urinary incontinence In addition to its potential for treating depression, duloxetine has shown promise in treating urinary incontinence, a serious disorder that can lead to embarrassment and even social isolation for those who suffer from it. Of the various types of incontinence, duloxetine appears best suited to address the kind that occurs due to physical stress, such as coughing, lifting, or straining. Stress incontinence, which accounts for 40 percent of the market, occurs primarily in women and is the most common condition leading to loss of bladder control. There are no approved drug therapies for stress incontinence, which is treated primarily with behavior modification or surgery.

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 12
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5913-012
Exhibit B, Page 12 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205091
Page 12

Gerald Becker, Ph.D., team leader, biochemical technologies group, operates a mass spectrometer as part of Lilly's emerging proteomics effort. Proteomics, the study of the protein component of a cell, tissue, or organism, is helping the company gain a deeper understanding of biology. Mass spectrometry is among the powerful new technologies that help define protein interactions and relationships that further novel drug development.

Protein Kinase C beta (PKCβ) inhibitor—diabetic retinopathy Few diseases have such widespread and varied negative effects on the body as diabetes because the high blood sugar associated with this disease damages the small and large blood vessels of a variety of organs. As a result, diabetes accounts for the largest share of health care expenses in many developed countries, and cardiovascular complications account for nearly 80 percent of deaths in patients with diabetes.

It's our theory that inhibition of PKCβ in blood vessels counteracts the destructive effects of high blood sugar, and we are studying the capability of our oral inhibitor to treat the vascular abnormalities associated with diabetes. Our initial target is diabetic retinopathy, a common diabetes-related complication in which damage to the vessels of the retina occurs and that can, ultimately, lead to blindness.

2004

Oritavancin—bacterial infections Oritavancin is part of our effort to build on our decades-long expertise in infectious disease and to develop a significant array of lifesaving products focused on intensive care units, emergency rooms, trauma centers, and operating rooms.

Oritavancin may be effective against many bacterial infections, including those resistant to conventional antibiotics. We're evaluating its potential use in bacteremia, a condition in which patients have bacteria circulating in their blood, and in complicated skin infections. Statistics suggest that, in 1999, in the U.S. alone, approximately 2.5 million hospital-based patients suffered from skin and skin structure infections and another 400,000 patients from bacteremia.

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Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 13
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Exhibit B, Page 13 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205092
Page 13

Modern pharmaceuticals are a vital, essential, and efficient part of good health care. Unfortunately, in the United States, some patients without drug insurance struggle to pay for the medicines they need. This is wrong.

While Americans as a whole enjoy the highest standard of health care in the world, our patchwork-quilt system of private insurance and various state and federal governmental programs fails to cover everyone. The gaps are especially large for those with lower incomes. They are also large with respect to coverage for drugs. As a result, we have seen a vigorous debate over the cost of pharmaceuticals, especially for low-income seniors, who enjoy Medicare coverage for many health care expenses other than drugs.

This debate is not about whether to provide drug coverage, but how. And because some would make the pharmaceutical industry the villain in this story, it is also a debate about the future of pharmaceutical research. The decisions made as a result of this discussion will affect not only how patients pay for their drugs but also whether new medications will be available in the future.

Throughout this debate, we have stood firmly in support of two principles: first, the Medicare system, through comprehensive reform, should be strengthened and modernized to better serve seniors, including the addition of a drug benefit; second, policymakers should take no action that would endanger our ability to bring forward for patients the full promise of this tremendously exciting new era in pharmaceutical innovation.

The U.S. cannot wait any longer to address these issues. We hope Congress will enact, as soon as possible, a comprehensive reform of Medicare, including a drug benefit. If this proves impossible in the short term, any interim program adopted to help those in greatest need should be consistent with and a step toward modernization of the Medicare system. At minimum, the interim program should not become an obstacle to achieving comprehensive Medicare reform.

Statistics show that well over 90 percent of all new medicines are discovered by research-based pharmaceutical companies and that the U.S. is the leader in pharmaceutical research. We are entering a defining period in medical history as scientists begin to understand the genetic makeup of humans. That knowledge promises to lead to an explosion in new drug development opportunities—opportunities that could one day lead to drugs that prevent or cure cancer, diabetes, and heart disease. The decisions policymakers make today will shape that future. They will determine how long we'll wait for new therapies for tough diseases.

Maggie Lutz didn't have time to wait. Fortunately for her, a novel new drug related to her need was in the late stages of development. To learn what pharmaceutical innovation meant for Maggie, please turn the page.

Who pays for progress?

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Zyprexa MDL Plaintiffs' Exhibit No.05913
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Exhibit B, Page 14 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI

ZY1 00205093
Page 14

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Each day, 1,400 people die from sepsis worldwide.

Caused by the overwhelming response of the body's immune system to infection, sepsis can occur in healthy people who develop an infection, such as pneumonia. It can also occur as a complication of trauma, cancer, or AIDS. In fact, many deaths officially linked to these diseases represent cases in which the patients actually died of sepsis.

Industrywide, approximately 30 research efforts to find a sepsis drug over the last several decades have all failed. We are hopeful that our investigational drug, Zovant, will break this cycle

Can we really beat a killer?

of disappointment. Zovant is our version of recombinant human Activated Protein C for sepsis.

In the summer of 2000, an independent panel of experts recommended that we suspend the enrollment of patients in our Phase III trial evaluating Zovant against placebo as a treatment for sepsis and submit the drug for regulatory approval quickly. The panel found positive results in this study of more than 1,500 patients, including a nearly 20 percent reduction in the relative risk of death in Zovant-treated patients.

We concluded our clinical trial work and we have submitted Zovant to the European Agency for the Evaluation of Medicinal Products and the U.S. Food and Drug Administration.

We believe Zovant may represent an important medical breakthrough against sepsis. It may provide hope for patients like Maggie Lutz, for whom, up to now, there has been very little.

Maggie's story

College student Maggie Lutz (*opposite*) had gone to the campus health center with a sore throat. A week later, she still had a sore throat and had been experiencing headaches and a low-grade fever. During the evening, she began to vomit. Maggie called an area hospital to see if she should come there to be seen by medical staff. She was told her symptoms sounded like flu and to rest. The next day, Maggie woke with a dark purple rash on the lower half of her body. Her muscles ached so badly she had difficulty getting out of bed. She knew something was very wrong.

With her roommates already gone to class, Maggie managed to take a bus to the health center. By the time a physician saw her, her blood pressure was dangerously low, her heart rate was racing, and she was disoriented. Presenting classic symptoms of a serious form of meningitis, Maggie was rushed to the emergency room of the university hospital. She was admitted with severe sepsis, which is brought about by a multitude of conditions triggered by the body's immune response to infection.

By that evening, Maggie was hardly recognizable, even to her family. Normally a very slim person, Maggie ballooned to more than 200 pounds as her body could no longer eliminate fluid. Her eyes were so swollen the lids would not cover them. Her organs had begun to shut down as her condition rapidly deteriorated. Finally, she was placed on a ventilator and sedated into an artificial coma to minimize the work required of the body to maintain itself.

The attending physician told Maggie's parents she had only a 10 percent chance of surviving. However, he was aware of Lilly's investigational drug for severe sepsis.

Believing Maggie might be helped by Lilly's clinical study drug, the physician immediately contacted the company. Lilly researchers obtained the necessary approvals for compassionate use of the experimental drug, and within 14 hours, Maggie's doctor began an infusion of rhAPC that would continue for the next 96 hours.

The rapidity of Maggie's response to rhAPC, now known as Zovant, was astonishing. Within 48 hours, her blood pressure improved and her lungs were clear. And, she continued to progress as her vital functions began to work on their own over another seven weeks in the hospital.

Once at home, Maggie worked for a year to regain her strength and the normal use of her muscles. She is now totally recovered and will graduate from college in the spring.

"I've always been a compassionate person," she said. "But I'm more so now. Thank God, there were people working for me at Lilly. And they work so hard—I never realized how much it takes to make a new drug. But it pays off. I'm proof that it pays off.

"People call me 'Miracle Maggie.' It was a miracle—I was almost gone. But, I'm back."

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Zyprexa MDL Plaintiffs' Exhibit No.05913
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Exhibit B, Page 16 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205095
Page 16

ZY 9553 916

15

Zyprexa MDL 1596
Zyprexa VDL Plaintiffs' Exhibit No 05913
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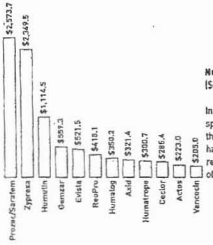
Exhibit B Page 17 of 32
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN 06-5630 CI
ZY1 00205096
Page 17

Review of Operations

Operating Results From Continuing Operations—2000

Summary

Income from continuing operations was $3.06 billion, or $2.79 per share, in 2000 and $2.55 billion, or $2.30 per share, in 1999. Comparisons between 2000 and 1999 are made difficult by the impact of several unusual items that are reflected in the company's operating results for both years. Excluding these unusual items, which are discussed further below, income from continuing operations for 2000 and 1999 would have been $2.90 billion, or $2.65 per share, and $2.52 billion, or $2.28 per share, respectively. This represents an increase in net income and earnings per share of 15 percent and 16 percent, respectively. The 2000 increases are attributed to growth in sales, improved gross margin, and increased interest income, offset by increases in operating expenses at a rate greater than sales growth. Earnings per share also benefited from a decrease in the number of shares outstanding as a result of the share repurchase plan.



Unusual Items

As noted above, several unusual items are reflected in the company's operating results for 2000 and 1999. These transactions are summarized as follows (see Note 3, Note 5, and Note 13 to the consolidated financial statements for additional information):

- A gain of $214.4 million on the sale of its interest in Kinetra LLC to WebMD Corporation (WebMD) and the subsequent sale of WebMD stock, which increased earnings per share by approximately $.20 in the first quarter of 2000
- Approximately $91 million in additional product sales in 1999 as a result of year-2000-related wholesaler buying that normally would have been realized during the first quarter of 2000, which increased earnings per share by approximately $.06 in the fourth quarter of 1999 and reduced earnings per share by the same amount in the first quarter of 2000
- A pretax gain of $110.0 million in settlement of litigation with Biochimica Opos S.p.A., which increased earnings per share by approximately $.06 in the fourth quarter of 1999
- A pretax charge of $26.0 million associated with the decommissioning of manufacturing facilities and other site charges, which decreased earnings per share by approximately $.02 in the fourth quarter of 1999
- A pretax gain of $67.8 million on the sale of U.S. and Puerto Rican Lorabid marketing rights, which increased earnings per share by approximately $.05 in the third quarter of 1999
- A pretax charge of $150.0 million as the result of a contribution to Eli Lilly and Company Foundation, which decreased earnings per share by approximately $.09 in the first quarter of 1999
- A pretax charge of $61.4 million associated with the impairment of certain manufacturing assets, which decreased earnings per share by approximately $.04 in the first quarter of 1999.

Sales

The company's reported worldwide sales for 2000 increased 9 percent, to $10.86 billion. Worldwide sales for 1999 included approximately $91 million of sales relating to year-2000 wholesaler buying that normally would have been recognized in 2000. Adjusting for the impact of year-2000 wholesaler buying, sales growth for 2000 would have been 10 percent. Sales growth was led by Zyprexa, a treatment for schizophrenia and related psychoses; diabetes care products; Evista, an osteoporosis treatment and prevention agent; and Gemzar, an oncolytic product. Sales in the U.S. increased 12 percent, to $7.00 billion. Sales outside the U.S. increased 2 percent, to $3.86 billion. Worldwide sales reflected volume growth of 11 percent, partially offset by a 2 percent decrease in exchange rates while prices remained flat.

Prozac and Sarafem had combined worldwide sales of $2.57 billion, representing a decrease of 2 percent. Sarafem, launched in the U.S. in August 2000 for the treatment of premenstrual dysphoric disorder (PMDD), had sales of $14.6 million in 2000. Combined sales of Prozac, an antidepressant, and Sarafem in the U.S. increased 7 percent, to $2.23 billion. The U.S. sales comparison benefited, in part, from wholesaler inventory reductions in 1999. Prozac sales outside the U.S. decreased 35 percent,

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
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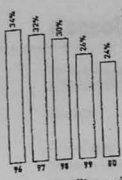
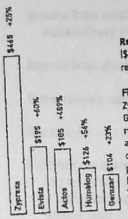
Exhibit B Page 1853 of 2917
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY 00205097
Page 18



Lilly's Decreasing Dependency on Prozac
(percentages represent the Prozac share of total net sales)

Through strong growth of newer products, Lilly is consistently lessening its reliance on sales of Prozac. In 2000, Prozac (including Sarafem) accounted for 24 percent of Lilly's total net sales, down from 34 percent in 1996.

to $341.0 million, primarily due to continuing generic competition in the U.K. On August 9, 2000, the Court of Appeals for the Federal Circuit affirmed a lower court decision upholding the company's February 2001 U.S. patent on Prozac but ruled that the company's December 2003 patent is invalid. Reference is made to the discussion of the Prozac patent litigation under "Legal and Environmental Matters." For additional information on the expected financial impact of the ruling, see the "Financial Expectations for 2001" section below.



Revenue Growth of Newer Products
($ millions; growth percentages represent change from 1999)

Five of the company's newer products—Zyprexa, Evista, Actos, Humalog, and Gemzar—generated $4.0 billion in revenues in 2000. These newer products and ReoPro now represent 41 percent of total net sales compared with 34 percent in 1999 and 26 percent in 1998. During the fourth quarter of 2000, Zyprexa became the company's top-selling product.

Zyprexa had worldwide sales of $2.35 billion in 2000, representing an increase of 25 percent. Sales in the U.S. increased 23 percent, to $1.69 billion. Sales in 2000 benefited from the U.S. Food and Drug Administration (FDA) approval of Zyprexa for the treatment of acute mania associated with bipolar disorder in the first quarter of 2000. Sales outside the U.S. increased 28 percent, to $659.3 million.

Gemzar had worldwide sales of $559.3 million in 2000, representing an increase of 23 percent. Sales in the U.S. increased 20 percent, to $315.9 million. Sales outside the U.S. increased 27 percent, to $243.3 million.

Evista had worldwide sales of $521.5 million in 2000, representing an increase of 60 percent. Sales in the U.S. increased 52 percent, to $433.8 million. Increases in sales in the U.S. were due, in part, to the FDA approval of Evista for the treatment of postmenopausal osteoporosis in the U.S., which was granted in September 1999. Sales outside the U.S. increased 115 percent, to $87.7 million.

ReoPro had worldwide sales of $418.1 million in 2000, representing a decrease of 7 percent. Sales in the U.S. decreased 12 percent, to $315.1 million. Sales outside the U.S. increased 15 percent, to $102.9 million. The decline in sales was due to increased competition in the U.S.

Diabetes care products, composed primarily of Humulin, the company's biosynthetic human insulin; Humalog, the company's insulin analog; and Actos, an oral diabetes agent introduced in the U.S. in 1999, had worldwide revenues of $1.76 billion in 2000, representing an increase of 22 percent. Diabetes care revenues in the U.S. increased 21 percent, to $1.08 billion. Diabetes care revenues outside the U.S. increased 22 percent, to $685.8 million. Humulin had worldwide sales of $1.11 billion, representing an increase of 2 percent. Humulin sales in the U.S. decreased 6 percent, to $617.4 million, largely as a result of patients shifting to Humalog and Humalog mixture products. Humulin sales outside the U.S. increased 15 percent, to $497.0 million. Humalog had worldwide sales of $350.2 million, representing an increase of 56 percent. Sales of Humalog benefited from the U.S. launch of Humalog Mix75/25™ Pen in the first quarter of 2000. The company received service revenues of $223.0 million in 2000 relating to sales of Actos. Actos, an oral agent for the treatment of type 2 diabetes, was introduced to the U.S. diabetes market in the third quarter of 1999. Actos is manufactured and sold in the U.S. by Takeda Chemical Industries, Ltd., and is copromoted by Takeda and the company.

Anti-infectives had worldwide sales of $894.3 million in 2000, representing a decrease of 13 percent, due to continuing competitive pressures. Cefaclor and Lorabid accounted for the majority of the decline. Sales in the U.S. decreased 12 percent, to $189.4 million. Sales outside the U.S. decreased 13 percent, to $702.9 million.

Animal health products had worldwide sales of $668.5 million in 2000, representing an increase of 6 percent. Sales in the U.S. increased 8 percent, to $307.5 million. Sales outside the U.S. increased 5 percent, to $360.9 million. The increases were balanced across the product line.

The company's payments under federally mandated Medicaid rebate programs reduced 2000 sales by approximately $464.0 million compared with approximately $352.5 million in 1999.

Gross Margin, Costs, and Expenses

The 2000 gross margin improved to 81.1 percent of sales compared with 79.0 percent for 1999. This increase was attributed primarily to favorable changes in product mix due to growth in sales of newer products and, to a lesser extent, increased production volume.

Operating expenses (the aggregate of research

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
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Exhibit B, Page 19 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205098
Page 19

Consolidated Statements of Income

Eli Lilly and Company and Subsidiaries (Dollars in millions, except per-share data) Year Ended December 31	2000	1999	1998
Net sales	$10,862.2	$10,002.9	$9,236.8
Cost of sales	2,055.7	2,098.0	2,015.1
Research and development	2,018.5	1,783.6	1,738.9
Marketing and administrative	3,228.3	2,757.6	2,658.3
Acquired in-process technology (Note 3)	—	—	127.5
Asset impairment and other site charges (Note 5)	—	87.4	—
Interest expense	182.3	183.8	181.3
Other income—net	(481.3)	(152.9)	(149.3)
	7,003.5	6,757.5	6,571.8
Income from continuing operations before income taxes and extraordinary item	3,858.7	3,245.4	2,665.0
Income taxes (Note 11)	800.9	698.7	568.7
Income from continuing operations before extraordinary item	3,057.8	2,546.7	2,096.3
Income from discontinued operations, net of tax (Note 4)	—	174.3	8.8
Extraordinary item, net of tax (Note 7)	—	—	(7.2)
Net income	$ 3,057.8	$ 2,721.0	$2,097.9
Earnings per share—basic (Note 10):			
Income from continuing operations before extraordinary item	$ 2.83	$ 2.34	$ 1.91
Income from discontinued operations	—	.16	.01
Extraordinary item	—	—	(.01)
Net income	$ 2.83	$ 2.50	$ 1.91
Earnings per share—diluted (Note 10):			
Income from continuing operations before extraordinary item	$ 2.79	$ 2.30	$ 1.87
Income from discontinued operations	—	.16	.01
Extraordinary item	—	—	(.01)
Net income	$ 2.79	$ 2.46	$ 1.87

See notes to consolidated financial statements.

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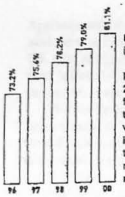
Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 20
005795
5913-020

Exhibit B, Page 20 of 52
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI

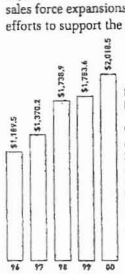
ZY1 00205099
Page 20



Gross Margin
(as a percent of total net sales)

In 2000, gross margin improved by 2.1 percentage points, primarily due to favorable changes in product mix and, to a lesser extent, increased production volume. This continuous improvement in gross margin has enabled the company to aggressively fund investments in research and development, sales, and marketing.

and development and marketing and administrative expenses) increased 16 percent in 2000. Research and development expenses increased 13 percent, to $2.02 billion, in 2000 as the company continued to invest in both the early and late stages of its internal product pipeline and external collaborations. Marketing and administrative expenses increased 17 percent primarily due to sales force expansions and increased marketing efforts to support the company's newer products.



Research and Development
($ millions)

Worldwide research and development expenditures increased 13 percent in 2000 in support of the company's strong pipeline. Research and development expenditures represented 19 percent of total net sales in 2000 compared with 18 percent in 1999. The late-stage pipeline includes 10 new products for a wide range of serious, unmet medical needs that are expected to be launched during the period from 2001 to 2004.

Net other income for 2000 was $267.9 million, an increase of $142.8 million, excluding the gain on the sale of Kinetra LLC in 2000 and the gains from the litigation settlement and the sale of Lorabid marketing rights and a charge for the contribution to Eli Lilly and Company Foundation in 1999. The increase was primarily due to an increase in interest income.

The company's effective tax rate for 2000 was 20.8 percent compared with 21.5 percent for 1999. Excluding the unusual items discussed previously, the effective tax rate for both 2000 and 1999 was 22.0 percent. See Note 11 to the consolidated financial statements for additional information.

Operating Results From Continuing Operations—1999

Summary

Income from continuing operations was $2.55 billion, or $2.30 per share, in 1999 and $2.10 billion, or $1.87 per share, in 1998 (before the 1998 extraordinary charge of $7.2 million, or $.01 per share). Comparisons between 1999 and 1998 are made difficult by the impact of several unusual items that are reflected in the company's operating results for both years. Excluding these unusual items, which are discussed further below, income from continuing operations before extraordinary item for 1999 and 1998 would have been $2.52 billion, or $2.28 per share, and $2.17 billion, or $1.94 per share, respectively. This represents an increase in net income and earnings per share of 16 percent and 18 percent, respectively. The 1999 increases are attributed to increased sales, improved gross margin, and increases in operating expenses at a rate less than sales growth. Earnings per share also benefited from a decrease in the number of shares outstanding as a result of the share repurchase plan.

Unusual Items

As noted above, several unusual items are reflected in the company's operating results for 1999 and 1998. The unusual items relating to 1999 are summarized under Operating Results From Continuing Operations—2000. During 1998, the company recognized a pretax charge of $127.5 million for acquired in-process technology associated with a collaboration with ICOS Corporation, which reduced earnings per share by approximately $.07 net of tax. See Note 3 to the consolidated financial statements for additional information.

Sales

The company's reported worldwide sales for 1999 increased 8 percent, to $10.0 billion. Approximately $91 million of worldwide sales were related to year-2000 wholesaler buying. Sales growth was led by Zyprexa, Evista, Gemzar, diabetes care products, and ReoPro. Sales in the U.S. were $6.23 billion, a 7 percent increase, while sales outside the U.S. were $3.77 billion, an 11 percent increase. Worldwide sales reflected volume growth of 9 percent and a 1 percent increase in prices, partially offset by a 2 percent decrease in exchange rates.

Worldwide sales of Prozac in 1999 were $2.61 billion, representing a decrease of 7 percent. Approximately $12 million of worldwide Prozac sales were related to year-2000 wholesaler buying. Prozac sales in the U.S. decreased 8 percent, to $2.09 billion. Sales of Prozac outside the U.S. decreased 3 percent, to $525.1 million. The decline in U.S. sales was largely caused by wholesaler stocking that occurred during 1998, creating a significant adverse impact on sales comparisons in 1999. Prozac sales in the U.S. were also adversely affected by increased competition from new antidepresants.

Zyprexa posted worldwide sales of $1.89 billion in 1999, representing an increase of 31 percent.

ZY 9553 920
Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 21
005796
5913-021
Exhibit B, Page 21 of 52
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205100
Page 21

Approximately $17 million of worldwide Zyprexa sales were related to year-2000 wholesaler buying. U.S. sales of Zyprexa increased 22 percent, to $1.37 billion. Sales outside the U.S. increased 62 percent, to $513.9 million.

Worldwide Gemzar sales of $455.8 million in 1999 reflected an increase of 49 percent. Sales in the U.S. increased 57 percent, to $264.2 million, and sales outside the U.S. increased 38 percent, to $191.6 million.

Worldwide ReoPro sales of $447.3 million in 1999 reflected an increase of 22 percent. U.S. sales of ReoPro increased 18 percent, to $357.5 million. ReoPro sales outside the U.S. increased 43 percent, to $89.8 million.

Worldwide diabetes care revenues, composed of Humulin, Humalog, Iletin, and Actos, increased 19 percent, to $1.38 billion, in 1999. Approximately $23 million of worldwide diabetes care revenues were related to year-2000 wholesaler buying. Diabetes care revenue in the U.S. increased 18 percent, to $827.7 million. Diabetes care revenue outside the U.S. increased 21 percent, to $547.5 million. Worldwide Humulin sales increased 13 percent, to $1.09 billion. U.S. Humulin sales increased 12 percent and Humulin sales outside the U.S. increased 15 percent. Worldwide Humalog sales were $224.5 million, representing an increase of 73 percent. The company received service revenues of $37.9 million in 1999 relating to sales of Actos.

Worldwide sales of anti-infectives decreased 12 percent in 1999, to $1.02 billion, as a result of continuing competitive pressures. U.S. and international anti-infectives sales declined 22 percent and 8 percent, respectively. Cefaclor and Lorabid accounted for the majority of the decline in anti-infectives sales, offsetting growth in Vancocin® outside the U.S.

Evista sales increased $182.0 million, or 126 percent, to $326.1 million in 1999. Evista was launched in the first quarter of 1998 in the U.S. for the prevention of osteoporosis in postmenopausal women. During 1999, the company received approval from the FDA to promote Evista for the treatment of postmenopausal osteoporosis. While most of the sales dollar growth for Evista occurred in the U.S., international Evista sales reflected strong percentage growth.

Worldwide sales of animal health products of $627.8 million in 1999 reflected a 2 percent increase. Sales were flat in the U.S. and increased 4 percent outside the U.S.

The company's payments under federally mandated Medicaid rebate programs reduced 1999 sales by approximately $352.5 million compared with approximately $278.6 million in 1998.

Gross Margin, Costs, and Expenses

The 1999 gross margin improved to 79.0 percent of sales compared with 78.2 percent for 1998. This increase was attributed primarily to production efficiencies and, to a lesser extent, favorable changes in product mix, as well as the expiration of Humulin and Humalog royalties in August 1998.

Operating expenses (the aggregate of research and development and marketing and administrative expenses) increased 3 percent in 1999. Research and development investments increased 3 percent, to $1.78 billion, in 1999 as the company continued to build internal and external capabilities. Reduced incentive compensation significantly offset the expense growth. In addition, Phase III clinical trials for certain compounds were discontinued in the first half of 1999, which contributed to the reduction in the growth rate. Marketing and administrative expenses increased 4 percent due to increased spending to support new product launches around the world and enhancements in the company's global information technology systems, including year-2000 readiness efforts. However, the impact of these increases was mitigated by expense management initiatives and reduced incentive compensation.

Excluding the gains from the litigation settlement, the sale of Lorabid marketing rights, and the charge for the contribution to Eli Lilly and Company Foundation, net other income for 1999 was $125.1 million, which represents a decrease of $24.2 million. Other income in 1998 benefited from gains generated from the sale of investments.

The company's effective tax rate for 1999 was 21.5 percent compared with 21.3 percent for 1998. Excluding the unusual items discussed previously, the effective tax rates for 1999 and 1998 were 22.0 percent and 22.2 percent, respectively.

Discontinued Operations

Discontinued operations consist of the company's PCS health-care-management business. In November 1998, the company entered into an agreement to sell PCS for $1.60 billion in cash. The sale was closed in January 1999 and the resulting net gain on disposal of $174.3 million, net of $8.7 million tax benefit, was recognized in the first quarter of 1999. See Note 4 to the consolidated financial statements for further information.

Financial Condition

As of December 31, 2000, cash, cash equivalents, and short-term investments totaled approximately $4.62 billion compared with $3.84 billion at December 31, 1999. The increase in cash was primarily due to cash generated from operations, partially offset by dividends paid, share repurchases, and

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 22
5913-022
005797
ZY 9553 921
Exhibit B, Page 22 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205101
Page 22

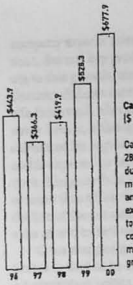
capital expenditures. The company acquired approximately 14.8 million shares, for approximately $1.09 billion, during 2000 pursuant to its previously announced $3 billion share repurchase program. Total debt at December 31, 2000, was $2.82 billion, a decrease of $235.4 million. The company believes that cash generated from operations, along with available cash and cash equivalents, will be sufficient to fund essentially all the company's operating needs, including debt service, capital expenditures, and dividends in 2001.

The company believes that amounts available through existing commercial paper programs should be adequate to fund maturities of short-term borrowings. The company's commercial paper program is also backed by $2.02 billion of committed bank credit facilities.

In the normal course of business, operations of the company are exposed to fluctuations in interest rates. These fluctuations can vary the costs of financing, investing, and operating. The company addresses a portion of these risks through a controlled program of risk management that includes the use of derivative financial instruments. The objective of controlling these risks is to limit the impact on earnings of fluctuations in interest rates. All derivative activities are for purposes other than trading.

The company's primary interest rate risk exposure results from changes in short-term U.S. dollar interest rates. In an effort to manage interest rate exposures, the company strives to achieve an acceptable balance between fixed and floating rate debt positions and may enter into interest rate swaps to help maintain that balance. Based on the company's overall interest rate exposure at December 31, 2000, including derivatives and other interest rate risk sensitive instruments, a hypothetical 10 percent change in interest rates applied to the fair value of the instruments as of December 31, 2000, would have no material impact on earnings, cash flows, or fair values of interest rate risk sensitive instruments over a one-year period. Similarly, a hypothetical 10 percent change in interest rates from 1999 applied to the fair value of the instruments as of December 31, 1999, would have had no material impact on earnings, cash flows, or fair values of interest rate risk sensitive instruments during 2000.

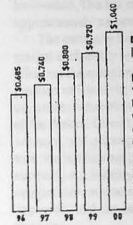
Capital expenditures of $677.9 million during 2000 were $149.6 million more than in 1999 as the company continued to invest in manufacturing and research and development initiatives and related infrastructure. The company expects near-term capital expenditures to increase from 2000 levels. Sufficient cash flows exist to meet these near-term requirements.



Capital Expenditures
($ millions)

Capital expenditures increased 28 percent from the 1999 level, primarily due to the increased support of various manufacturing and research initiatives and related infrastructure. The company expects near-term capital expenditures to increase from 2000 levels due to continuing investment in research and manufacturing capacity to support its growing portfolio.

Dividends of $1.04 per share were paid in 2000, an increase of 13 percent from the $.92 per share paid in 1999. In the fourth quarter of 2000, effective for the first-quarter dividend in 2001, the quarterly dividend was increased to $.28 per share (8 percent), resulting in an indicated annual rate for 2001 of $1.12 per share. The year 2000 was the 116th consecutive year in which the company made dividend payments and the 33rd consecutive year in which dividends have been increased.



Dividends Paid per Share
(dollars)

Dividends paid during 2000 increased 13 percent over 1999. The year 2000 became the 33rd consecutive year in which dividends were increased. The continued earnings growth in 2000 enabled the company to declare a first-quarter 2001 dividend of $.28 per share, an 8 percent increase over 2000. The increase reflects the company's continued commitment to delivering shareholder value.

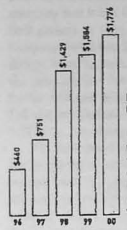
Euro Conversion

On January 1, 1999, 11 European nations adopted a common currency, the euro, and formed the European Economic and Monetary Union (EMU). For a three-year transition period, both the euro and individual participants' currencies will remain in circulation. After July 1, 2002, at the latest, the euro will be the sole legal tender for EMU countries. Greece has joined the original 11 countries adopting the euro in 2002. The adoption of the euro affects a multitude of financial systems and business applications as the commerce of these nations is transacted in the euro and the existing national currency.

The company has created the capability to transact in both the euro and the legacy currency and has converted the underlying information systems within the EMU countries from the legacy currencies to the euro. The company will continue

ZY 9553 922
Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
Exhibit B, Page 23 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205102
Page 23
5913-001 / 23
005798
5913-023

to address euro-related issues and their impact on information systems, currency exchange rate risk, taxation, contracts, competition, and pricing. Action plans currently being implemented are expected to result in compliance with all laws and regulations; however, there can be no certainty that such plans will be successfully implemented or that external factors will not have an adverse effect on the company's operations. Any costs of compliance associated with the adoption of the euro are expensed as incurred and the company does not expect these costs to be material to its results of operations, financial condition, or liquidity.



Economic Value Added
($ millions)

In 2000, Lilly's Economic Value Added (EVA) was $1.8 billion, an increase of 12 percent, reflecting the company's commitment to effective asset management and focus on earnings growth in order to deliver shareholder value.

Financial Expectations for 2001

As noted above, a federal appeals court has upheld the company's February 2001 U.S. Prozac patent but ruled that the 2003 patent is invalid. In addition, the FDA has granted the company an additional six months of market exclusivity for Prozac under a federal statute encouraging pediatric studies of certain medicines, extending market exclusivity for Prozac to August, 2, 2001, assuming the 2003 Prozac patent ruling is not overturned. The company expects a very substantial decline in Prozac sales in the U.S. in the 12 months following the entry of generic fluoxetine in the U.S. market. Prozac sales in the U.S. represent a significant portion of the company's overall sales, accounting for approximately 20 percent of the company's consolidated worldwide sales in 2000.

As a result of the above, excluding any unusual items, the company anticipates earnings per share for 2001 to be in the range of $2.75 to $2.85, assuming the entry of generic fluoxetine in the U.S. in August 2001. Strong earnings growth in the first half of 2001 is expected to more than offset declines in the second half, resulting in single-digit earnings growth for the full year compared with 2000 earnings per share of $2.65, excluding unusual items.

In addition, excluding any unusual items, the company expects to post single-digit sales growth in 2001. Excluding worldwide sales of Prozac, the company expects sales to grow in the mid-teens for 2001. Several key products are expected to contribute to this growth, including Zyprexa; Evista; Gemzar; diabetes care products; and drotrecogin alfa (activated), also known by the proposed trade name Zovant, a therapy for sepsis, which was submitted for regulatory approval in early 2001 and is expected to launch in the second half of 2001. The growth in these products is anticipated to more than offset the very substantial expected decline of Prozac sales and continuing decreases in sales of anti-infectives and ReoPro.

Gross margins as a percent of sales are expected to decline in 2001 in the range of .5 to 1.0 percentage points as a result of the decline in Prozac sales. The company anticipates marketing and administrative expenses will grow in the low-to-mid single digits. Underlying marketing expenses for continuing products, excluding Prozac, are expected to grow in the double digits as the company continues to invest in sales force expansions and increased marketing efforts. Research and development expenses are expected to grow in the low double digits, demonstrating the company's continued commitment to invest in scientific innovation. The tax rate is expected to remain at approximately 22 percent for the full year.

The company believes that the loss of Prozac market exclusivity will not have a material adverse effect on the company's consolidated financial position or liquidity. The actual impact will depend on, among other things, the outcome of the appeal of the Federal Circuit ruling; the timing, number of entrants, and pricing strategies of generic competitors; the continuing growth of the company's other currently marketed products; developments with competitive products; the timing of regulatory approvals; and the expected introduction of new products.

Legal and Environmental Matters

Barr Laboratories, Inc. (Barr), and Geneva Pharmaceuticals, Inc. (Geneva), have each submitted an Abbreviated New Drug Application (ANDA) seeking FDA approval to market generic forms of Prozac before the expiration of the company's patents. The ANDAs assert that two U.S. patents held by Lilly covering Prozac are invalid and unenforceable. The company filed suit against Barr and Geneva in federal court in Indianapolis seeking a ruling that Barr's challenge to Lilly's patents is without merit. In January 1999, the trial court granted summary judgment in favor of Lilly on two of the four claims raised by Barr and Geneva against Lilly's patents. That decision was appealed to the Court of Appeals for the Federal Circuit. Barr and Geneva dismissed their other two claims in exchange for a $4 million

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 24
005799
5913-024
Exhibit B, Page 24 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205103
Page 24

payment. On August 9, 2000, the Court of Appeals upheld the 2001 compound patent but held that the 2003 method of use patent was invalid. The company has filed a petition requesting a rehearing by the Court of Appeals.

Several other generic manufacturers have also filed ANDAs for generic forms of Prozac, challenging one or both of the patents. In late 1998, Zenith Goldline Pharmaceuticals, Inc.; Teva Pharmaceuticals USA (Teva); and Cheminor Drugs, Ltd., together with one of its subsidiaries (Cheminor), notified the company that they had filed ANDAs challenging the 2003 patent. Also in 1998, Novex Pharma, a division of Apotex, Inc., notified the company that it had filed an ANDA challenging both patents. In 1999, Cheminor notified the company that it had filed an ANDA for a different dosage form. In 2000, Barr and Teva both notified the company that they had filed additional ANDAs for the different dosage form, and Alphapharm Pty. Ltd. also notified the company that it had filed ANDAs for two dosage forms.

The company has filed lawsuits in the United States District Court of the Southern District of Indiana seeking rulings that all these challenges to the patent(s) are without merit. The cases are awaiting resolution of the petition for rehearing by the Court of Appeals in the original Barr case.

For additional information on the impact of the Prozac patent litigation, see the "Financial Expectations for 2001" section above.

In addition, the company is a defendant in numerous product liability suits involving primarily two products, diethylstilbestrol (DES) and Prozac. See Note 13 to the consolidated financial statements for further information on those matters.

The company's worldwide operations are subject to complex and changing environmental and health and safety laws and regulations, which will continue to require capital investment and operational expenses. The company has also been designated a potentially responsible party with respect to fewer than 10 sites under the federal environmental law commonly known as Superfund. For more information on those matters, see Note 13 to the consolidated financial statements.

While it is not possible to predict or determine the outcome of the patent, product liability, or other legal actions brought against the company or the ultimate cost of environmental matters, the company believes that, except as noted above with respect to the Prozac patent litigation, the costs associated with all such matters will not have a material adverse effect on its consolidated financial position or liquidity but could possibly be material to the consolidated results of operations in any one accounting period.

Other Matters

On October 28, 2000, President Clinton signed the Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act for fiscal year 2001. This legislation includes a provision that repeals the federal ban on the reimportation of most prescription drugs by anyone other than the manufacturer. Consequently, under the new law, wholesalers and pharmacists may be permitted to reimport certain drugs approved for sale in the U.S. and originally sold abroad, subject to several conditions. The law authorizes reimportation from select jurisdictions, including Australia, Canada, the European Union, Israel, Japan, New Zealand, South Africa, and Switzerland.

Before the law takes effect, the secretary of Health and Human Services (HHS) must "demonstrate" to Congress that the law poses no additional risk to public health and safety and will result in significant reductions in drug costs for American consumers. If HHS can make that demonstration, then the FDA must draft regulations prior to implementing the law. In December 2000, the secretary of HHS stated that she would be unable to make the demonstration required by the law. It is uncertain what action, if any, may be taken on this bill by the incoming secretary of HHS or whether Congress will modify the legislation.

The company cannot predict at this time the extent to which it will be affected by this legislation or potential future legislative or regulatory developments in this area. However, if widespread reimportation of the company's products were to occur, this could have a material adverse effect on the company's results of operations.

Private Securities Litigation Reform Act of 1995—A Caution Concerning Forward-Looking Statements

Under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, the company cautions investors that any forward-looking statements or projections made by the company, including those made in this document, are based on management's expectations at the time they are made, but they are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Economic, competitive, governmental, technological, and other factors that may affect the company's operations and prospects are discussed in Exhibit 99 to the company's most recent report on Forms 10-Q and 10-K filed with the Securities and Exchange Commission.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 25
005800
5913-025
Exhibit B, Page 25 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205104
Page 25

Consolidated Balance Sheets

Eli Lilly and Company and Subsidiaries (Dollars in millions) December 31	2000	1999
Assets		
Current Assets		
Cash and cash equivalents	$ 4,114.9	$ 3,700.4
Short-term investments	593.3	135.6
Accounts receivable, net of allowances of $115.3 (2000) and $79.9 (1999)	1,630.7	1,443.2
Other receivables	335.4	399.6
Inventories	883.1	899.6
Deferred income taxes (Note 11)	269.5	240.3
Prepaid expenses	206.1	236.8
Total current assets	7,943.0	7,055.5
Other Assets		
Prepaid retirement (Note 12)	1,032.5	741.1
Investments	395.7	180.3
Sundry	1,143.0	866.8
	2,571.2	1,788.2
Property and Equipment	4,176.6	3,981.5
	$14,690.8	$12,825.2

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 26
5913-026
005801
Exhibit B, Page 26 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205105
Page 26

(Dollars in millions) December 31	2000	1999
Liabilities and Shareholders' Equity		
Current Liabilities		
Short-term borrowings (Note 7)	$ 184.3	$ 241.5
Accounts payable	661.9	445.5
Employee compensation	468.3	489.3
Dividends payable	315.4	283.0
Income taxes payable (Note 11)	2,200.2	1,445.3
Other liabilities	1,130.6	1,030.8
Total current liabilities	4,960.7	3,935.4
Other Liabilities		
Long-term debt (Note 7)	2,633.7	2,811.9
Deferred income taxes (Note 11)	91.6	137.0
Retiree medical benefit obligation (Note 12)	83.3	115.7
Other noncurrent liabilities	874.6	812.2
	3,683.2	3,876.8
Commitments and contingencies (Note 13)	—	—
Shareholders' Equity (Notes 8 and 9)		
Common stock—no par value		
Authorized shares: 3,200,000,000		
Issued shares: 1,126,567,407 (2000) and 1,091,226,806 (1999)	704.4	682.0
Additional paid-in capital	2,610.0	—
Retained earnings	6,223.2	4,985.6
Employee benefit trust	(2,635.0)	—
Deferred costs—ESOP	(135.0)	(139.9)
Accumulated other comprehensive income (Note 14)	(611.2)	(406.4)
	6,156.4	5,121.3
Less cost of common stock in treasury:		
2000—1,007,235 shares		
1999—988,902 shares	109.5	108.3
	6,046.9	5,013.0
	$14,690.8	$12,825.2

See notes to consolidated financial statements.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 27
005802
5913-027
Exhibit B, Page 27 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205106
Page 27

Consolidated Statements of Cash Flows

Eli Lilly and Company and Subsidiaries (Dollars in millions) Year Ended December 31	2000	1999	1998
Cash Flows From Operating Activities			
Net income	$ 3,057.8	$ 2,721.0	$ 2,097.9
Adjustments To Reconcile Net Income to Cash Flows From Operating Activities			
Depreciation and amortization	435.8	439.7	490.4
Change in deferred taxes	(442.7)	27.1	25.4
Gain on sale of Kinetra, net of tax	(214.4)	—	—
Gain on sale of PCS, net of tax	—	(174.3)	—
Asset impairment and other site charges, net of tax	—	58.1	—
Other, net	117.3	96.6	153.5
	2,953.8	3,168.2	2,767.2
Changes in operating assets and liabilities:			
Receivables—increase	(165.4)	(179.0)	(403.6)
Inventories—(increase) decrease	9.8	16.9	(55.6)
Other assets—increase	(210.5)	(88.8)	(81.1)
Accounts payable and other liabilities—increase (decrease)	1,143.8	(174.9)	649.4
	777.7	(425.8)	109.1
Net Cash Provided by Operating Activities	3,731.5	2,742.4	2,876.3
Cash Flows From Investing Activities			
Purchase of property and equipment	(677.9)	(528.3)	(419.9)
Disposals of property and equipment	5.1	78.3	30.6
Proceeds from sale of investments	983.9	216.1	273.1
Purchase of investments	(1,233.2)	(162.8)	(57.6)
Proceeds from sale of PCS	—	1,600.0	—
Other, net	(134.4)	(116.6)	(195.1)
Net Cash Provided by (Used in) Investing Activities	(1,056.5)	1,086.7	(368.9)
Cash Flows From Financing Activities			
Dividends paid	(1,126.0)	(1,000.5)	(877.7)
Purchase of common stock and other capital transactions	(1,052.8)	(2,453.0)	(1,999.8)
Issuances under stock plans	178.4	187.5	242.5
Redemption of subsidiary stock	—	—	(172.8)
Net change in short-term borrowings	(203.0)	(139.4)	(170.0)
Proceeds from issuance of long-term debt	1.1	843.5	23.8
Repayments of long-term debt	(27.2)	(13.5)	(30.2)
Net Cash Used for Financing Activities	(2,229.5)	(1,575.4)	(2,984.2)
Effect of exchange rate changes on cash	(31.0)	(49.0)	25.0
Net increase (decrease) in cash and cash equivalents	414.5	2,204.7	(451.8)
Cash and cash equivalents at beginning of year	3,700.4	1,495.7	1,947.5
Cash and cash equivalents at end of year	$ 4,114.9	$ 3,700.4	$ 1,495.7

See notes to consolidated financial statements.

ZY 9553 927

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 28
5913-028
005803
Exhibit B, Page 28 of 32
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205107
Page 28

Segment Information

The company operates in one significant business segment—pharmaceutical products. Operations of the animal health business segment are not material and share many of the same economic and operating characteristics as pharmaceutical products. Therefore, they are included with pharmaceutical products for purposes of segment reporting.

Eli Lilly and Company and Subsidiaries (Dollars in millions) Year Ended December 31	2000	1999	1998
Net sales—to unaffiliated customers			
Neurosciences	$ 5,157.6	$ 4,729.3	$4,487.8
Endocrinology	2,583.5	2,075.5	1,626.6
Anti-infectives	894.3	1,022.3	1,160.9
Animal health	668.5	627.8	614.4
Cardiovascular	587.9	637.6	536.9
Oncology	580.5	486.1	339.2
Gastrointestinal	321.4	354.7	418.0
Other pharmaceutical	68.5	69.6	53.0
Net sales	$10,862.2	$10,002.9	$9,236.8
Geographic Information			
Net sales—to unaffiliated customers[1]:			
United States	$ 7,002.9	$ 6,226.4	$5,836.2
Western Europe	1,773.9	1,888.0	1,692.3
Other foreign countries	2,085.4	1,888.5	1,708.3
	$10,862.2	$10,002.9	$9,236.8
Long-lived assets:			
United States	$ 3,621.0	$ 3,416.8	$3,363.5
Western Europe	735.3	744.2	808.4
Other foreign countries	472.1	470.3	459.3
	$ 4,828.4	$ 4,631.3	$4,631.2

[1]Net sales are attributed to the countries based on the location of the subsidiary making the sale.

The largest category of products is the neurosciences group, which includes Prozac, Zyprexa, Permax®, and Darvon®. Endocrinology products consist primarily of Humulin, Evista, Humalog, Humatrope®, and Actos. Anti-infectives include primarily Ceclor®, Vancocin, Keflex®, Nebcin®, and Lorabid. Cardiovascular products consist primarily of ReoPro and Dobutrex®. The gastrointestinal category is entirely composed of Axid®. Oncology products consist primarily of Gemzar. Animal health products include Tylan®, Rumensin®, Micotil®, Surmax®, Coban®, and other products for livestock and poultry. The other pharmaceutical product group includes other miscellaneous pharmaceutical products and services.

Most of the pharmaceutical products are distributed through wholesalers that serve physicians and other health care professionals, pharmacies, and hospitals. In 2000, the company's three largest wholesalers each accounted for between 14 percent and 18 percent of consolidated net sales. Animal health products are sold primarily to wholesale distributors.

The company's business segments are distinguished by the ultimate end user of the product: humans or animals. Performance is evaluated based on profit or loss from operations before income taxes. The accounting policies of the individual segments are substantially the same as those described in the summary of significant accounting policies in Note 1. Income before taxes for the animal health business was approximately $180.0 million, $165.0 million, and $141.0 million in 2000, 1999, and 1998, respectively. The assets of the animal health business are intermixed with those of the pharmaceutical products business and are not separately determinable. Long-lived assets disclosed above consist of property and equipment and certain sundry assets of the continuing operations.

The company is exposed to the risk of changes in social, political, and economic conditions inherent in foreign operations, and the company's results of operations and the value of its foreign assets are affected by fluctuations in foreign currency exchange rates.

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 29
5913-029
005804

Exhibit B, Page 29 of 52
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI

ZY1 00205108
Page 29

Consolidated Statements of Comprehensive Income

Eli Lilly and Company and Subsidiaries (Dollars in millions) — Year Ended December 31	2000	1999	1998
Net income	$3,057.8	$2,721.0	$2,097.9
Other comprehensive income (loss):			
Foreign currency translation adjustments	(170.7)	(177.7)	69.2
Net unrealized gains (losses) on securities (Note 14)	(20.5)	27.8	(2.6)
Minimum pension liability adjustment	(33.6)	(26.7)	(30.8)
Other comprehensive income (loss) before income taxes	(224.8)	(176.6)	35.8
Provision for income taxes related to other comprehensive income items	20.0	—	15.6
Other comprehensive income (loss)	(204.8)	(176.6)	51.4
Comprehensive income	$2,853.0	$2,544.4	$2,149.3

See notes to consolidated financial statements.

ZY 9553 929

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 30
5913-030
005805

Exhibit B, Page 30 of 52
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI

ZY1 00205109
Page 30

Selected Quarterly Data (unaudited)

Eli Lilly and Company and Subsidiaries (Dollars in millions, except per-share data) 2000	Fourth	Third	Second	First
Net sales	$2,977.7	$2,811.9	$2,621.5	$2,451.1
Cost of sales	565.2	490.1	491.7	508.7
Operating expenses	1,489.4	1,306.4	1,304.2	1,146.8
Other (income) expense—net	(60.6)	17.0	(28.5)	(226.9)
Income before income taxes	983.7	998.4	854.1	1,022.5
Net income	767.3	778.8	666.2	845.5
Earnings per share—basic	.71	.72	.62	.78
Earnings per share—diluted	.70	.71	.61	.77
Dividends paid per share	.26	.26	.26	.26
Common stock prices:				
High	94.50	108.24	101.33	70.86
Low	80.64	67.18	64.13	54.34

1999	Fourth	Third	Second	First
Net sales	$2,820.5	$2,585.2	$2,341.6	$2,255.6
Cost of sales	565.2	548.2	491.1	493.5
Operating expenses	1,285.8	1,139.3	1,110.1	1,006.0
Asset impairment and other site charges	26.0	—	—	61.4
Other (income) expense—net	(80.2)	(41.5)	1.4	151.2
Income from continuing operations before income taxes	1,023.7	939.2	739.0	543.5
Income from: Continuing operations	786.3	732.6	576.4	451.4
Discontinued operations	—	—	—	174.3
Net income	786.3	732.6	576.4	625.7
Earnings per share—basic:				
Continuing operations	.73	.68	.53	.41
Discontinued operations	—	—	—	.16
Net income	.73	.68	.53	.57
Earnings per share—diluted:				
Continuing operations	.71	.67	.52	.40
Discontinued operations	—	—	—	.16
Net income	.71	.67	.52	.56
Dividends paid per share	.23	.23	.23	.23
Common stock prices:				
High	77.38	77.19	90.25	97.44
Low	64.13	61.50	65.19	76.19

The company's common stock is listed on the New York, London, Tokyo, and other stock exchanges.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 31
005806
5913-031
Exhibit B, Page 31 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205110
Page 31

Selected Financial Data (unaudited)

Eli Lilly and Company and Subsidiaries (Dollars in millions, except per-share data)	2000	1999	1998	1997	1996
Operations					
Net sales	$10,862.2	$10,002.9	$9,236.8	$7,987.7	$6,998.3
Research and development	2,018.5	1,783.6	1,738.9	1,370.2	1,189.5
Other costs and expenses	4,985.0	4,973.9	4,832.9	4,348.2	3,677.5
Gain on sale of DowElanco	—	—	—	(631.8)	—
Income from continuing operations before taxes and extraordinary item	3,858.7	3,245.4	2,665.0	2,901.1	2,131.3
Income taxes	800.9	698.7	568.7	885.2	505.6
Income (loss) from:					
Continuing operations before extraordinary item	3,057.8	2,546.7	2,096.3	2,015.9	1,625.7
Discontinued operations	—	174.3	8.8	(2,401.0)	(102.2)
Net income (loss)	3,057.8	2,721.0	2,097.9[2]	(385.1)	1,523.5
Income from continuing operations before extraordinary item as a percent of sales	28.2%	25.5%	22.7%	25.2%	23.2%
Per-share data—diluted:					
Income (loss) from:					
Continuing operations before extraordinary item	$ 2.79	$ 2.30	$ 1.87	$ 1.78	$ 1.45
Discontinued operations	—	.16	.01	(2.12)	(.09)
Net income (loss)	2.79	2.46	1.87[2]	(.34)	1.36
Dividends declared per share	1.06	.95	.83	.76	.694
Weighted-average number of shares outstanding—diluted (thousands)	1,097,725	1,106,055	1,121,486	1,130,579	1,117,110
Financial Position					
Current assets	$ 7,943.0	$ 7,055.5	$ 5,406.8	$ 5,320.7	$ 3,891.3
Current liabilities	4,960.7	3,935.4	4,607.2	4,191.6	4,222.2
Property and equipment—net	4,176.6	3,981.5	4,096.3	4,101.7	4,307.0
Total assets	14,690.8	12,825.2	12,595.5	12,577.4	14,307.2
Long-term debt	2,633.7	2,811.9	2,185.5	2,326.1	2,516.5
Shareholders' equity	6,046.9	5,013.0	4,429.6	4,645.6	6,100.1
Supplementary Data[1]					
Return on shareholders' equity	55.3%	53.9%	46.2%	37.5%	28.2%
Return on assets	22.9%	21.3%	17.0%	15.4%	11.4%
Capital expenditures	$ 677.9	$ 528.3	$ 419.9	$ 366.3	$ 443.9
Depreciation and amortization	435.8	439.7	490.4	509.8	543.5
Effective tax rate	20.8%	21.5%	21.3%	30.5%[3]	23.7%
Number of employees	35,700	31,300	29,800	28,900	27,400
Number of shareholders of record	59,190	62,300	62,300	58,200	54,500

1 All supplementary financial data have been computed using income from continuing operations except for capital expenditures and depreciation and amortization, which include amounts from discontinued operations. The number of employees reflects continuing operations, including controlled joint ventures.

2 Reflects the impact of an extraordinary item (see Note 7).

3 Excluding the impacts of the unusual transactions reflected in 1997, the effective tax rate would have been 24.1 percent.

ZY 9553 931

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 32
005807
5913-032
Exhibit B, Page 32 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205111
Page 32

Eli Lilly and Company and Subsidiaries
(Dollars in millions, except per-share data)

Note 1: Summary of Significant Accounting Policies

Basis of presentation: The accounts of all wholly owned and majority-owned subsidiaries are included in the consolidated financial statements. All intercompany balances and transactions have been eliminated.

The preparation of financial statements in conformity with generally accepted accounting principles requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenues, expenses, and related disclosures at the date of the financial statements and during the reporting period. Actual results could differ from those estimates.

All per-share amounts, unless otherwise noted in the footnotes, are presented on a diluted basis, that is, based on the weighted-average number of outstanding common shares and the effect of all potentially dilutive common shares (primarily unexercised stock options).

Reclassifications: Certain reclassifications have been made to prior-year amounts to conform with current-year presentation.

Cash equivalents: The company considers all highly liquid investments, generally with a maturity of three months or less, to be cash equivalents. The cost of these investments approximates fair value.

Inventories: The company states all its inventories at the lower of cost or market. The company uses the last-in, first-out (LIFO) method for substantially all its inventories located in the continental United States, or approximately 60 percent of its total inventories. Other inventories are valued by the first-in, first-out (FIFO) method. Inventories at December 31 consisted of the following:

	2000	1999
Finished products	$284.3	$295.1
Work in process	380.6	372.7
Raw materials and supplies	230.1	224.7
	895.0	892.5
Increase (decrease) to LIFO cost	(11.9)	7.1
	$883.1	$899.6

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Investments: All short-term debt securities are classified as held-to-maturity because the company has the positive intent and ability to hold the securities to maturity. Held-to-maturity securities are stated at amortized cost, adjusted for amortization of premiums and accretion of discounts to maturity. Substantially all long-term debt and marketable equity securities are classified as available-for-sale. Available-for-sale securities are carried at fair value, with the unrealized gains and losses, net of tax, reported in other comprehensive income. Realized gains and losses on sales of available-for-sale securities are computed based upon initial cost adjusted for any other than temporary declines in fair value. The company owns no investments that are considered to be trading securities.

Derivative financial instruments: The company's derivative activities, all of which are for purposes other than trading, are initiated within the guidelines of documented corporate risk-management policies and do not create additional risk because gains and losses on derivative contracts offset losses and gains on the assets, liabilities, and transactions being hedged. As derivative contracts are initiated, the company designates the instruments individually as hedges of underlying financial instruments or anticipated transactions (i.e., underlying exposures). Management reviews the correlation and effectiveness of its derivatives on a periodic basis. Derivative contracts that do not qualify for deferral hedge accounting are marked to market.

For terminations of derivatives receiving deferral accounting, gains and losses are deferred when the related underlying exposures remain outstanding and are included in the measurement of the related transaction or balance. In addition, upon termination of the underlying exposures, the derivative is marked to market and the resulting gain or loss is included with the gain or loss on the related transaction. The company may redesignate the remaining derivative instruments as hedges of other underlying exposures.

The company enters into foreign currency forward and option contracts to reduce the effect of fluctuating currency exchange rates (principally the Japanese yen and the euro). Generally, foreign currency derivatives used for hedging are put in place using the same or like currencies and duration as

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 33
005808
5913-033
Exhibit B, Page 33 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205112
Page 33

the underlying exposures. Forward contracts are principally used to manage exposures arising from affiliate foreign currency balances. These contracts are marked to market with gains and losses recognized currently in income to offset the respective losses and gains recognized on the underlying exposures. The company also enters into purchased option contracts to hedge anticipated foreign currency transactions, primarily intercompany inventory activities expected to occur within the next year, and foreign currency forward contracts and currency swaps to hedge firm commitments. The contracts are designated and effective as hedges of those future transactions. Gains and losses on these contracts that qualify as hedges are deferred and recognized as an adjustment of the subsequent transaction when it occurs. Forward and option contracts generally have maturities not exceeding 12 months.

The company also enters into interest rate swaps to manage interest rate exposures. The company designates the interest rate swaps as hedges of the underlying debt. Interest expense on the debt is adjusted to include the payments made or received under the swap agreements.

Goodwill and other intangibles: Goodwill and other intangibles arising from acquisitions and research alliances are amortized over their estimated useful lives, ranging from 5-25 years, using the straight-line method. Goodwill and other intangibles are reviewed to assess recoverability when impairment indicators are present. Assets are considered to be impaired and are written down to fair value if expected future operating cash flows of the related assets are less than their carrying amounts. Fair value is the present value of the expected future cash flows of the related assets using a discount rate commensurate with the risk involved. Assets are grouped at the lowest level for which there are identifiable cash flows for purposes of impairment testing. Goodwill and other intangibles and the related allowances for amortization were $233.2 million and $117.8 million, respectively, at December 31, 2000, and $226.2 million and $107.6 million, respectively, at December 31, 1999, and are included in sundry assets in the consolidated balance sheets.

Property and equipment: Property and equipment is stated on the basis of cost. Provisions for depreciation of buildings and equipment are computed generally by the straight-line method at rates based on their estimated useful lives (generally 12 to 50 years for buildings and 5 to 18 years for equipment). At December 31, property and equipment consisted of the following:

	2000	1999
Land	$ 103.5	$ 104.6
Buildings	2,395.1	2,255.8
Equipment	4,638.5	4,458.9
Construction in progress	647.6	528.0
	7,784.7	7,347.3
Less allowances for depreciation	3,608.1	3,365.8
	$4,176.6	$3,981.5

Depreciation expense related to continuing operations for 2000, 1999, and 1998 was $393.5 million, $406.7 million, and $393.4 million, respectively. Approximately $43.1 million, $29.0 million, and $17.0 million of interest costs were capitalized as part of property and equipment in 2000, 1999, and 1998, respectively. Total rental expense for all leases related to continuing operations, including contingent rentals (not material), amounted to approximately $172.3 million for 2000, $154.9 million for 1999, and $134.8 million for 1998. Capital leases included in property and equipment in the consolidated balance sheets, capital lease obligations entered into, and future minimum rental commitments are not material.

Revenue recognition: Revenue from sales of products is recognized at the time title of goods passes to the buyer and the buyer assumes the risks and rewards of ownership. This is generally at the time products are shipped to the customer. Revenue from copromotion services is recognized at the time the copromotion partner records sales.

Income taxes: Deferred taxes are recognized for the future tax effects of temporary differences between financial and income tax reporting based on enacted tax laws and rates. Federal income taxes are provided on the portion of the income of foreign subsidiaries that is expected to be remitted to the United States and be taxable.

Earnings per share: Basic earnings per share are calculated based on the weighted-average number of outstanding common shares and incremental shares. Diluted earnings per share are calculated based on the weighted-average number of outstanding common shares plus the effect of dilutive stock options and other incremental shares.

ZY 9553 933

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 34
005809
5913-034
Exhibit B, Page 34 of 52
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205113
Page 34

Note 2: Implementation of New Financial Accounting Pronouncements

In June 1998, Statement of Financial Accounting Standards (SFAS) No. 133, "Accounting for Derivative Instruments and Hedging Activities," was issued. Statement 133 was amended in June 1999 and is now required to be adopted in years beginning after June 15, 2000. The company will adopt Statement 133 effective as of January 1, 2001. The statement will require the company to recognize all derivatives on the balance sheet at fair value. Derivatives that are not hedges must be adjusted to fair value through income. If the derivative is a hedge, depending on the nature of the hedge, changes in the fair value of derivatives will either be offset against the change in fair value of the hedged assets, liabilities, or firm commitments through earnings or recognized in other comprehensive income until the hedged item is recognized in earnings. Hedge ineffectiveness, the amount by which the change in the value of a hedge does not exactly offset the change in the value of the hedged item, will be immediately recognized in earnings. The company estimates that the adoption of Statement 133 will not have a material effect on the consolidated results of operations or financial position of the company.

Note 3: Collaboration and Dispositions

During the first quarter of 2000, the company sold its interest in Kinetra LLC, a joint venture between the company and EDS, to WebMD Corporation (WebMD) in exchange for shares of WebMD common stock. A gain of $214.4 million was recognized on the combined effect of the transaction and the subsequent sale of the majority of those shares of WebMD stock. The gain is included in other income in the consolidated statements of income.

During 1999, the company recognized a pretax gain of $67.8 million on the sale of the U.S. and Puerto Rican marketing rights of Lorabid, an antibiotic used in the treatment of bacterial infections, to King Pharmaceuticals, Inc. The gain has been included in other income in the consolidated statements of income. The company has an opportunity to receive additional payments if certain sales performance milestones are achieved.

During 1998, the company announced a collaboration with ICOS Corporation to jointly develop and globally commercialize a phosphodiesterase type 5 (PDE5) inhibitor as an oral therapeutic agent for the treatment of male erectile dysfunction and female sexual dysfunction. The compound was in the development phase (Phase II clinical trials) and no alternative future uses were identified. As with many Phase II compounds, launch of the product, if successful, was not expected in the near term. The company's payments to acquire rights to this compound were required to be charged as an expense of $127.5 million.

Note 4: Discontinued Operations

In January 1999, the company sold PCS, its health-care-management subsidiary, to Rite Aid Corporation for $1.6 billion in cash. The transaction generated a gain of $174.3 million ($.16 per share), net of $8.7 million tax benefit, in the first quarter of 1999.

The results of operations of PCS have been classified as discontinued operations in the consolidated statements of income. Selected 1998 income statement information for PCS follows:

Revenues	$814.5
Income tax expense	32.2
Income from discontinued operations	8.8

Note 5: Asset Impairment and Other Site Charges

The company recognized two separate asset impairments and other site charges totaling $87.4 million in 1999 ($61.4 million and $26.0 million in the first and fourth quarters, respectively). The impairment charges were necessary to adjust the carrying value of certain manufacturing assets to fair value. The major portion of the charges ($75.0 million) related to the decommissioning of manufacturing buildings and the related equipment, which resulted from the consolidation of certain manufacturing processes. The company plans to continue ownership of the vacated buildings although no planned future uses have been identified. The fair values of the facilities were estimated based upon anticipated future cash flows, discounted at a rate commensurate with the risk involved.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 35
005810
5913-035
Exhibit B, Page 35 of 52
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205114
Page 35

Note 6: Financial Instruments

Risk-Management Instruments and Off-Balance-Sheet Risk

In the normal course of business, operations of the company are exposed to fluctuations in currency values and interest rates. These fluctuations can vary the costs of financing, investing, and operating. The company addresses a portion of these risks through a controlled program of risk management that includes the use of derivative financial instruments.

The notional amounts of derivatives summarized in the following paragraphs do not represent amounts exchanged by the parties and thus are not a measure of the exposure of the company through its use of derivatives. The company is exposed to credit-related losses in the event of nonperformance by counterparties to financial instruments, but it does not expect any counterparties to fail to meet their obligations given their high credit ratings.

At December 31, the stated, or notional, amounts of the company's outstanding derivative financial instruments were as follows:

	2000	1999
Forward exchange contracts	$1,384.9	$608.7
Foreign currency options—purchased	639.8	756.0
Interest rate swaps	445.0	295.0

Financial instruments that potentially subject the company to credit risk consist principally of trade receivables and interest-bearing investments. Wholesale distributors of life-sciences products and managed care organizations account for a substantial portion of trade receivables; collateral is generally not required. The risk associated with this concentration is mitigated by the company's ongoing credit review procedures. The company places substantially all its interest-bearing investments with major financial institutions, in U.S. government securities, or with top-rated corporate issuers. In accordance with documented corporate policies, the company limits the amount of credit exposure to any one financial institution.

Fair Value of Financial Instruments

A summary of the company's outstanding financial instruments at December 31 follows. As summarized, "cost" relates to investments while "carrying amount" relates to long-term debt.

	2000		1999	
	Cost/ Carrying Amount	Fair Value	Cost/ Carrying Amount	Fair Value
Short-term investments:				
Debt securities	$ 503.3	$ 504.3	$ 135.6	$ 136.0
Noncurrent investments:				
Marketable equity	79.8	90.1	63.9	96.8
Debt securities	266.2	271.2	35.6	35.6
Nonmarketable equity	7.5	7.5	14.9	14.9
Long-term debt, including current portion	2,796.6	2,861.7	3,026.7	2,990.6

The company determines fair values based on quoted market values where available or discounted cash flow analyses (principally long-term debt). The fair values of nonmarketable equity securities, which represent either equity investments in start-up technology companies or partnerships that invest in start-up technology companies, are estimated based on the fair value information provided by these ventures. The fair value and carrying amount of risk-management instruments were not material at December 31, 2000 and 1999.

At December 31, 2000 and 1999, the gross unrealized holding gains on available-for-sale securities were $24.3 million and $42.5 million, respectively, and the gross unrealized holding losses were $14.9 million and $12.6 million, respectively. Substantially all these gains and losses are associated with the marketable equity securities. The proceeds from sales of available-for-sale securities totaled $773.8 million, $56.2 million, and $36.3 million in 2000, 1999, and 1998, respectively. Purchases of available-for-sale securities totaled $443.0 million in 2000 and were not material in 1999 and 1998. Realized gains on sales of available-for-sale securities were $71.6 million, $25.0 million, and $20.6 million in 2000, 1999, and 1998, respectively. Realized losses on sales of available-for-sale securities were $16.5 million, negligible, and $2.5 million in 2000, 1999, and 1998, respectively. The net adjustment to unrealized gains and losses on available-for-sale

ZY 9553 935

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 36
5913-036
005811
Exhibit B, Page 36 of 52
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205115
Page 36

securities decreased other comprehensive income by $12.3 million in 2000 and increased other comprehensive income by $18.6 million in 1999.

Note 7: Borrowings

Long-term debt at December 31 consisted of the following:

	2000	1999
6.57 to 7.13 percent notes (due 2016–2036)	$1,000.0	$1,000.0
6.25 to 8.38 percent notes (due 2001–2006)	650.0	650.0
Floating rate capital securities (due 2029)	525.0	525.0
8.38 percent eurodollar bonds (due 2005)	150.0	350.0
Resettable coupon capital securities (due 2029)	300.0	300.0
6.55 percent ESOP debentures (due 2017)	97.6	98.6
Other, including capitalized leases	74.0	103.1
	2,796.6	3,026.7
Less current portion	162.9	214.8
	$2,633.7	$2,811.9

On August 5, 1999, the company issued $525.0 million floating rate capital securities and $300.0 million adjustable rate capital securities. These capital securities are subordinated to the notes, bonds, and debentures listed above. The floating rate capital securities pay cumulative interest at an annual rate equal to LIBOR plus a predetermined spread, reset quarterly. The rates at December 31, 2000 and 1999, were 7.951 percent and 7.355 percent, respectively. The securities may be redeemed any time on or after August 5, 2004, for a defined redemption price. The resettable coupon capital securities pay cumulative interest at an annual rate of 7.717 percent until August 1, 2004. At this date and every fifth anniversary thereafter, the interest rate will be reset equal to the weekly average interest rate of U.S. treasury securities having an index maturity of five years for the week immediately preceding the reset date plus a predetermined spread. The securities may be redeemed on August 1, 2004, and anytime thereafter for a defined redemption price.

The 6.55 percent Employee Stock Ownership Plan (ESOP) debentures are obligations of the ESOP but are shown on the consolidated balance sheet because they are guaranteed by the company. The principal and interest on the debt are funded by contributions from the company and by dividends received on certain shares held by the ESOP. Because of the amortizing feature of the ESOP debt, bondholders will receive both interest and principal payments each quarter. These debentures replaced other ESOP debentures pursuant to a refinancing in March 1998. An extraordinary charge of $7.2 million, net of a $4.8 million income tax benefit, was recorded as a result of this refinancing.

The aggregate amounts of maturities on long-term debt for the next five years are as follows: 2001, $162.9 million; 2002, $13.5 million; 2003, $212.0 million; 2004, $8.8 million; and 2005, $157.9 million.

At December 31, 2000 and 1999, short-term borrowings included $21.4 million and $26.7 million, respectively, of notes payable to banks. At December 31, 2000, unused committed lines of credit totaled approximately $2.01 billion. Compensating balances and commitment fees are not material, and there are no conditions that are probable of occurring under which the lines may be withdrawn.

Cash payments of interest on borrowings totaled $195.9 million, $170.6 million, and $188.2 million in 2000, 1999, and 1998, respectively.

Note 8: Stock Plans

Stock options are granted to employees at exercise prices equal to the fair market value of the company's stock at the dates of grant. Generally, options vest 100 percent three years from the grant date and have a term of 10 years. Performance awards are granted to officers and key employees and are payable in shares of the company's common stock. The number of performance award shares actually issued varies depending upon the achievement of certain earnings targets. In general, performance awards vest 100 percent at the end of the second fiscal year following the grant date.

In 1999, the company issued its third grant under the GlobalShares program. Essentially all employees were given an option to buy 100 shares of the company's stock at a price equal to the fair market value of the company's stock on the date of the grant. Options to purchase approximately 2.8 million shares were granted as part of the program. Individual grants generally become exercisable on or after the third anniversary of the grant date and have a term of 10 years.

ZY 9553 936

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 37
005812
5913-037
Exhibit B, Page 37 of 52
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205116
Page 37

The company has elected to follow Accounting Principles Board Opinion (APB) No. 25, "Accounting for Stock Issued to Employees" and related interpretations in accounting for its stock options and performance awards. Under APB No. 25, because the exercise price of the company's employee stock options equals the market price of the underlying stock on the date of grant, no compensation expense is recognized. Total compensation expense for stock-based performance awards reflected in income on a pretax basis was $88.3 million, $117.1 million, and $257.8 million in 2000, 1999, and 1998, respectively. However, SFAS No. 123, "Accounting for Stock-Based Compensation," requires presentation of pro forma information as if the company had accounted for its employee stock options and performance awards granted subsequent to December 31, 1994, under the fair value method of that statement. For purposes of pro forma disclosure, the estimated fair value of the options and performance awards at the date of the grant is amortized to expense over the vesting period. Under the fair value method, the company's net income and earnings per share would have been as follows:

	2000	1999	1998
Net income	$2,969.3	$2,639.6	$2,120.9
Earnings per share—diluted	2.70	2.39	1.89

The weighted-average per-share fair value of the individual options and performance awards granted during 2000, 1999, and 1998 were as follows on the date of grant:

	2000	1999	1998
Employee stock options	$29.25	$20.27	$16.64
Performance awards	93.06	66.50	88.88

The fair values of the options were determined using a Black-Scholes option-pricing model with the following assumptions:

	2000	1999	1998
Dividend yield	2.26%	2.73%	2.96%
Volatility	32.7%	25.2%	23.5%
Risk-free interest rate	5.02%	6.15%	4.29%
Forfeiture rate	0	0	0
Expected life	7 years	7 years	7 years

Stock option activity during 1998-2000 is summarized below:

	Shares of Common Stock Attributable to Options (in thousands)	Weighted-Average Exercise Price of Options
Unexercised at January 1, 1998	60,894	$24.05
Granted	6,803	74.18
Exercised	(13,697)	16.88
Forfeited	(1,047)	24.29
Unexercised at December 31, 1998	52,953	32.35
Granted	12,494	68.22
Exercised	(10,849)	19.04
Forfeited	(875)	50.46
Unexercised at December 31, 1999	53,723	43.08
Granted	1,315	86.75
Exercised	(9,242)	22.33
Forfeited	(671)	64.97
Unexercised at December 31, 2000	45,125	48.28

The following table summarizes information concerning outstanding and exercisable options at December 31, 2000 (shares in millions, contractual life in years):

	Options Outstanding			Options Exercisable	
Range of Exercise Prices	Number Outstanding	Weighted-Average Remaining Contractual Life	Weighted-Average Exercise Price	Number Exercisable	Weighted-Average Exercise Price
$10–$25	16.27	2.82	13.56	16.27	13.56
$25–$65	9.13	5.55	38.23	9.04	38.11
$65–$95	19.73	8.50	71.39	.82	71.97

ZY 9553 937
Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 38
005813
5913-038
Exhibit B, Page 38 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205117
Page 38

Shares exercisable at December 31, 2000, were 26.1 million (1999—29.9 million shares, 1998—35.8 million shares).

As noted above, the number of shares ultimately issued pursuant to the performance award program is dependent upon the earnings achieved during the vesting period. Pursuant to this plan, approximately 1.2 million shares, 2.2 million shares, and 1.5 million shares were issued in 2000, 1999, and 1998, respectively. At December 31, 2000, plan participants had the right to receive up to 4.1 million additional shares (reduced to the extent necessary to satisfy payroll tax withholdings), contingent upon earnings achieved.

At December 31, 2000, additional options, performance awards, or restricted stock grants may be granted under the 1998 Lilly Stock Plan and the Lilly GlobalShares Stock Plan, for not more than 32.8 million shares and 7.9 million shares, respectively.

Note 9: Shareholders' Equity

Changes in certain components of shareholders' equity were as follows:

	Additional Paid-in Capital	Retained Earnings	Deferred Costs—ESOP	Common Stock in Treasury Shares (in thousands)	Common Stock in Treasury Amount
Balance at January 1, 1998	$ —	$4,497.3	$(155.7)	1,000	$ 109.5
Net income		2,097.9			
Cash dividends declared per share: $.83		(908.9)			
Retirement of treasury shares	(2,035.2)			(29,010)	(2,053.3)
Purchase for treasury				28,350	2,005.8
Issuance of stock under employee stock plans	558.7			660	47.5
ESOP transactions	23.6		8.8		
Other	5.4	(10.0)		(5)	(0.5)
Reclassification	1,447.5	(1,447.5)			
Balance at December 31, 1998	—	4,228.8	(146.9)	995	109.0
Net income		2,721.0			
Cash dividends declared per share: $.95		(1,030.5)			
Retirement of treasury shares	(1,488.4)			(19,689)	(1,500.8)
Purchase for treasury				19,147	1,455.1
Issuance of stock under employee stock plans	530.6			542	45.7
ESOP transactions	20.8		7.0		
Other	3.3			(6)	(0.7)
Reclassification	933.7	(933.7)			
Balance at December 31, 1999	—	4,985.6	(139.9)	989	108.3
Net income		3,057.8			
Cash dividends declared per share: $1.06		(1,158.4)			
Retirement of treasury shares	(1,117.6)			(15,256)	(1,126.9)
Purchase for treasury				14,794	1,089.8
Issuance of stock under employee stock plans	405.6			494	39.8
Issuance of stock for employee benefit trust	2,610.0				
ESOP transactions	16.7		4.9		
Other	33.7	(0.2)		(14)	(1.5)
Reclassification	661.6	(661.6)			
Balance at December 31, 2000	$2,610.0	$6,223.2	$(135.0)	1,007	$ 109.5

As shown above, the company completed $1.09 billion of its announced $3.0 billion share repurchase program in 2000. A $1.5 billion share repurchase program was completed in 1999. The company acquired approximately 14.8 million and 19.1 million shares in 2000 and 1999, respectively, pursuant to these programs.

ZY 9553 938

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 39
005814
5913-039
Exhibit B_Page 39 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205118
Page 39

In connection with the share repurchase program, the company has entered into agreements to purchase shares of the company's stock. As of December 31, 2000, the company has agreements to purchase up to approximately 4.0 million shares of company stock from an independent third party at various times through the expiration of the agreements in December 2002, at prices ranging from $83 to $100 per share. The number of shares to be purchased will be reduced ratably each quarter through the expiration of the agreements. In addition, as of December 31, 2000, written equity put options, purchased call options, and other derivative contracts, which provide for purchase of a total of approximately 4.6 million shares, remain outstanding at prices ranging from $69 to $98 per share with expiration dates ranging from February 2001 to November 2002. If the options are exercised, the contracts allow the company, at its option, to repurchase the shares for cash or deliver to the holder cash or shares for the difference between the contractual exercise price and the market price of the company's stock. The company's objective with the above agreements is to reduce the average price of repurchased shares.

During the second quarter of 2000, the company funded an employee benefit trust with 40 million shares of Lilly common stock to provide a source of funds to assist the company in meeting its obligations under various employee benefit plans. The funding had no net impact on shareholders' equity as the employee benefit trust is consolidated with the company. The cost basis of the shares held in the trust was $2.64 billion and is shown as a reduction in shareholders' equity, which offsets the resulting increases of $2.61 billion in additional paid-in capital and $25 million in common stock. Any dividend transactions between the company and the trust are eliminated. Stock held by the trust is not considered outstanding in the computation of earnings per share.

The company has an ESOP as a funding vehicle for the existing employee savings plan. The ESOP used the proceeds of a loan from the company to purchase shares of common stock from the treasury. The ESOP issued $200 million of third-party debt, repayment of which was guaranteed by the company (see Note 7). The proceeds were used to purchase shares of the company's common stock on the open market. Shares of common stock held by the ESOP will be allocated to participating employees annually through 2017 as part of the company's savings plan contribution. The fair value of shares allocated each period is recognized as compensation expense.

Under a Shareholder Rights Plan adopted by the company's board of directors in 1998, all shareholders receive along with each common share owned a preferred stock purchase right entitling them to purchase from the company one one-thousandth of a share of Series B Junior Participating Preferred Stock (the "Preferred Stock") at a price of $325. The rights are not exercisable until after the "Distribution Date," which is generally the 10th business day after the date of a public announcement that a person (the "Acquiring Person") has acquired ownership of 15 percent or more of the company's common stock. The company may redeem the rights for $.005 per right up to and including the Distribution Date. The rights will expire on July 28, 2008, unless redeemed earlier by the company.

The plan provides that, if an Acquiring Person acquires 15 percent or more of the outstanding common stock of the company and the company's redemption right has expired, generally each holder of a right (other than the Acquiring Person) will have the right to purchase at the exercise price the number of shares of common stock of the company as have a value of two times the exercise price.

Alternatively, if, in a transaction not approved by the board of directors, the company is acquired in a business combination transaction or sells 50 percent or more of its assets or earning power after a Distribution Date, generally each holder of a right (other than the Acquiring Person) will have the right to purchase at the exercise price the number of shares of common stock of the acquiring company as have a value of two times the exercise price.

At any time after an Acquiring Person has acquired 15 percent or more but less than 50 percent of the company's outstanding common stock, the board of directors may exchange the rights (other than those owned by the Acquiring Person) for company common stock or Preferred Stock at an exchange ratio of one common share (or one one-thousandth of a share of Preferred Stock) per right.

ZY 9553 939

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 40
005815
5913-040

Exhibit B, Page 40 of 52
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI

ZY1 00205119
Page 40

Note 10: Earnings per Share

The following is a reconciliation of the numerators and denominators used in computing earnings per share from continuing operations before extraordinary item:

(Shares in thousands)	2000	1999	1998
Income from continuing operations before extraordinary item available to common shareholders:			
Income from continuing operations before extraordinary item	$3,057.8	$2,546.7	$2,096.3
Preferred stock dividends	—	(0.1)	(1.7)
Income from continuing operations before extraordinary item available to common shareholders	$3,057.8	$2,546.6	$2,094.6
Basic earnings per share:			
Weighted-average number of common shares outstanding, including incremental shares	1,081,559	1,087,652	1,095,834
Basic earnings per share from continuing operations before extraordinary item	$2.83	$2.34	$1.91
Diluted earnings per share:			
Weighted-average number of common shares outstanding	1,081,409	1,087,368	1,095,537
Stock options and other incremental shares	16,316	18,687	25,949
Weighted-average number of common shares outstanding—diluted	1,097,725	1,106,055	1,121,486
Diluted earnings per share from continuing operations before extraordinary item	$2.79	$2.30	$1.87

Note 11: Income Taxes

Following is the composition of income taxes attributable to continuing operations before extraordinary item:

	2000	1999	1998
Current:			
Federal	$ 928.4	$439.2	$322.1
Foreign	322.4	260.4	238.9
State	(7.2)	(4.9)	(8.9)
	1,243.6	694.7	552.1
Deferred:			
Federal	(81.2)	104.0	36.3
Foreign	(58.6)	22.4	9.4
State	.9	2.7	9.6
	(138.9)	129.1	55.3
Utilization of capital loss carryforwards	(303.8)	(125.1)	(38.7)
Income taxes	$ 800.9	$698.7	$568.7

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 41
005816
5913-041
Exhibit B, Page 41 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205120
Page 41

Significant components of the company's deferred tax assets and liabilities as of December 31 are as follows:

	2000	1999
Deferred tax assets:		
Tax credit carryforwards and carrybacks	$ 734.5	$ 496.0
Other carryforwards	450.4	243.9
Sale of intangibles	230.6	76.5
Capital loss carryforward	158.8	561.7
Compensation and benefits	109.0	188.8
Inventory	70.2	172.9
Other	378.6	300.4
	2,132.1	2,040.2
Valuation allowances	(408.0)	(703.4)
Total deferred tax assets	1,724.1	1,336.8
Deferred tax liabilities:		
Property and equipment	(527.7)	(527.2)
Prepaid employee benefits	(429.2)	(257.4)
Unremitted earnings	(182.0)	(381.9)
Other	(29.2)	(65.1)
Total deferred tax liabilities	(1,168.1)	(1,231.6)
Deferred tax assets—net	$ 556.0	$ 105.2

At December 31, 2000, the company had capital loss and other carryforwards for income tax purposes of $694.7 million: $643.4 million will expire within five years and $43.9 million thereafter; $7.4 million of the carryforwards will never expire. The company also has tax credit carryforwards of $734.5 million available to reduce future income taxes: $495.1 million will expire within five years and $183.2 million thereafter; $56.2 million of the tax credit carryforwards will never expire.

As discussed in Note 4, the company sold its PCS health-care-management subsidiary in January 1999. As a consequence of the sale, the company recorded a deferred tax asset of $655.3 million for the tax capital loss that resulted from this transaction. A portion of this loss carryforward has been used; the remainder can be carried forward four more years. A valuation allowance was established for this asset due to the uncertain realization of the benefit.

Domestic and Puerto Rican companies contributed approximately 56 percent, 56 percent, and 60 percent in 2000, 1999, and 1998, respectively, to consolidated income from continuing operations before income taxes and extraordinary item. Unremitted earnings of foreign subsidiaries that have been, or are intended to be, permanently reinvested for continued use in foreign operations and that, if distributed, would result in taxes at approximately the U.S. statutory rate aggregated $5.2 billion at December 31, 2000. Cash payments of income taxes totaled $294.0 million, $252.0 million, and $273.0 million in 2000, 1999, and 1998, respectively.

Following is a reconciliation of the effective income tax rate applicable to income from continuing operations:

	2000	1999	1998
United States federal statutory tax rate	35.0%	35.0%	35.0%
Add (deduct):			
International operations, including Puerto Rico	(12.9)	(7.5)	(10.5)
General business credits	(1.2)	(1.6)	(2.4)
Sundry	(0.1)	(4.4)	(0.8)
Effective income tax rate	20.8%	21.5%	21.3%

ZY 9553 941

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 42
005817
5913-042
Exhibit B, Page 42 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205121
Page 42

Note 12: Retirement Benefits

The change in benefit obligation, change in plan assets, funded status, and amounts recognized in the consolidated balance sheets at December 31 for the company's defined benefit pension and retiree health benefit plans were as follows:

	Defined Benefit Pension Plans		Retiree Health Benefits	
	2000	1999	2000	1999
Change in benefit obligation:				
Benefit obligation at beginning of year	$3,004.4	$2,898.8	$687.6	$621.5
Service cost	130.1	127.7	23.2	16.8
Interest cost	219.6	193.7	49.6	41.5
Actuarial loss	144.3	16.5	51.4	60.5
Benefits paid	(179.8)	(175.0)	(61.5)	(48.5)
Foreign currency exchange rate changes and other adjustments	61.5	(57.3)	1.0	(4.2)
Benefit obligation at end of year	3,380.1	3,004.4	751.3	687.6
Change in plan assets:				
Fair value of plan assets at beginning of year	3,532.0	3,069.6	332.1	252.5
Actual return on plan assets	138.7	543.6	(16.4)	80.4
Employer contribution	270.0	122.1	95.0	47.7
Benefits paid	(179.8)	(175.0)	(61.5)	(48.5)
Foreign currency exchange rate changes and other adjustments	(28.8)	(28.3)	—	—
Fair value of plan assets at end of year	3,732.1	3,532.0	349.2	332.1
Funded status	352.0	527.6	(402.1)	(355.5)
Unrecognized net actuarial (gain) loss	298.8	(36.0)	317.1	240.9
Unrecognized prior service cost (benefit)	227.2	119.3	(.1)	(1.1)
Unrecognized net obligation at January 1, 1986	1.7	2.0	1.8	—
Net amount recognized	$ 879.7	$ 612.9	$ (83.3)	$(115.7)
Amounts recognized in the consolidated balance sheet consisted of:				
Prepaid benefit cost	$1,032.5	$ 741.1	$ —	$ —
Accrued benefit liability	(302.9)	(237.6)	(83.3)	(115.7)
Intangible asset	41.1	34.0	—	—
Accumulated other comprehensive income before income taxes	109.0	75.4	—	—
Net amount recognized	$ 879.7	$ 612.9	$ (83.3)	$(115.7)

(Percents)	Defined Benefit Pension Plans		Retiree Health Benefits	
	2000	1999	2000	1999
Weighted-average assumptions as of December 31:				
Discount rate	7.4	7.4	7.5	7.5
Expected return on plan assets	10.5	10.5	10.5	10.5
Rate of compensation increase	3.5–8.0	3.5–8.0	—	—

Health-care-cost trend rates were assumed to increase at an annual rate of 6.5 percent in 2001 for participants under age 65, decreasing one-half percent to 6.0 percent in 2002 and thereafter. For participants over age 65, the rate was assumed to increase 6.0 percent in 2001 and thereafter.

The projected benefit obligation, accumulated benefit obligation, and fair value of the plan assets for the defined benefit pension plans with projected benefit obligations in excess of plan assets were $736.8 million, $616.8 million, and $381.6 million, respectively, as of December 31, 2000, and $637.1 million, $539.0 million, and $364.5 million, respectively, as of December 31, 1999.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 43
005818
5913-043
Exhibit B, Page 43 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205122
Page 43

Net pension and retiree health benefit expense included the following components related to continuing operations:

	Defined Benefit Pension Plans			Retiree Health Benefits		
	2000	1999	1998	2000	1999	1998
Components of net periodic benefit cost:						
Service cost	$130.1	$127.7	$112.9	$ 23.2	$ 16.8	$ 12.8
Interest cost	219.6	193.7	184.2	49.6	42.5	34.3
Expected return on plan assets	(341.0)	(295.1)	(277.1)	(30.1)	(24.2)	(23.0)
Amortization of prior service cost (benefit)	16.9	11.5	9.7	.1	—	(3.3)
Recognized actuarial loss	5.9	3.7	3.4	21.9	17.6	7.3
Net periodic benefit cost	$ 31.5	$ 41.5	$ 33.1	$ 64.7	$ 51.7	$ 28.1

The assumed health-care-cost trend rates have a significant effect on the amounts reported. If these trend rates were to be increased by one percentage point each future year, the December 31, 2000, accumulated postretirement benefit obligation would increase by 13 percent and the aggregate of the service cost and interest cost components of 2000 annual expense would increase by 15 percent. A one-percentage-point decrease in these rates would decrease the December 31, 2000, accumulated postretirement benefit obligation by 12 percent and the aggregate of the 2000 service cost and interest cost by 13 percent.

The company has defined contribution savings plans that cover its eligible employees worldwide. The purpose of these defined contribution plans is generally to provide additional financial security during retirement by providing employees with an incentive to make regular savings. Company contributions to the plan are based on employee contributions and the level of company match. Expenses under the plans related to continuing operations totaled $65.2 million, $56.4 million, and $50.3 million for the years 2000, 1999, and 1998, respectively.

The company provides certain other postemployment benefits primarily related to disability benefits and accrues for the related cost over the service lives of the employees. Expenses associated with these benefit plans in 2000, 1999, and 1998 were not significant.

Note 13: Contingencies

Barr Laboratories, Inc. (Barr), and Geneva Pharmaceuticals, Inc. (Geneva), have each submitted an Abbreviated New Drug Application (ANDA) seeking FDA approval to market generic forms of Prozac before the expiration of the company's patents. The ANDAs assert that two U.S. patents held by Lilly covering Prozac are invalid and unenforceable. The company filed suit against Barr and Geneva in federal court in Indianapolis seeking a ruling that Barr's challenge to Lilly's patents is without merit. In January 1999, the trial court granted summary judgment in favor of Lilly on two of the four claims raised by Barr and Geneva against Lilly's patents. That decision was appealed to the Court of Appeals for the Federal Circuit. Barr and Geneva dismissed their other two claims in exchange for a $4 million payment. On August 9, 2000, the Court of Appeals upheld the 2001 compound patent but held that the 2003 method of use patent was invalid. The company has filed a petition requesting a rehearing by the Court of Appeals.

Several other generic manufacturers have also filed ANDAs for generic forms of Prozac, challenging one or both of the patents. In late 1998, Zenith Goldline Pharmaceuticals, Inc.; Teva Pharmaceuticals USA (Teva); and Cheminor Drugs, Ltd., together with one of its subsidiaries (Cheminor), notified the company that they had filed ANDAs challenging the 2003 patent. Also in 1998, Novex Pharma, a division of Apotex, Inc., notified the company that it had filed an ANDA challenging both patents. In 1999, Cheminor notified the company that it had filed an ANDA for a different dosage form. In 2000, Barr and Teva both notified the company that they had filed additional ANDAs for the different dosage form, and Alphapharm Pty. Ltd. also notified the company that it had filed ANDAs for two dosage forms.

The company has filed lawsuits in the United States District Court of the Southern District of Indiana seeking rulings that all these challenges to the patent(s) are without merit. The cases are awaiting resolution of the petition for rehearing by the Court of Appeals in the original Barr case.

Assuming the Prozac patent ruling is not overturned, the company expects a very substantial decline in Prozac sales in the U.S. in the 12 months following the entry of generic fluoxetine in the U.S. market in August 2001. Prozac sales in the U.S. represent a significant portion of the company's overall sales, accounting for approximately 20 percent of the company's consolidated worldwide sales in 2000. The company believes that the Prozac patent litigation will not have a material adverse effect on the company's consolidated financial position or liquidity.

ZY 9553 943

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 44
005819
5913-044
Exhibit B, Page 44 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205123
Page 44

The company has been named as a defendant in numerous product liability lawsuits involving primarily two products, diethylstilbestrol (DES) and Prozac. The company has accrued for its estimated exposure with respect to all current product liability claims. In addition, the company has accrued for certain claims incurred, but not filed, to the extent the company can formulate a reasonable estimate of their costs. The company's estimates of these expenses are based primarily on historical claims experience and data regarding product usage. The company expects the cash amounts related to the accruals to be paid out over the next several years. The majority of costs associated with defending and disposing of these suits are covered by insurance. The company's estimate of insurance recoverables is based on existing deductibles, coverage limits, and the existing and projected future level of insolvencies among its insurance carriers.

Under the Comprehensive Environmental Response, Compensation, and Liability Act, commonly known as Superfund, the company has been designated as one of several potentially responsible parties with respect to fewer than 10 sites. Under Superfund, each responsible party may be jointly and severally liable for the entire amount of the cleanup. The company also continues remediation of certain of its own sites. The company has accrued for estimated Superfund cleanup costs, remediation, and certain other environmental matters, taking into account, as applicable, available information regarding site conditions, potential cleanup methods, estimated costs, and the extent to which other parties can be expected to contribute to payment of those costs. The company has reached a settlement with its primary liability insurance carrier and certain excess carriers providing for coverage for certain environmental liabilities. Litigation seeking coverage from certain other excess carriers is ongoing.

The environmental liabilities and litigation accruals have been reflected in the company's consolidated balance sheet at the gross amount of approximately $138.9 million at December 31, 2000. Estimated insurance recoverables of approximately $74.1 million at December 31, 2000, have been reflected as assets in the consolidated balance sheet.

The company recognized a pretax gain of $110.0 million as a result of a cash payment received in settlement of litigation with Biochimica Opos S.p.A. relating to the manufacture, sale, or distribution of cefaclor and certain other products made by Biochimica Opos S.p.A. The gain, which was recorded in other income, increased earnings per share by approximately $.06 in the fourth quarter of 1999.

While it is not possible to predict or determine the outcome of the patent, product liability, or other legal actions brought against the company or the ultimate cost of environmental matters, the company believes that, except as noted above with respect to the Prozac patent litigation, the costs associated with all such matters will not have a material adverse effect on its consolidated financial position or liquidity but could possibly be material to the consolidated results of operations in any one accounting period.

Note 14: Other Comprehensive Income

The accumulated balances related to each component of other comprehensive income were as follows:

	Foreign Currency Translation	Unrealized Gains (Losses) on Securities	Minimum Pension Liability	Accumulated Other Comprehensive Income
Beginning balance at January 1, 2000	$(375.6)	$ 20.1	$(50.9)	$(406.4)
Other comprehensive income (loss)	(170.7)	(12.3)	(21.8)	(204.8)
Balance at December 31, 2000	$(546.3)	$ 7.8	$(72.7)	$(611.2)

The amounts above are net of income taxes. The income taxes related to other comprehensive income were not significant as income taxes were generally not provided for foreign currency translation.

The unrealized gains (losses) on securities is net of reclassification adjustments of $43.9 million, $8.5 million, and $4.8 million, net of tax, in 2000, 1999, and 1998, respectively, for realized gains and losses on sales of securities included in net income.

Generally, the assets and liabilities of foreign operations are translated into U.S. dollars using the current exchange rate. For those operations, changes in exchange rates generally do not affect cash flows; therefore, resulting translation adjustments are made to shareholders' equity rather than to income.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 45
005820
5913-045
Exhibit B, Page 45 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205124
Page 45

Responsibility for Financial Statements

Eli Lilly and Company and Subsidiaries

The consolidated financial statements and related notes have been prepared by management, who are responsible for their integrity and objectivity. The statements have been prepared in accordance with generally accepted accounting principles and include amounts based on judgments and estimates by management. The other financial information in this annual report is consistent with that in the financial statements.

The company maintains internal accounting control systems that are designed to provide reasonable assurance that assets are safeguarded, that transactions are executed in accordance with management's authorization and are properly recorded, and that accounting records are adequate for preparation of financial statements and other financial information. The design, monitoring, and revision of internal accounting control systems involve, among other things, management's judgments with respect to the relative cost and expected benefits of specific control measures. A staff of internal auditors regularly monitors, on a worldwide basis, the adequacy and effectiveness of internal accounting controls.

In addition to the system of internal accounting controls, the company maintains guidelines of company policy emphasizing proper overall business conduct, possible conflicts of interest, compliance with laws, and confidentiality of proprietary information. The guidelines are reviewed on a periodic basis with employees worldwide.

The financial statements have been audited by Ernst & Young LLP, independent auditors. Their responsibility is to examine the company's financial statements in accordance with generally accepted auditing standards and to express their opinion with respect to the fairness of presentation of the statements.

The members of the audit committee of the board of directors, none of whom are employees of the company, recommend independent auditors for appointment by the board of directors, review the services performed by the independent auditors, and receive and review the reports submitted by them. The audit committee meets several times during the year with management, the internal auditors, and the independent auditors to discuss audit activities, internal controls, and financial reporting matters. The internal auditors and the independent auditors have full and free access to the committee.

Sidney Taurel, Chairman of the Board, President, and Chief Executive Officer

Charles E. Golden, Executive Vice President and Chief Financial Officer

January 29, 2001

ZY 9553 945

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 46
005821
5913-046
Exhibit B, Page 46 of 52
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205125
Page 46

Report of Independent Auditors

Board of Directors and Shareholders
Eli Lilly and Company

We have audited the accompanying consolidated balance sheets of Eli Lilly and Company and subsidiaries as of December 31, 2000 and 1999, and the related consolidated statements of income, cash flows, and comprehensive income for each of the three years in the period ended December 31, 2000. These financial statements are the responsibility of the company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with auditing standards generally accepted in the United States. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Eli Lilly and Company and subsidiaries at December 31, 2000 and 1999, and the consolidated results of their operations and their cash flows for each of the three years in the period ended December 31, 2000, in conformity with accounting principles generally accepted in the United States.

Ernst & Young LLP

Indianapolis, Indiana
January 29, 2001

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 47
5913-047
005822

Exhibit B Page 47 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205126
Page 47

Board of Directors

Sidney Taurel
Chairman of the Board, President, and Chief Executive Officer

Steven C. Beering, M.D.[2,3,6]
President Emeritus, Purdue University

Sir Winfried F. W. Bischoff[1,3]
Chairman, Citigroup Europe

George M. C. Fisher[2,6]
Retired Chairman of the Board and Chief Executive Officer, Eastman Kodak Company

Alfred G. Gilman, M.D., Ph.D.[3,5]
Regental Professor and Chairman, Department of Pharmacology, The University of Texas Southwestern Medical Center

Charles E. Golden[4]
Executive Vice President and Chief Financial Officer

Karen N. Horn, Ph.D.[2,4,5]
President, Marsh Private Client Services, Marsh, Inc.

Kenneth L. Lay, Ph.D.[2,4,5]
Chairman of the Board, Enron Corp.

Franklyn G. Prendergast, M.D., Ph.D.[1,3,6]
Edmond and Marion Guggenheim Professor of Biochemistry and Molecular Biology and Director, Mayo Clinic Cancer Center

Kathi P. Seifert[1,3,4]
Executive Vice President, Kimberly-Clark Corporation

August M. Watanabe, M.D.[6]
Executive Vice President, Science and Technology

Alva O.Way[1,2,5]
Chairman of the Board, IBJ Whitehall Bank & Trust Company

Board Committees
1 Audit Committee
2 Compensation Committee
3 Public Policy Committee
4 Finance Committee
5 Directors and Corporate Governance Committee
6 Science and Technology Committee

ZY 9553 947

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 48
5913-048
005823

Exhibit B, Page 48 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205127
Page 48

LEFT: BOARD OF DIRECTORS
[Standing, left to right] Sidney Taurel; Steven C. Beering, M.D.; Alfred G. Gilman, M.D., Ph.D.; Sir Winfried F. W. Bischoff; Kathi P. Seifert; Kenneth L. Lay, Ph.D.; August M. Watanabe, M.D.; Franklyn G. Prendergast, M.D., Ph.D. [Seated, left to right] Alva O. Way; Charles E. Golden; George M. C. Fisher; Karen N. Horn, Ph.D.

RIGHT: POLICY COMMITTEE
[Standing, left to right] Sidney Taurel; August M. Watanabe, M.D.; John C. Lechleiter, Ph.D.; Rebecca O. Kendall. [Seated, left to right] Gerhard N. Mayr; Pedro P. Granadillo; Charles E. Golden.

Senior Management

Sidney Taurel [A,B]
Chairman of the Board, President, and Chief Executive Officer

Charles E. Golden [A,B]
Executive Vice President and Chief Financial Officer

Pedro P. Granadillo [A,B]
Senior Vice President, Human Resources and Manufacturing

Rebecca O. Kendall [A,B]
Senior Vice President and General Counsel

John C. Lechleiter, Ph.D. [A,B]
Executive Vice President, Pharmaceutical Products and Corporate Development

Gerhard N. Mayr [A,B]
Executive Vice President, Pharmaceutical Operations

August M. Watanabe, M.D. [A,B]
Executive Vice President, Science and Technology

Bryce D. Carmine [B]
President, Primary Care Products

Newton F. Crenshaw [B]
Vice President, e.Lilly

Richard D. DiMarchi, Ph.D. [B]
Group Vice President, Research Technologies and Product Development

W. Roy Dunbar [B]
Vice President and Chief Information Officer

Michael L. Eagle [B]
Vice President, Manufacturing

Brendan P. Fox, D.V.M. [B]
President, Elanco Animal Health

James A. Harper [B]
Group Vice President, Global Marketing and Sales

Elizabeth H. Klimes [B]
President, Diabetes and Growth Disorders Products

Steven M. Paul, M.D. [B]
Group Vice President, Therapeutic Area Discovery Research and Clinical Investigation

Richard D. Pilnik [B]
President, European Operations

Gino Santini [B]
President, U.S. Operations

Lorenzo Tallarigo, M.D. [B]
President, Intercontinental Operations

Albertus J. van den Bergh [B]
President, Neuroscience Products

Alfonzo M. G. Zulueta [B]
President, Oncology and Critical Care Products

Senior Management Committees
A Policy Committee
Establishes corporate strategy and policy and ensures compliance
B Senior Management Forum
Implements corporate strategies and ensures corporate performance, identifies issues and opportunities, and facilitates communication and learning

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 49
005824
5913-049
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205128
Page 49

Corporate Information

Annual meeting

The annual meeting of shareholders will be held at the Hilbert Circle Theatre, 45 Monument Circle, Indianapolis, Indiana, on Monday, April 16, 2001. Formal notice of the meeting, together with the proxy statement and form of proxy, is sent to each holder of common stock.

10-K and 10-Q reports

The company's Annual Report to the Securities and Exchange Commission on Form 10-K will be available in April. Quarterly reports on Form 10-Q are also available upon request. Anyone wishing to receive copies of the company's 10-K or 10-Q reports may send a written request to:

Eli Lilly and Company
P.O. Box 88665
Indianapolis, Indiana 46208-0665

or access these reports electronically on the Internet. Lilly's address on the Internet is http://www.lilly.com

Stock listings

Eli Lilly and Company common stock is listed on the U.S. New York and Pacific stock exchanges and the London, Tokyo, and Swiss stock exchanges. NYSE ticker symbol: LLY

Transfer agent and registrar

Wells Fargo Shareowner Services
Mailing address:
Shareowner Relations Department
P.O. Box 64854
St. Paul, Minnesota 55164-0854
Overnight address:
161 North Concord Exchange
South St. Paul, Minnesota 55075
Telephone: 1-800-833-8699
E-mail: stocktransfer@wellsfargo.com
Internet: http://www.wellsfargo.com/com/shareowner_services

Environmental report

Eli Lilly and Company's Environmental, Health and Safety Report, which summarizes the company's efforts in these areas, is available on the Internet. The address is http://www.lilly.com/environment

Dividend reinvestment and stock purchase plan

Wells Fargo Shareowner Services administers the Shareowner Service Plus Plan, which allows registered shareholders to purchase additional shares of Lilly common stock through the automatic investment of dividends. The plan also allows registered shareholders and new investors to purchase shares with cash payments, either by check or by automatic deductions from checking or savings accounts. The minimum initial investment for new investors is $1,000. Subsequent investments must be at least $50. The maximum cash investment during any calendar year is $150,000.

Please direct inquiries concerning the Shareowner Service Plus Plan to:

Wells Fargo Shareowner Services
Shareowner Relations Department
P.O. Box 64854
St. Paul, Minnesota 55164-0854
Telephone: 1-800-833-8699

Online delivery of proxy materials

Registered shareholders may now elect to receive annual reports and proxy materials online. This reduces paper mailed to the shareholder's home and saves the company printing and mailing costs. To enroll, go to http://proxyonline.lilly.com and follow the directions provided.

Trademarks

Actos® (pioglitazone, Takeda), Takeda
Alimta™ (multitargeted antifolate, Lilly)
Axid® (nizatidine, Lilly), Reliant Pharmaceuticals LLC
Ceclor® (cefaclor, Lilly)
Cialis™ (IC351), Lilly-ICOS LLC
Coban® (monensin sodium, Elanco)
Darvon® (propoxyphene hydrochloride, Lilly)
Dobutrex® (dobutamine hydrochloride, Lilly)
Evista® (raloxifene hydrochloride, Lilly)
Forteo™ (teriparatide, Lilly)
Gemzar® (gemcitabine hydrochloride, Lilly)
Humalog® (insulin lispro injection of recombinant DNA origin, Lilly)
Humalog® Mix75/25™ (75% insulin lispro protamine suspension 25% insulin lispro injection of recombinant DNA origin, Lilly)
Humatrope® (somatropin of recombinant DNA origin, Lilly)
Humulin® (human insulin of recombinant DNA origin, Lilly)
Iletin® (insulin, Lilly)
Keflex® (cephalexin, Dista)
Lorabid® (loracarbef, Lilly), King Pharmaceuticals, Inc.
Micotil® (tilmicosin, Lilly)
Nebcin® (tobramycin sulfate, Lilly)
Permax® (pergolide mesylate, Lilly)
Prozac® (fluoxetine hydrochloride, Dista)
ReoPro® (abciximab, Centocor), Lilly
Rumensin® (monensin sodium, Elanco)
Sarafem™ (fluoxetine hydrochloride, Lilly)
Surmax® (avilamycin, Elanco)
Tylan® (tylosin, Elanco)
Vancocin® (vancomycin hydrochloride, Lilly)
Zyprexa® (olanzapine, Lilly)
Zovant™ (proposed trade name for drotrecogin alfa (activated), Lilly)

Actos® is a registered trademark of Takeda Chemical Industries, Ltd.
Axid® is a registered trademark of Reliant Pharmaceuticals LLC
Cialis™ is a trademark of Lilly-ICOS LLC.
EVA® is a registered trademark of Stern Stewart & Co.
Lorabid® is a registered trademark of King Pharmaceuticals, Inc.

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ZY 9553 949

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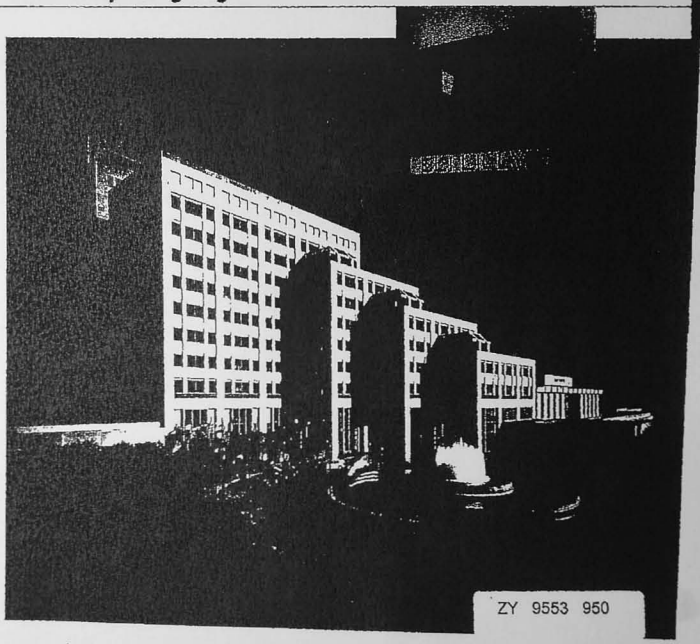
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 50
005825
5913-050
Exhibit B, Page 50 of 52
SOA Request for Clarification of the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00205129
Page 50

Our people do. There were only four of them when Lilly opened its doors on Pearl Street in Indianapolis in 1876. Today, as we celebrate our 125th year in business, they number more than 35,700 worldwide.

With passion for their work and for the welfare of patients, Lilly employees have exemplified the company's values and driven its success. They have been steadfast in their commitment through the ups and downs of external history and the rewards and pain of internal expansion and culture change. They are, indeed, the source of all that we are and all that we have achieved for the advance of medicine.

The people of Eli Lilly and Company have brought us this far, and it's Lilly people who will take us forward over the next 125 years.

What keeps us going?



ZY 9553 950

Lilly

Answers That Matter.

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
www.lilly.com

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
5913-001 / 52
005827
5913-052

Bill Robinson

Vice President
US Sales and Marketing

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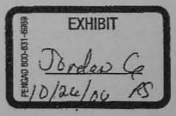
ZYZ00370634



YOU make us Number 1 !!!

YOU, the Neuroscience division of Lilly:

- Made us "Number 1" in the **PAST** with:
  Prozac - Depression
- Are **NOW** making us "Number 1" with:
  Zyprexa, redacted - Schizophrenia, Bipolar Mania, Depression

redacted

Thank You for making us "Number 1":

PAST, PRESENT, ALWAYS!

Zyprexa MDL 1596; Confidential-Subject to Protective Order
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ph 3/12 @ 4:30pm

AW-11-01 3:30PM

ZYPREXA PRIMARY CARE PRESENTATION

MIKE BANDICK ZYPREXA BRAND MANAGER

ELI LILLY NATIONAL SALES MEETING, MARCH 13, 2001

[MIKE:

Good afternoon,

Team Viva!

We're here to do

3 things:

1) We're going to have fun --

in the Viva Tradition!

2) We're going to focus on winning:

What we've accomplished and where we're headed.

3) We're going to reflect on why we do what we do, and the impact of our efforts on real people.

It's profound to think that in the few short months since we

ZY 7119 1345

launched in Orlando,
we have helped nearly 50,000 new patients.

For me, personally,
this is why I am so passionate about Zyprexa.

Because I've seen first hand what it can do for patients and their families.

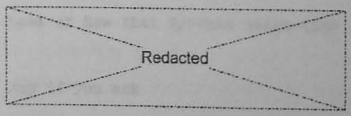
What you do --
is extremely important.

It's a big responsibility.

And an awesome opportunity.

The results would suggest that,
so far, you're up to the challenge.

We usually measure share change in tenths of a point, up or down.



ZY 7119 1346

Simply outstanding.

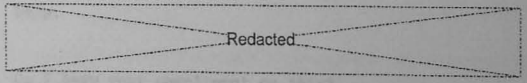
And it's important to note that during our first 3 months, we had limited frequency and limited customer programs.

Just imagine the added impact that better sales messages, competitive differentiation and peer-to-peer activity will have on our future sales line.

Don't get me wrong--
unit share growth is good, and what we have accomplished in that area has not gone unnoticed.

But dollars pay the bills and boost the stock price,
so let's look at
$ growth.

Again, we're redefining the market.



ZY 7119 1347

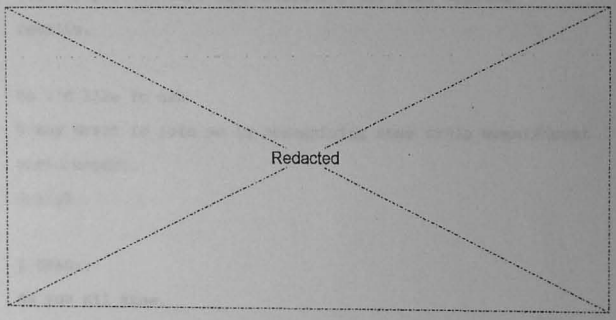
Look at how that Zyprexa sales line jumps.

And if you ask

Bill Robinson,

our timing is impeccable.

This is Year X for Eli Lilly, and the conventional wisdom is that companies just don't "bounce back" from losing patent protection from their biggest product.



We need to OWN this target, because the affiliate needs our help.

Do I have your commitment on this?

I personally challenge each of you drive toward a goal that will help turn Year X into Year X-ceptional.

ZY 7119 1348

Behind every strong team performance is a list of standout individual contributions,
and it's important to recognize those individuals and their success.

It's especially appropriate to do this with Sigma, since each of you has sole accountability for your Zyprexa results.

So I'd like to ask
Grady Grant to join me in recognizing some truly magnificent performances.
Grady?

[GRADY:
As you all know,
we're now in a special time of year called
March Madness,
and in that spirit,
it gives me great pleasure to recognize the Zyprexa Primary Care "Sweet Sixteen,"
16 sales representatives whose individual performance during the last two months of 2000 was nothing short of outstanding.

ZY 7119 1349

Please stand when I call your name, and stay standing as we go through the four areas.

And let's hold the applause until the end, but it's fine with me if you want to shout your support when a teammate's name is called.

Behind me on the JumboTron scoreboard, you'll see a photo and some key stats.

First, from the Northeast:

Jeffrey Heshler,
DuBois, Pennsylvania
+42

Marla Cutler,
Penns Landing, Pennsylvania
+46

Brian Adelson,
Glens Falls,
New York
+49

ZY 7119 1350

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Zyprexa MDL Plaintiffs' Exhibit No.01079
1079-001 / 6
1079-006
005837

Exhibit E, Page 6 of 7
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI
ZY1 00041635
Page 6

Virginia Taylor,

Lynchburg, Virginia

+49

Next, let's hear it for the top four in the Midwest:

Jim Fondon,

Muncie, Indiana

+55

My Hoang,

Dearborn, Michigan

+69

Mary Jo Kirwan,

Sioux City, Iowa

+69

Richard Offenhauser,

Mankato, Minnesota

+78

Give it up for the West:

ZY 7119 1351

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Zyprexa MDL Plaintiffs' Exhibit No.01079
1079-001 / 7
005838
1079-007

Exhibit E, Page 7 of 7
SOA Request for Clarification of
the Court's Order re: Net Worth
Case No. 3AN-06-5630 CI

ZY1 00041636
Page 7

Zyprexa Product Team Off-site
July 25, 2001

Lilly
Answers That Matter.

TORRES
EXHIBIT NO. 2
12-15-06
L. GOLKOW

Objectives

Morning

Review Brand Architecture

Develop vision, value drivers, CSFs for Product Team

Begin identifying the culture required to achieve our vision

Discuss next steps

Afternoon

"Challenge Team" review with Working Team

Kick-off Next Steps

Agenda

8-8:30	Opening, Review of Brand Architecture and Implications
9-11	Vision, Value Drivers and CSFs
11:00-11:30	Culture Discussion (from-to)
11:30-12	Next Steps
12-1	Lunch
1-3:30	Review with Working Team
3:30-5	Kick-off Next Steps

The Chance to Make History

Olanzapine: the **first** team to dramatically speed time to registration ... making history and setting the new Lilly ***registration standard***

Zyprexa: the **first** team to achieve excellence in global product uptake ... making history and setting the new pharma industry ***launch standard***

Zyprexa: the **first** team with the **opportunity** to set the all industry ***commercialization standard*** for the most successful pharma brand in history

Straight Talk - What's at Stake

The company is betting the farm on Zyprexa ... the ability of Eli Lilly to remain independent and emerge as the fastest growing pharma company of the decade depends solely on our ability to achieve *world class commercialization of Zyprexa*

If we succeed, Zyprexa will be the most successful pharmaceutical product ever ... we will have made history

Leadership Wish List

Vision and/or "burning platform" for team change .... In order to engage team members in the need for continued improvement

Clarity of what we mean by "world class commercialization" and what this will take

World-class integration of medical/marketing in strategy and operation

Integrated strategy-driven team decisions for aligned impact

Optimizing Our Work

What is change in the product team work?

- Zyprexa launch focus ⟶ Brand focus
- are there gaps?
- how well do work priorities match strategy?

Is there non-focus work?

Are we clear on roles?

- product team v Brand teams in 'top 10'
- product team v non-top 10 countries

How well do we do the work? (GMAP, other)

Implications of Brand Architecture

What has changed?

What has stayed the same?

What are some early thoughts on what this mean's for the work that we do today?

Visioning (the whats)

Defining success...

Who are our customers?

What would success look like to our external customers?

What would success look like to our internal partners?

How would our competition describe us?

How would we be distinguished from our competitors in the eyes of our customers?

What would our competitive advantage be? How would we build and sustain it?

Value Drivers and CSFs (the hows)

Value Drivers

What are the top key levers which will enable *us* to achieve this vision?

Critical Success Factors

What must we achieve with each of these levers in order to achieve this vision

Describing Our Culture: current and future

illustrative

FROM	TO
Beauracratic and slow	To flexible and fast
Consensus-driven	Single point of accountability

Components of Culture include:

Leadership and management behaviors

"Unwritten" rules

Established processes

Reward and recognition processes

Communication processes, frequency, style, etc.

Other???

Next Steps

Agree on objectives for this afternoon's "challenge team" review

Discuss overall next steps

- Objectives
- Scope
- Timing
- Roles and responsibilities

Agenda

1-2:30 Review of Vision, Value Drivers and CSFs

2:30-3 Discuss/finalize next steps

Back-up Slides

Value Driver Team Formation

What

Who

When

Design Team

Decision Makers

Team Sponsor: Alan Breier

Team Leaders: Vin Rampey, Denice Torres

Medical: Mauricio Tohen

Project Mgr and Communications: Jennifer Beaulieu

Medical: Patrizia Cavazzoni, John Krueger

GMAP incorporation: Bill Hess

Marketing: John Bamforth, Tim Parshall

Scientific Communications: Jeff Ramsey

Marketing: Tim Parshall

Market Research: Ralph Robinson

Support

Process Owner: Karl Lyon

Process Consultant/US Integration: Mel Halkyard

Observers:

GMAP: Gayle Crick

GMSO: Chad McBride

Process Overview.. its all about building capabilities

Brand Architecture delivered positioning

↓

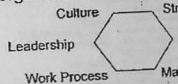
Create vision, value drivers and objectives for the product team to realize this new positioning

↓

Identify capabilities required to reach this vision

↓

Design organization required to build these capabilities



Expected Deliverables to include

Identification of short and long-term priorities
Key Value Drivers
Required meeting structure
Communication processes with affiliates and within PT
PR process
Thought Leader Development Process
Best Practice ID and sharing
Issues Management Process
Review and tracking of key metrics
Marketing Planning Process
Competitive Info Collection, Analysis and Dissemination
Clearly defined roles and responsibilities
Process for budgeting and buy-up submissions
Coordination with the US
Team Building
New Marketing orientation
CT strategy, integration and management
Regulatory and label reviews
Product formulation and innovation processes
Process for reviewing promotional items
Pricing strategy process
Supply chain and production management
Congress and GMC management
Scientific communications strategy and management process
Publication strategy and execution
CT prioritization
Registration process for top 10 affiliates
Team governance structure

Team Charter

Draft to be determined by working team

POD Timeline and Milestones

Phase I: Brand Architecture		**Completed**
Phase II: Celebration/Kick off of POD		**July 24**
Working Team Kick-off Meeting	4 hours	**July 25**
Develop Charter and Operating Principles		
Review Vision, objectives/Value Drivers		
Phase III: Working Team Meeting	2 days	**August 16, 17 (tbd)**
Identify/classify/assess capabilities required to achieve position		
Validation of vision/value drivers/strategies/capabilities		**August 17-September 17**
GMAP findings	1 day	**August 24**
Phase IV: Working Team Meeting	2 days	**September 16, 17**
Review/finalize capabilities Prioritize capability gaps Develop organizational design criteria Determine organizational structure option and micro design elements Develop Change Agenda		
IMPLEMENTATION		**October 1**

Our Operating Principles

What are our boundaries?

How will we make decisions?

How will we operate when team members are absent?

How/when will we seek approval?

How do we want to communicate with the stakeholders?

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

vs.

ELI LILLY AND COMPANY,

Defendant.

RECEIVED
Chambers of
Judge Rindner
FEB 25 REC'D
State of Alaska Superior Court
Third Judicial District
in Anchorage

Case No. 3AN-06-5630 CIV

NOTICE OF FILING UNDER SEAL

On this date the State of Alaska is filing a pleading titled "**Request for Clarification of the Court's Order Excluding Testimony or Argument Regarding Other Drugs Manufactured by Defendant Eli Lilly and Company**." Because one or more exhibits filed with this pleading may be confidential documents under the Court's April 6, 2007 oral ruling, the State of Alaska is submitting this pleading and the attached exhibits under seal.

DATED this 25th day of February, 2008.

FELDMAN ORLANSKY & SANDERS
Counsel for Plaintiff

BY _____
Eric T. Sanders
AK Bar No. 7510085

See Judge Rindner's order 9/13/08, pages 14:15
#14 Documents unsealed
lwade 8/11/08

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By Peggy J. Crowe
Date 3/25/08

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Page 5861B-6051

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
v.	)	
	)	
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	Case No. 3AN-06-05630 CI
	)	

ORDER CLARIFYING THE COURT'S ORDER EXCLUDING TESTIMONY OR ARGUMENT REGARDING OTHER DRUGS MANUFACTURED BY DEFENDANT ELI LILLY AND COMPANY

IT IS HEREBY ORDERED that the Court's Order Excluding Testimony or Argument Regarding Other Drugs Manufactured by Lilly is clarified as follows:

The parties may not offer any testimony or argument that: (1) relates to the quality or efficacy of any of Lilly's non-Zyprexa products (including characterizations that the products are generally "good" or "bad"), or (2) that any of Lilly's conduct unconnected to Zyprexa has been good or bad.

The parties may, however, refer to and introduce evidence reflecting (1) the names of Lilly's non-Zyprexa drugs and may, in particular, Lilly's manufacture of Prozac and Symbayax (which is in part Zyprexa), and (2) the fact that Lilly has represented itself as a "Diabetes Care" company.

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DATED this ____ day of _____, 2008.

BY THE COURT

_____
Mark Rindner
Superior Court Judge

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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, v. ELI LILLY AND COMPANY, Defendant.	)	Case No. 3AN-06-05630 CI

REQUEST FOR CLARIFICATION OF THE COURT'S ORDER EXCLUDING TESTIMONY OR ARGUMENT REGARDING OTHER DRUGS MANUFACTURED BY DEFENDANT ELI LILLY AND COMPANY

INTRODUCTION

In this type of lawsuit, the defendant often attempts to influence the jury by presenting evidence of other well-known and "good" drugs it manufactures and sells. In essence, the defendant seeks to present "character" evidence, which is inadmissible under Alaska Evidence 404(a). Thus, in the instant case, the State of Alaska filed a motion in limine to preclude Lilly from "eliciting testimony regarding the uses or benefits of any drugs other than Zyprexa manufactured by defendant." In response, Lilly "concurred" with the State's motion and filed a cross-motion; it proposed an order which was misleading and overbroad. Before the State had an opportunity to file either a reply or a response to the cross-motion, the Court signed Lilly's proposed order. For the reasons set

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forth below, the Court should clarify the scope of its order limiting evidence the State may present at trial.

BACKGROUND

The State seeks clarification of the Court's recent order excluding testimony about drugs manufactured by Eli Lilly and Company, other than Zyprexa. The State wishes to confirm its understanding that the Court's order bars the parties from introducing evidence about the quality or efficacy of Lilly's non-Zyprexa products, but that it does not preclude the State from properly orienting the jury to its claims by making mention of the fact that Lilly (1) manufactures Prozac and Symbyax, and (2) holds itself out as the "diabetes care" company. These facts are of central relevance to the State's claims about Lilly's marketing of Zyprexa, will provide jury members with necessary orientation and essential background, and cannot be sensibly redacted from the documentary evidence that supports the state's case. The State believes that this clarification may be necessary to dispel lingering confusion, and that it is best made now, before the parties are in the presence of the jury.

PROCEDURAL BACKGROUND

On February 4, the State filed a motion to prevent Lilly from making reference to, or eliciting testimony about, the "uses or benefits" of drugs that Lilly manufactures other

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than Zyprexa.[1] Lilly generally concurred with the motion,[2] but filed a "qualified opposition" that correctly noted that the proposed order which the State had filed with its motion was incorrectly framed to place limitations on Lilly alone, not both parties.[3] The Court signed Lilly's proposed substitute order on the morning of Friday, February 22, hours before the State was due to file its reply and opposition to Lilly's opposition and cross-motion. The substance of this motion is largely co-extensive with the brief that the State intended to file before the court issued its ruling.

DISCUSSION

The Alaska Rules of Evidence provide that, subject to enumerated exceptions, "all relevant evidence is admissible."[4] Under the Rules, evidence that has "any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable" is relevant,[5] regardless of whether the evidence is

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1 Plaintiff's Motion in Limine to Exclude Testimony or Argument Regarding Other Drugs Manufactured By Defendant Eli Lilly and Company (Feb. 4, 2008).

2 Defendant Eli Lilly and Company's Qualified Opposition and Cross-Motion at 1 (Feb. 14, 2008).

3 *Id.* at 2.

4 ALASKA RULE OF EVIDENCE 402 *Relevant Evidence Admissible—Exceptions—Irrelevant Evidence Inadmissible.*

5 ALASKA RULE OF EVIDENCE 401 *Definition of Relevant Evidence.*

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probative of a fact that is "ultimate, intermediate, . . . evidentiary,"[6] or merely "background in nature."[7]

In this case, the State intends to prove that Lilly over-promoted and failed to issue inadequate warnings about Zyprexa. The State's case is authenticated by Lilly's own documents, which reflect that the company's decision to engage in unlawful behavior was occasioned by Lilly's degraded financial position in the wake of a court decision which unexpectedly advanced the expiration date of the patent on its top-selling drug; that the company has now admitted that Zyprexa has at least some of the capacity to harm alleged by the state; and that the company's deceptive Zyprexa marketing campaign depending on preexisting awareness of the Lilly's brand positioning. These are critical elements of the story that the State must be allowed to tell to the jury, and they cannot be

---

[6] *See Commentary* to ALASKA RULE OF EVIDENCE 401 ("The fact to be proved may be ultimate, intermediate, or evidentiary; it matters not, so long as it is of consequence in the determination of the action.") *Cf. id.* ("The standard of probability under the Rule is "more . . . probable than it would be without the evidence." Any more stringent requirement is unworkable and unrealistic. As McCormick (2d ed.) § 185, at 436, says, "A brick is not a wall," or, as Falknor, Extrinsic Policies Affecting Admissibility, 10 Rutgers L. Rev. 574, 576 (1956), quotes Professor McBaine," . . . [I]t is not to be supposed that every witness can make a home run." Dealing with probability in the language of the Rule has the added virtue of avoiding confusion between questions of admissibility and questions of the sufficiency of the evidence.").

[7] *Cf. id.* ("Evidence which is essentially background in nature can scarcely be said to involve disputed matter, yet it is universally offered and admitted as an aid to understanding.").

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sensibly conveyed without mentioning the fact that Lilly manufactures "Prozac" and "Symbyax," and that it refers to itself as the "Diabetes Care" company.

I. THE COURT'S ORDER SHOULD NOT BE UNDERSTOOD TO PRECLUDE THE STATE FROM MENTIONING PROZAC AND SYMBYAX.

While the only product that is the subject of the State's claims in this case is Zyprexa, two other Lilly products have a significant nexus to the State's claims and Lilly's conduct regarding Zyprexa. The first product is Prozac (or "fluoxetine"), and the second is Symbyax, which is a combination of Prozac and Zyprexa ("fluoxetine" and "olanzapine"). Testimony and documentary evidence regarding these two products have been significant during discovery and are extremely relevant to the issues in this case.

A. The Expiration of Lilly's Patent on Prozac Gave Rise to the Conduct At Issue in this Suit.

Prozac was Lilly's biggest selling product before Zyprexa, and was critical to Lilly's financial success for a number of years.[8] In August 2000, however, Lilly was stunned by a U.S. Court of Appeals decision that would result in Lilly losing its patent on Prozac in 2001 rather than late 2003 or early 2004 as it had expected. On the day that news of that ruling broke, Lilly's stock value fell off the table, wiping out over $36

[8] *See* Exhibit A attached, Exhibit 8 to the Deposition of John Lechleiter, March 28, 2007, at 6.

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billion in equity in a single day.[9] In Lilly's 2000 annual report, the loss of Prozac — an event ominously referred to internally as "Year X" — is described in detail, and it is clear that Zyprexa was Lilly's primary focus for a replacement of its former blockbuster.[10]

The inference that arises from the annual report is corroborated by the deposition testimony of Lilly's executive officers. In Sidney Taurel's deposition, Lilly's then-CEO testified that he not only recalled the precipitous loss of stock value on the day of the appellate court's ruling, but that he "still ha[s] the scar tissue."[11] He then further admitted that a primary goal in furtherance of "weather[ing] Year X" was to "maximize sales of Zyprexa."[12] Lilly's former COO and President (and current CEO) John Lechleiter agreed: he testified the company was "surprised" by the appellate court ruling on Prozac, and that Lilly viewed Zyprexa as a "blockbuster" and key to resuming its growth.[13] Indeed, a July 2001 Zyprexa Product Team document set forth the stakes very clearly when it noted that the company was self-consciously "betting the farm" on Zyprexa:

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9 Exhibit B, Plaintiffs Zyprexa MDL Exhibit 9070, at 7.

10 Exhibit A, at 6, 9.

11 Exhibit C, Deposition of Sidney Taurel, September 19, 2007, at 204.

12 *Id.* Exhibit D, Exhibit 5 to the Deposition of Sidney Taurel (Exhibit C).

13 Exhibit E, Deposition of John Lechleiter, March 28, 2007, at 110-11, 119-20, 122-26.

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> *The company is betting the farm on Zyprexa* . . . the ability of Eli Lilly to remain independent and emerge as the fastest growing pharma company of the decade depends solely on our ability to achieve *world class commercialization of Zyprexa.*
>
> If we succeed, Zyprexa will be the most successful pharmaceutical product ever . . . we will have made history.[14]

Evidence related to the loss of the Prozac patent and what it meant to Lilly is also specifically relevant to Lilly's intent and motive to launch Zyprexa into the primary care physician (PCP) market in 2000 and to Lilly's motive and efforts to promote Zyprexa for off-label uses. Lilly desperately needed a replacement blockbuster for Prozac and saw the PCP market for Zyprexa as its savior. That fact is relevant to the state's claims, and it will specifically rebut necessary any argument or testimony that Lilly entered the PCP market for other reasons. Evidence revealing Lilly's motive to engage in the behavior that forms the basis of the state's claims in this case is relevant and should not be excluded.

B. Lilly's Acknowledged Zyprexa's Heightened Capacity to Cause Harm Only After The FDA Denied Lilly's Proposed Label for Symbyax.

The other Lilly product that is relevant to the State's claims regarding Zyprexa is Symbyax. Symbyax is a combination of Prozac and Zyprexa and was in part the subject

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[14] Exhibit F, Exhibit 9 to the Deposition of John Lechleiter (Exhibit E)). *Cf. See* Exhibit A, at 9 (placing Zyprexa first in a list of key growth products for Lilly, despite the fact that it is alphabetically last).

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of a critical March 28, 2007 letter from the U.S. Food and Drug Administration ("FDA") to Lilly.[15]

When Lilly submitted a proposed label for Symbyax to the FDA, it included language regarding hyperglycemia and diabetes that was very similar to that which it had been in the Zyprexa label since September 2003. But when Lilly proposed the language for Zyprexa in its Symbyax form, the FDA balked. In its March 28th letter, the FDA stated, "we are concerned that the labeling is deficient with regard to weight gain, hyperglycemia, and hyperlipidemia that is associated with olanzapine [i.e., Zyprexa] use, whether taken alone or in combination with fluoxetine [i.e., Prozac]."[16] The FDA noted that the rate of hyperglycemia in patients taking the combination drug was ten times higher than in the placebo group in a clinical study conducted by Lilly and stated, "we are troubled that this important finding was not included in your proposed label."[17] The FDA's analysis treated Symbyax and Zyprexa in the same breath:

> Our overall goal is to improve labeling with regard to these findings so that clinicians will be better informed on what the risks are for their patients. They cannot make reasonable treatment decisions until they have such information. We do not feel that the current labeling for either Symbyax or Zyprexa provides sufficient information on these risks, and we fully intend

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15 Exhibit G, March 28, 2007 letter from FDA to Lilly.

16 *Id.* at 1.

17 *Id.* at 2.

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to insure that these labels are enhanced with the best available information to characterize these risks.[18]

The end result of FDA's communication with Lilly in the following months was a demand for Lilly to craft an interim update to Zyprexa's label that more accurately reflects the true nature of Zyprexa's risks,[19] in order "to protect the public health."[20] Lilly complied and its new label belies its repeated misrepresentations over the course of years that the rates of diabetes between the various atypical antipsychotics were "comparable." The October 2007 label now admits: "the association between atypical antipsychotics and increases in blood glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics."[21]

This evidence is relevant and admissible on the issues of Zyprexa's defect, i.e., the lack of an adequate warning, the feasibility of certain safety precautions, notice of the extent of Zyprexa's risks, and the falsity of Lilly's claim of "comparable rates" of diabetes.

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18 *Id.* at 2 (emphasis added).

19 Exhibit H, October 5, 2007 "Dear Health Care Professional" letter.

20 Exhibit I, Exhibit 8 to Deposition of Robin Pitts-Wojcieszek, December 11, 2007.

21 *Id.* at 1, 3 (emphasis added).

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II. THE COURT'S ORDER SHOULD NOT BE UNDERSTOOD TO PRECLUDE THE STATE FROM NOTING THAT LILLY REFERRED TO ITSELF AS A "DIABETES CARE" COMPANY.

It should also be made clear that Court's order barring testimony and argument about "other drugs" does not prevent the State from noting that Lilly referred to itself as a "Diabetes Care Company" (an observation that makes no mention of any "other drug" or specific Lilly product).

Again, deposition testimony reveals the importance of the claim. To begin, because diabetes care is an important aspect of Lilly's business and has been for over eighty years,[22] Lilly was uniquely positioned to investigate and respond to the risk of weight gain associated with Zyprexa:

> Olanzapine-associated weight gain and possible hyperglycemia is a major threat to the long-term success of this critically important molecule. In addition, it could be argued that Eli Lilly, with its strengths in neuroscience, metabolism, endocrinology and diabetology is better positioned than any other institution to elucidate the mechanisms and developed treatments for this side effect. Thus, we have formed a cross-functional action team to meet these challenges. Success of this effort will contribute to securing the future of olanzapine and the financial health of our company, and likely spur the development of the next generation antipsychotic drugs (i.e. olanzapine without the weight gain) and drugs for obesity.[23]

In October 2000 Lilly began the process by meeting with a group of consulting endocrinologists who advised the company regarding its diabetes drugs, and Lilly

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22 Exhibit E, at 58.

23 Exhibit J, Plaintiffs' Zyprexa MDL Exhibit 8262, at 1 and 2 (November 1999 email of Lilly's Dr. Alan Breier) (emphasis added).

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presented its weight gain and hyperglycemia data to them. But to say the consultants were skeptical of Lilly's positions on weight gain and hyperglycemia would be an understatement. In an email describing the consultant's reactions, Lilly employee Thomas Brodie stated:

> [C]learly, this group of Endocrinologists (who spoke up and I would rate those who did speak up as the leaders of the pack) are very concerned with the approach Lilly is taking towards the issue that Zyprexa leads to diabetes. I can only hope that you and all of the team who attended the NADAB meeting are gaining the ear of senior leadership and articulating this finding. Although the board's recommendation is probably not the way Lilly typically does business, I do believe they made a very strong point that unless we come clean on this, it could get much more serious than we might anticipate.[24]

Critically, Lilly's senior leadership was not interested in taking the advice of its "diabetes care" consultants to "com[e] clean." The recipient of Dr. Brodie's email, Robert Baker expressly advised against Brodie's recommendation when he forwarded the email on:

> I believe that what Tom [Brodie] is referring to as "not the way Lilly typically does business" are suggestions to more vocally assert that olanzapine may have a problem on the glucose issue and, rather than moving forward with our analyses, turning all info over to an independent board for review, conclusions, and dissemination. Neither strikes me as the appropriate step. . . .[25]

In the end, Lilly took Baker's suggestion and adopted a medical and marketing focus that was exactly the opposite of what its consultants recommended—and one that

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24 Exhibit K, Plaintiffs' Zyprexa MDL Exhibit 1453, at 4 (emphasis added).

25 *Id.* at 3 (emphasis added).

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worked only because Lilly could exploit its position as a recognized "diabetes care" company. Thus, instead of following the recommendations of its consultants and using its experience with diabetes to educate physicians and patients regarding the actual risks posed by Zyprexa use, Lilly used its reputation as the "diabetes care" company to *deflect* physician concerns over weight gain with Zyprexa and to falsely reassure physicians that there was no connection between such weight gain and diabetes. Specifically, Lilly taught its representatives to use the "Diabetes Care Company" slogan to pad its messages regarding diabetes in an effort to increase the credibility of those messages. For example, a 2001 "Hyperglycemia/Diabetes Sell Sheet" encouraged sales representatives to use the "Diabetes Care" name to deliver the company's demonstrably false "comparable rates" message.[26] Further, rather than continue to work with its endocrinology consultants on these issues, it instead returned to work with its psychiatrists and marketing employees on ways in which it could avoid the recommendations of the endocrinologists to "come clean" or "aggressively face" the issues of weight gain and hyperglycemia.

Lilly's "diabetes care" branding is therefore relevant to the State's claims in this case (and potentially to Lilly's defenses) because Lilly both consciously disregarded the recommendations of consultants it knew to be most knowledgeable about weight gain and diabetes (waiting four years to involve them in the issue, and then only to ignore their

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[26] Exhibit L, Plaintiffs Zyprexa MDL Exhibit 1962, at 4.

recommendations) and purposefully exploited its reputation as a "Diabetes Care" company to aid in its obfuscation of the true risks of Zyprexa.

CONCLUSION

The State has no interest in introducing evidence about the quality or efficacy of Lilly's non-Zyprexa products, but must be allowed to properly orient the jury to the State's claims by making mention of the fact that Lilly (1) manufactures Prozac and Symbyax, and (2) holds itself out as the "diabetes care" company. These facts are of central relevance to the State's claims about Lilly's marketing of Zyprexa, will provide jury members with necessary orientation and essential background, and cannot be sensibly redacted from the documentary evidence that supports the state's case. The State respectfully requests that its motion be granted.

Dated this 25th day of February 2008.

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Date 2/25/08

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Lilly

Answers That Matter.

talk

2000 Annual Report

Lechliter
EXHIBIT NO. 8
9-28-07
L. GOLKOW

ZY 9553 900

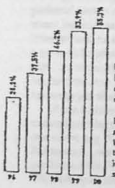
Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 1 of 52 –
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

2000 Financial Highlights

Eli Lilly and Company and Subsidiaries (Dollars in millions, except per-share data) Year Ended December 31	2000	1999	Change %
Net sales	$10,862.2	$10,002.9	9
Research and development	2,018.5	1,783.6	13
Income from continuing operations	3,057.8	2,546.7	20
Net income	3,057.8	2,721.0	12
Earnings per share—basic	$ 2.83	$ 2.50	13
Earnings per share—diluted	2.79	2.46	13
Normalized[1]:			
Income from continuing operations	$ 2,904.6	$ 2,516.7	15
Income from continuing operations as a percent of normalized sales	26.5%	25.4%	
Earnings per share—diluted	$ 2.65	$ 2.28	16
Dividends paid per share	$ 1.04	$ .92	13
Capital expenditures	$ 677.9	$ 528.3	28
Economic Value Added (EVA®)	$ 1,776	$ 1,584	12

[1]Normalized income from continuing operations reflects the results of continuing operations adjusted for significant unusual items. In 2000, these items were the gain on the sale of Kinetra LLC and the net impact of year-2000-related sales made in the fourth quarter of 1999 that ordinarily would have been realized in the first quarter of 2000. In 1999, these items were a contribution to Eli Lilly and Company Foundation, the asset impairment and other site charges, the net impact of year-2000-related sales, income recognized from the sale of Lorabid® marketing rights, and proceeds from a patent infringement settlement. Normalized earnings per share reflects net income from continuing operations adjusted for these same items. See notes to the consolidated financial statements.



Return on Shareholders' Equity (based on income from continuing operations before extraordinary item divided by average shareholders' equity)

Earnings growth and strong asset management, combined with measures to enhance shareholder value, such as the share repurchase program, resulted in a continued increase in return on shareholders' equity.

ZY 9553 901

To Our Shareholders

In keeping with our pledge to answer important questions, I want to address one that I am sure is on your minds.

For several years, we have been preparing for the expiration of the U.S. patents that have protected our exclusive rights to our top-selling product, Prozac®. Due to uncertainty over the exact timing of this event, we have referred to it as "Year X." In January 1999, a federal district court had affirmed our 2003 Prozac patent. Last August, we were very surprised when a federal appeals court reversed that ruling.

We strongly disagree with the ruling—and we are making every effort in the courts to secure our rights to the 2003 patent. At the same time, prudence dictates that we prepare and implement our plans with the assumption that Prozac will face generic competition in the United States in early August 2001.

Given this turn of events involving a product with U.S. sales of $2.2 billion, you may well ask whether Lilly can successfully navigate the next several years. My response is a strong "Yes." We fully recognize the magnitude of our challenge. And we are prepared not only to manage the short-term challenges of Year X but also to embark soon thereafter on a period of renewed growth. Here is why I am confident.

We continue to sharpen the implementation of our simple, clear-cut strategy that focuses on two areas: generating scientific innovations that meet patients' unmet medical needs and then helping as many patients as possible benefit from those innovations. As a result, our net sales increased 9 percent in 2000, to $10.9 billion. Adjusted for significant one-time items in 1999 and 2000, our net income rose 15 percent, to $2.9 billion, and our earnings per share grew 16 percent, to $2.65.

For a number of years, we have also implemented contingency plans that would help us overcome any Year X outcome we might face. For instance, we have invested aggressively in our products with the strongest growth potential. We have sped the development of high-potential molecules. And we have partnered with other companies to get access to additional molecules that further expand our opportunities.

In 2000, the investment community responded favorably to our progress. Our stock price rose 40 percent during the year. This gain was among the best in the pharmaceutical industry. Furthermore, it represented a major step in the right direction after our disappointing stock performance in 1999.

Strong product line fuels growth

Powering our growth in 2000 were six newer best-in-class products that accounted for 41 percent of our pharmaceutical sales and grew at a rate of 31 percent.

Zyprexa® exemplifies our growth opportunities. Initially introduced in 1996 as a treatment for schizophrenia, this molecule was approved in 2000 as a therapy for the manic phase of bipolar disease, a lifelong illness that affects as many as 34 million people worldwide. Late last year, Zyprexa was also approved for the long-term treatment of schizophrenia, making it the first product in its class to demonstrate such ongoing effectiveness. In 2000, our sales of Zyprexa were $2.3 billion, a 25 percent increase. During the fourth quarter, this neuroscience blockbuster surpassed Prozac as our top-selling product.

Two products surpassed the $500 million sales mark for the first time in 2000. Sales of Evista®, our novel product for the prevention and treatment of osteoporosis in postmenopausal women, were $522 million, an increase of 60 percent. Gemzar®, one of the world's top-selling anticancer agents, generated sales of $559 million, up 23 percent.

Sales of the human insulin analog, Humalog®, rose 56 percent, to $350 million. As more patients used Humalog, Humalog mixtures, and our pen-cartridge delivery systems, our total insulin sales grew 10 percent, to $1.5 billion. We also continued to expand our diabetes care presence through the copromotion of Actos®, an oral treatment for type 2 diabetes discovered by our partner, Takeda. Our revenue from Actos was $223 million during 2000—its first full year on the market.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
Exhibit A, Page 3 of 52
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205082

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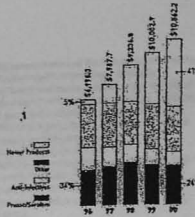

Net sales during 2000 reflect the strong growth of Lilly's newer products and a consistent lessening of the company's reliance on the sales of Prozac. The company's newer products—Zyprexa, Evista, Actos, Humalog, Gemzar, and ReoPro—grew by a combined 31 percent over 1999, representing 41 percent of total net sales compared with 24 percent in 1999. Prozac sales accounted for 24 percent of total net sales in 2000, down from 34 percent in 1996.

The growth of those five products more than offset sales decreases for two other important products. The sales of our sixth newer product, the cardiovascular agent ReoPro® discovered by the Centocor unit of Johnson & Johnson, fell 7 percent, to $418 million. The worldwide sales of Prozac declined 2 percent, to $2.6 billion, largely due to the initial impact of generic competition in the United Kingdom.

Intense competition is a fact of life throughout the pharmaceutical industry. To meet that competition, we significantly elevated our marketing investments in 2000 with the goal of making our growth products available to more patients throughout the world. More specifically, we added some 2,000 sales representatives worldwide, an increase of more than 20 percent. We recruited scores of experienced marketing professionals to support our growing product line. And we pursued clinical studies supporting new indications and formulations for key products that will further expand our growth opportunities.

Outstanding pipeline adds further growth potential

Even as we capitalize on our current generation of products, we are speeding our next generation of new products candidates to the global marketplace. As you will see later in this report, we could introduce as many as 30 more medicines by the end of 2004. Several of those candidates are potential first-in-class products that could address medical problems for which there are no current treatments. All are potential best-in-class products that could provide superior results for patients.

In the near term, we are immersed in our preparations for the launches of two unique biotech products. Clinical data indicate that drotrecogin alfa (activated), also known by the proposed trade name Zovant, may be the first therapy that effectively treats patients with sepsis, a condition that kills an estimated half million people worldwide annually. Forteo™ is an innovative molecule that appears in clinical trials to rapidly rebuild bone diminished by osteoporosis. We filed regulatory submissions for Forteo in late 2000 and for Zovant in early 2001. We expect to launch both in 2001.

Beyond Zovant and Forteo, we hit the development targets last year for nearly all the molecules in our near-term pipeline. Two exceptions were the anticancer agent oxaliplatin, which was not approved by the FDA, and the antidepressant candidate R-fluoxetine, which did not meet its clinical-trial goals. We returned both potential products to partners.

While Lilly scientists have discovered most of the molecules in our pipeline, we continue to work with other companies to add more opportunities. For example, Cialis™ is a promising near-term drug candidate from ICOS Corporation for the treatment of male erectile dysfunction that Lilly and ICOS are working together to develop. During 2000, we announced agreements with three other companies—Ono, Sankyo, and Mitsubishi-Tokyo—that each added a molecule to our pipeline.

We currently have well over 100 scientific collaborations. Those cooperative efforts not only help us enhance our pipeline with additional drug candidates but also give us access to more biological targets for drug discovery and important new R&D technologies. Because collaborations are an essential part of our strategy, we created an Office of Alliance Management with the mission of helping Lilly become the pharmaceutical industry's best business partner. We are making good progress in that pursuit.

In 2000, we strengthened our internal research capabilities by recruiting nearly 700 scientists and expanding our "innovation engine," Lilly Research Laboratories, to 6,900 people at 11 sites worldwide. We also increased our global R&D investment by 13 percent, to $2 billion. This represented 19 percent of our sales.

Those actions are paying off. Last year was one of the best ever for Lilly Research Laboratories. Our scientists met or exceeded virtually all our rising research-productivity targets for identifying high-potential molecules and initiating early-stage clinical trials of drug candidates. A key factor in those productivity gains is the early impact of the biotech revolution about which we hear so much.

ZY 9553 903

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 4 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205083
Page 4

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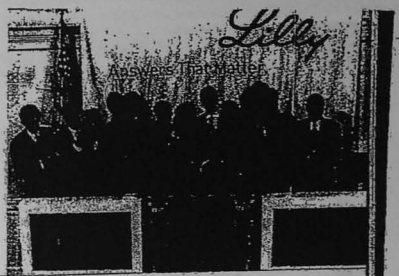


Last October, the company marked the 30th anniversary of the listing of Lilly stock on the New York Stock Exchange. Chairman Sidney Taurel and the board of directors celebrated the occasion with a day of activities at the exchange, hosted by NYSE Chairman and Chief Executive Officer Richard Grasso. Capping the activities at 4 p.m., Taurel struck the ceremonial gavel at the exchange podium as the final bell sounded, signaling the close of trading for the day.

Prior to its initial listing on the NYSE on July 9, 1970, Lilly stock had been sold in the over-the-counter market. During those first days of trading on the New York exchange, the company's market capitalization was about $3 billion. Today, it's nearly $180 billion.

Technology revolutions create new opportunities

Over time, the biomedical revolution will transform all areas of pharmaceutical R&D. In the near term, however, we believe the greatest potential involves the use of new research tools to identify previously undiscovered genes that trigger the production of natural proteins in the body involved in major diseases. Those natural proteins, or modified versions, sometimes prove to be outstanding biotech drug candidates.

This trend plays directly into our strengths. We are established leaders in the discovery, development, and production of protein medicines. The upcoming launches of Forteo and Zovant will expand our protein portfolio to seven products. And we have a number of additional protein candidates in various stages of development.

We are also using revolutionary new R&D capabilities to expedite our searches for so-called "small-molecule" medicines similar to Prozac and Zyprexa that constitute the majority of our drug candidates. Our scientists are committed to helping patients benefit from this unfolding biotech revolution as soon as possible.

Additionally, we are exploiting the power of the e-business revolution on behalf of patients. In 2000, we created a new organization, e.Lilly, that is generating, attracting, and testing scores of new approaches based on information technology. These concepts have the potential to accelerate improvement in virtually every aspect of our business, from the earliest stages of research to providing information for patients.

Ready for the future

In 2000, we enthusiastically welcomed two outstanding leaders to our board of directors. Sir Winfried "Win" Bischoff is chairman of Citigroup Europe and former chairman and CEO of Schroders, plc. George M. C. Fisher recently retired as chairman and CEO of Eastman Kodak Company and previously served as chairman and CEO of Motorola, Inc. Together, these men reinforce the leadership experience and global perspective of our board that will be great assets during this challenging period.

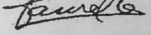
I also wish great success to Mitchell E. Daniels, Jr., who recently became director of the U.S. Office of Management and Budget for President George W. Bush. This cabinet-level appointment is a great honor for Mitch, who served most recently as our senior vice president for corporate strategy and policy. Among his many contributions to the company during the past 11 years, Mitch built an outstanding team in public affairs and communications and played a pivotal role in our preparations for Year X. We will long benefit from his legacy.

As I look ahead, our strategy is on target and our implementation is getting better and better. We are not only applying traditional R&D and sales-and-marketing capabilities but also capitalizing on the revolutions in biotechnology and information technology. Our ongoing progress throughout the company reflects the achievements and the aspirations of 35,700 Lilly colleagues in whom I take great pride.

Later this year, we will celebrate the 125th anniversary of Lilly's founding. Over these many years, our company has made history with medical breakthroughs—from the first insulin product and major antibiotic advances to Prozac and Zyprexa. So, we are very thankful for the Lilly family and Lilly retirees who created the heritage that we are working to extend into the twenty-first century.

As we face Year X, we intend to make history again with the greatest outpouring of innovation in Lilly history—beginning with Zovant and Forteo. We plan to emerge from Year X a stronger company that is ready for a new growth era. We are prepared to write the next great chapters in the Lilly story.

For the board of directors,



ZY 9553 904

Sidney Taurel
Chairman of the Board, President, and Chief Executive Officer

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 5 of 32
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205084
Page 5

005879

No company would relish losing the patent on its biggest product three years early. We certainly don't.

We were very surprised and disappointed by the judicial ruling that invalidated our 2003 U.S. patent on Prozac. We strongly disagree with the court's decision, and we are doing everything we can through the judicial process to reestablish our rights.

In the meantime, the U.S. Food and Drug Administration has granted us market exclusivity until August 2, 2001, under a federal statute encouraging pediatric studies of certain medicines.

We intend to focus on Prozac in the United States right up to the last day of its exclusivity. And we'll pursue related opportunities. One is our patented once-weekly formulation aimed at preventing the recurrence of depression. A second is Sarafem™, a newly introduced brand for women

What happened with Prozac?

who suffer from premenstrual dysphoric disorder, the severe mood and physical symptoms associated with their menstrual cycle that interfere with their daily activity and relationships.

We won't miss any opportunities for Prozac—or the rest of our business. For the last four years, we've been preparing to bridge the gap that would be created by generic competition for Prozac. We're ready.

We've invested aggressively in our next generation of innovative drugs and shortened their timelines to launch. We've accelerated development of additional indications and formulations for our newer products. And we've intensified our efforts to partner with other companies on their high-potential compounds in later stages of development.

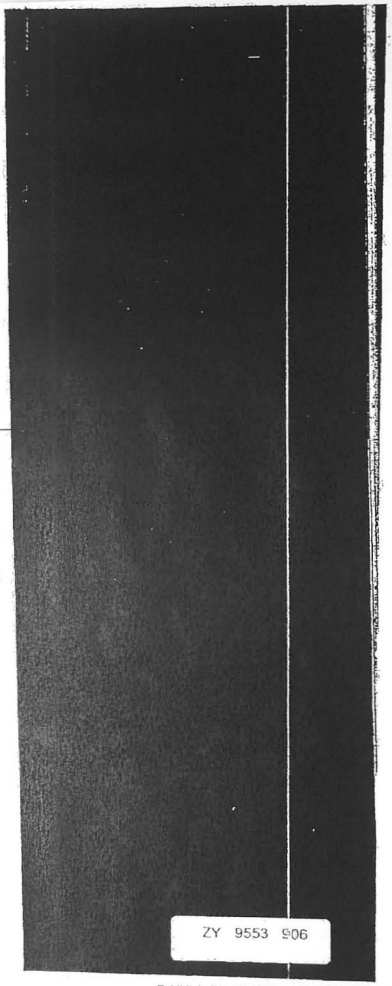
We've significantly increased the size of our global sales force and will continue to do so in order to have the "firepower" we need to successfully launch and sell the next wave of products from our pipeline. We've also been sharpening our marketing and selling skills to help us realize the full potential of all our products worldwide.

In short, faced with the enormous challenge presented by the Prozac patent expiration, we've positioned ourselves to produce earnings growth through the immediate postexpiration period and resume fast growth following that.

Millions of people worldwide have benefited from Prozac. This remarkable product has revolutionized the way mental illness is viewed and treated. The success of Prozac has helped make possible the outstanding accomplishments of Lilly

research over the last decade and has provided us with the ability to pursue the breakthroughs we expect to introduce in this new decade. It's a wonderful story—for medical science, for patients, and for us. We are proud of Prozac.

And yet, as important as Prozac has been for patients and to our business, it's not the future. For patients, the future is the next generation of medicines with the ability to treat and cure difficult diseases in ways now only hoped for. For us, the future is our newer products already driving our growth and our pipeline of innovative products yet to come. Our focus is on the next Prozac—and the one after that.



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So, what now?

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
Exhibit A Page 8 of 32
SOA Request for Clarification of the Court's Order re Other Drugs
Case No 3AN-06-5630 CI
ZY1 00205087

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Gemzar Gemzar has been described as a "pipeline within a molecule." It's being used to treat the vast majority of pancreatic-cancer patients in both Europe and the United States, and it's become the standard of care for non-small-cell lung cancer in several countries. We're evaluating Gemzar in several types of solid tumors. Our goal is to make it a cornerstone of treatment for lung, pancreatic, bladder, breast, and ovarian cancers.

Our newer products will stand as our front line against inevitable generic competition for Prozac. Introduced throughout the last half of the 1990s, they'll be the key to our ability to produce earnings growth during that time and resume our strong performance thereafter.

Zyprexa Zyprexa is a genuine blockbuster, surpassing the $2 billion sales mark in 2000 and becoming Lilly's number-one-selling product in the fourth quarter. Just as Prozac changed the treatment of depression, Zyprexa has redefined the standard of care for schizophrenia, a devastating disease that ravages the mind and has been called the "cancer of mental illness."

Introduced as a therapy for schizophrenia in 1996, Zyprexa was approved in the U.S. last year for the additional indications of acute mania associated with bipolar disorder and the maintenance of treatment response in schizophrenia. We're exploring broader uses for Zyprexa in schizophrenia and other key segments of the antipsychotic market, including bipolar depression and the psychotic or behavioral disturbances that accompany dementia.

Evista Evista is a blockbuster in the making. The growth of our product for the prevention and treatment of osteoporosis in postmenopausal women continues to be outstanding. Evista has been shown to significantly reduce a woman's risk of clinical spinal fracture within one year of treatment and increase bone mineral density as early as six months.

We continue to investigate the potential of Evista beyond osteoporosis—including its potential effect on heart disease and the reduction of risk of breast cancer in postmenopausal women. Given the breadth of Evista's efficacy potential and its favorable tolerability, we believe it will ultimately set a new standard for women's health products.

Insulins In 1999, the world's first insulin company established itself as the world's leading insulin company, becoming number one worldwide in market share. This leadership was strengthened in 2000. We've achieved this success through the introduction of the Humalog family of insulins and the launch of world-class pen delivery devices. Patients are switching to our Humalog and Humalog mixture formulations and pen delivery devices from their earlier-generation insulin products and their vials and syringes.

Actos The quick uptake of Actos, the oral diabetes agent we launched with our copromotion partner Takeda in the United States during 1999, marked our successful expansion in diabetes care beyond insulins. Actos provides an excellent complement to our insulin business as an oral agent for type 2 diabetes, the most prevalent form of the disease. Our newest product, it is recognized as therapy for reducing insulin resistance, an underlying cause of type 2 diabetes.

New Submissions In addition, we expect 2001 launches for two new products currently under review by regulatory agencies. Drotrecogin alfa (activated), known by the proposed trade name Zovant, targets sepsis, a disease that kills approximately 3,400 people per day worldwide and for which there currently is no approved treatment. Results of a study indicated a nearly 20 percent reduction in the risk of death in patients who were given Zovant. And clinical trials of Forteo, our novel bone-formation agent for osteoporosis, have demonstrated that it strengthens overall skeletal architecture very rapidly. In addition, the trials showed it can significantly reduce fractures caused by thinning bones at both the spine and nonspine sites.

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 9 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205088
Page 9

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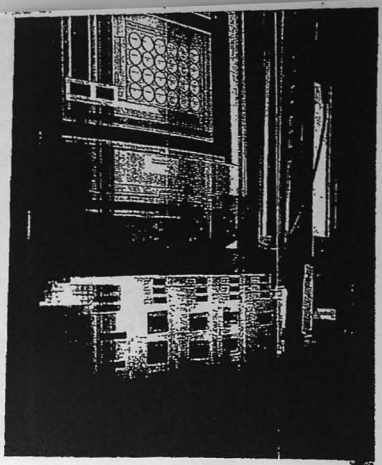

"Drug hunters" in pharmaceutical research examine thousands of compounds annually, searching for molecules that may have activity against identified disease targets. The lead optimization biology laboratory researchers can process up to 2000 compounds in one day, a task that once took weeks. Shahrzad Montrose and Kevin Tichenor dissolve compounds and place them in various plate formats required for biological screening.

How good is our pipeline?

The opening years of this new century could well become the most productive period of innovation in Lilly's history.

From 2001 to 2004, we may launch as many as 10 new products for a wide range of serious, unmet medical needs. This is unprecedented for Lilly. It's nearly twice the number we introduced in the last half of the 1990s. All these novel, late-stage compounds support our focus on the development of either first-in-class or best-in-class products. And they all represent significant commercial opportunities. In fact, some analysts have said that the near-term Lilly pipeline is the richest in the pharmaceutical industry.

2001

Zovant—sepsis. Zovant is our innovative, investigational biotech product for sepsis with associated acute organ dysfunction (severe sepsis), a disease caused by the body's overwhelming response to infection that can lead to organ failure and, ultimately, to death. More than 1.5 million people worldwide contract sepsis annually. A person dies from sepsis, on average, every minute.

Zovant has shown great promise against sepsis—so much so that an independent advisory board recommended last June that we stop enrolling patients in a late-stage clinical trial and submit Zovant for regulatory approval as soon as possible. We have submitted our regulatory package in support of Zovant to European and U.S. authorities. We hope to do something no pharmaceutical company has been able to do—bring to the market a specific treatment for this deadly disease.

Forteo—osteoporosis Our recombinant parathyroid hormone Forteo will target osteoporosis, the often "silent" disease that leads to the breakdown of bone, primarily in postmenopausal women. While other products for osteoporosis work by reducing the rate of bone loss, studies indicate that Forteo puts bone back into its natural growth phase and stimulates the creation of healthy new bone.

Forteo, if approved, has the potential to become a leading agent for the treatment of osteoporosis. We're also exploring how Forteo and our osteoporosis product Evista might work together to strengthen bone. Forteo is currently under review by the FDA.

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2002

Cialis—male erectile dysfunction We're collaborating with ICOS Corporation to study Cialis, an oral agent discovered by ICOS scientists, for male erectile dysfunction. The condition affects an estimated 70 million men and their partners worldwide.

In Phase II trials, more than 88 percent of men taking Cialis reported improved erections. Multiple studies to date have shown a promising side effect profile.

Atomoxetine—attention-deficit hyperactivity disorder Attention-deficit hyperactivity disorder (ADHD) is one of the most common mental disorders among children, affecting between 3 and 5 percent of school-aged children. It's primarily characterized by symptoms of inattentiveness, hyperactivity, and impulsive behavior. ADHD often continues into adolescence and adulthood. The most widely prescribed drugs for ADHD are psychostimulants. But these products can have undesirable side effects, such as insomnia, and often carry a stigma because of their classification as scheduled substances (narcotics).

Atomoxetine (formerly tomoxetine), our investigational drug for ADHD, is not a stimulant; it belongs to a different class of medications. It works by blocking a neurotransmitter that plays an important role in modulating brain systems that control attention and activity. Atomoxetine would be the first such agent approved for the treatment of ADHD.

Duloxetine—depression Depression is a leading cause of disability worldwide, robbing its sufferers of their ability to make decisions, work, or function at a basic level. The World Health Organization estimates that depression is present in 10 percent of all people seeking care at primary health care facilities globally.

Duloxetine is one of two compounds (the other is a combination of Zyprexa and Prozac) we're evaluating that address unmet needs in different segments of patients with depression. We're looking at duloxetine for the treatment of major depression. Duloxetine enhances levels of two important brain chemicals and has shown promise as a step forward in the treatment of depression.

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Our pipeline: late-stage compounds

Anticipated launches for high-potential new products

2001	2002	2003	2004
Zovant Severe sepsis	Cialis Male erectile dysfunction	Alimta Mesothelioma, other cancers	Oritavancin Bacterial infections
Fortéo Osteoporosis	Atomoxetine Attention-deficit hyperactivity disorder	OFC Treatment-resistant depression	
	Duloxetine Depression	Duloxetine Stress urinary incontinence	
		Protein Kinase C beta inhibitor Diabetic retinopathy (In Europe)	

The search for new drugs is risky and uncertain. While we believe each of these molecules holds great promise, we know from experience that remaining scientific and regulatory hurdles may cause a late-stage compound to be delayed or even fail to reach the market at all.

2003

Alimta™—cancer In addition to inestimable costs in human suffering and loss, cancer generates enormous financial costs—an estimated $107 billion annually in the U.S. alone. Our novel multitargeted antifolate, Alimta, is one of a number of cancer drugs we have in various stages of development. It represents one of a variety of approaches we're taking in attacking cancer.

Alimta blocks at least three enzymes that are very important to cell replication. We think it may be possible for Alimta, by blocking any one of these enzymes, to disrupt a cancer cell's machinery and prevent it from replicating. It's also our goal with Alimta to develop a drug with a predictable, preventable, and manageable toxicity profile. Alimta has shown activity in mesothelioma, breast, non-small-cell lung, pancreatic, colon, and gastric cancers.

OFC—treatment-resistant depression We're studying a combination of olanzapine and fluoxetine (Zyprexa/Prozac) in treatment-resistant depression. Approximately one in every three depressed patients does not benefit from current therapies. Early clinical trial studies suggest that OFC may also address psychotic depression. Conventional antidepressants have produced a low response rate in such patients.

Duloxetine—stress urinary incontinence In addition to its potential for treating depression, duloxetine has shown promise in treating urinary incontinence, a serious disorder that can lead to embarrassment and even social isolation for those who suffer from it. Of the various types of incontinence, duloxetine appears best suited to address the kind that occurs due to physical stress, such as coughing, lifting, or straining. Stress incontinence, which accounts for 40 percent of the market, occurs primarily in women and is the most common condition leading to loss of bladder control. There are no approved drug therapies for stress incontinence, which is treated primarily with behavior modification or surgery.

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 12 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205091
Page 12

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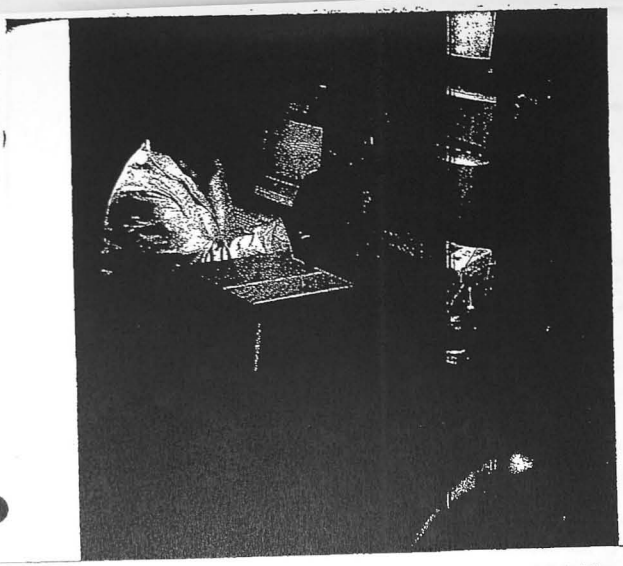

Protein Kinase C beta (PKCβ) inhibitor—diabetic retinopathy Few diseases have such widespread and varied negative effects on the body as diabetes because the high blood sugar associated with this disease damages the small and large blood vessels of a variety of organs. As a result, diabetes accounts for the largest share of health care expenses in many developed countries, and cardiovascular complications account for nearly 80 percent of deaths in patients with diabetes.

It's our theory that inhibition of PKCβ in blood vessels counteracts the destructive effects of high blood sugar, and we are studying the capability of our oral inhibitor to treat the vascular abnormalities associated with diabetes. Our initial target is diabetic retinopathy, a common diabetes-related complication in which damage to the vessels of the retina occurs and that can, ultimately, lead to blindness.

Gerald Becker, Ph.D., team leader, biochemical technologies group, operates a mass spectrometer as part of Lilly's emerging proteomics effort. Proteomics, the study of the protein component of a cell, tissue, or organism, is helping the company gain a deeper understanding of biology. Mass spectrometry is among the powerful new technologies that help define protein interactions and relationships that further novel drug development.

2004

Oritavancin—bacterial infections Oritavancin is part of our effort to build on our decades-long expertise in infectious disease and to develop a significant array of lifesaving products focused on intensive care units, emergency rooms, trauma centers, and operating rooms.

Oritavancin may be effective against many bacterial infections, including those resistant to conventional antibiotics. We're evaluating its potential use in bacteremia, a condition in which patients have bacteria circulating in their blood, and in complicated skin infections. Statistics suggest that, in 1999, in the U.S. alone, approximately 2.5 million hospital-based patients suffered from skin and skin structure infections and another 400,000 patients from bacteremia.

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
Exhibit A, Page 13 of 52
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205092
Page 13
005887

Modern pharmaceuticals are a vital, essential, and efficient part of good health care. Unfortunately, in the United States, some patients without drug insurance struggle to pay for the medicines they need. This is wrong.

While Americans as a whole enjoy the highest standard of health care in the world, our patchwork-quilt system of private insurance and various state and federal governmental programs fails to cover everyone. The gaps are especially large for those with lower incomes. They are also large with respect to coverage for drugs. As a result, we have seen a vigorous debate over the cost of pharmaceuticals, especially for low-income seniors, who enjoy Medicare coverage for many health care expenses other than drugs.

This debate is not about whether to provide drug coverage, but how. And because some would make the pharmaceutical industry the villain in this story, it is also a debate about the future of pharmaceutical research. The decisions made as a result of this discussion will affect not only how patients pay for their drugs but also whether new medications will be available in the future.

Throughout this debate, we have stood firmly in support of two principles: first, the Medicare system, through comprehensive reform, should be strengthened and modernized to better serve seniors, including the addition of a drug benefit; second, policymakers should take no action that would endanger our ability to bring forward for patients the full promise of this tremendously exciting new era in pharmaceutical innovation.

The U.S. cannot wait any longer to address these issues. We hope Congress will enact, as soon as possible, a comprehensive reform of Medicare, including a drug benefit. If this proves impossible in the short term, any interim program adopted to help those in greatest need should be consistent with and a step toward modernization of the Medicare system. At minimum, the interim program should not become an obstacle to achieving comprehensive Medicare reform.

Statistics show that well over 90 percent of all new medicines are discovered by research-based pharmaceutical companies and that the U.S. is the leader in pharmaceutical research. We are entering a defining period in medical history as scientists begin to understand the genetic makeup of humans. That knowledge promises to lead to an explosion in new drug development opportunities—opportunities that could one day lead to drugs that prevent or cure cancer, diabetes, and heart disease. The decisions policymakers make today will shape that future. They will determine how long we'll wait for new therapies for tough diseases.

Maggie Lutz didn't have time to wait. Fortunately for her, a novel new drug related to her need was in the late stages of development. To learn what pharmaceutical innovation meant for Maggie, please turn the page.

Who pays for progress?

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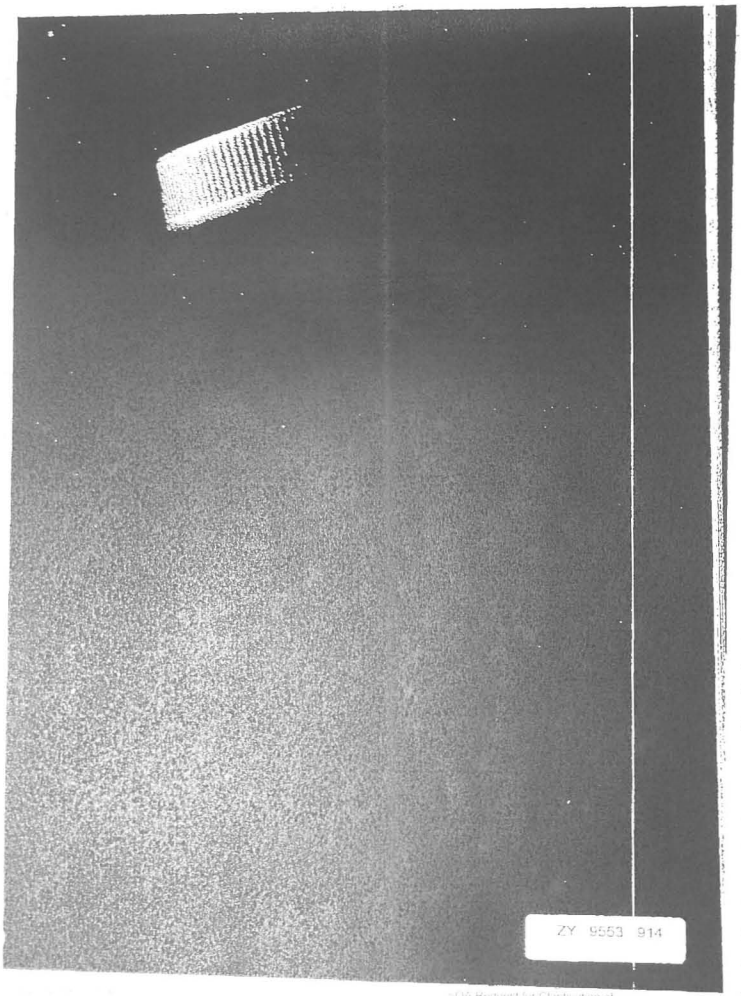
Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 14 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205093
Page 14

005888



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Each day, 1,400 people die from sepsis worldwide.

Caused by the overwhelming response of the body's immune system to infection, sepsis can occur in healthy people who develop an infection, such as pneumonia. It can also occur as a complication of trauma, cancer, or AIDS. In fact, many deaths officially linked to these diseases represent cases in which the patients actually died of sepsis.

Industrywide, approximately 30 research efforts to find a sepsis drug over the last several decades have all failed. We are hopeful that our investigational drug, Zovant, will break this cycle

Can we really beat a killer?

of disappointment. Zovant is our version of recombinant human Activated Protein C for sepsis.

In the summer of 2000, an independent panel of experts recommended that we suspend the enrollment of patients in our Phase III trial evaluating Zovant against placebo as a treatment for sepsis and submit the drug for regulatory approval quickly. The panel found positive results in this study of more than 1,500 patients, including a nearly 20 percent reduction in the relative risk of death in Zovant-treated patients.

We concluded our clinical trial work and we have submitted Zovant to the European Agency for the Evaluation of Medicinal Products and the U.S. Food and Drug Administration.

We believe Zovant may represent an important medical breakthrough against sepsis. It may provide hope for patients like Maggie Lutz, for whom, up to now, there has been very little.

Maggie's story

College student Maggie Lutz (*opposite*) had gone to the campus health center with a sore throat. A week later, she still had a sore throat and had been experiencing headaches and a low-grade fever. During the evening, she began to vomit. Maggie called an area hospital to see if she should come there to be seen by medical staff. She was told her symptoms sounded like flu and to rest. The next day, Maggie woke with a dark purple rash on the lower half of her body. Her muscles ached so badly she had difficulty getting out of bed. She knew something was very wrong.

With her roommates already gone to class, Maggie managed to take a bus to the health center. By the time a physician saw her, her blood pressure was dangerously low, her heart rate was racing, and she was disoriented. Presenting classic symptoms of a serious form of meningitis, Maggie was rushed to the emergency room of the university hospital. She was admitted with severe sepsis, which is brought about by a multitude of conditions triggered by the body's immune response to infection.

By that evening, Maggie was hardly recognizable, even to her family. Normally a very slim person, Maggie ballooned to more than 200 pounds as her body could no longer eliminate fluid. Her eyes were so swollen the lids would not cover them. Her organs had begun to shut down as her condition rapidly deteriorated. Finally, she was placed on a ventilator and sedated into an artificial coma to minimize the work required of the body to maintain itself.

The attending physician told Maggie's parents she had only a 10 percent chance of surviving. However, he was aware of Lilly's investigational drug for severe sepsis.

Believing Maggie might be helped by Lilly's clinical study drug, the physician immediately contacted the company. Lilly researchers obtained the necessary approvals for compassionate use of the experimental drug, and within 14 hours, Maggie's doctor began an infusion of rhAPC that would continue for the next 96 hours.

The rapidity of Maggie's response to rhAPC, now known as Zovant, was astonishing. Within 48 hours, her blood pressure improved and her lungs were clear. And, she continued to progress as her vital functions began to work on their own over another seven weeks in the hospital.

Once at home, Maggie worked for a year to regain her strength and the normal use of her muscles. She is now totally recovered and will graduate from college in the spring.

"I've always been a compassionate person," she said. "But I'm more so now. Thank God, there were people working for me at Lilly. And they work so hard—I never realized how much it takes to make a new drug. But it pays off. I'm proof that it pays off.

"People call me 'Miracle Maggie.' It was a miracle—I was almost gone. But, I'm back."

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 16 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205095
Page 16

005890

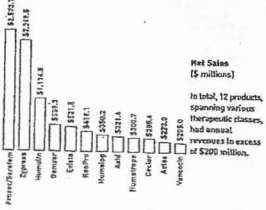
ZY 9553 916

15

Operating Results From Continuing Operations—2000

Summary

Income from continuing operations was $3.06 billion, or $2.79 per share, in 2000 and $2.55 billion, or $2.30 per share, in 1999. Comparisons between 2000 and 1999 are made difficult by the impact of several unusual items that are reflected in the company's operating results for both years. Excluding these unusual items, which are discussed further below, income from continuing operations for 2000 and 1999 would have been $2.90 billion, or $2.65 per share, and $2.52 billion, or $2.28 per share, respectively. This represents an increase in net income and earnings per share of 15 percent and 16 percent, respectively. The 2000 increases are attributed to growth in sales, improved gross margin, and increased interest income, offset by increases in operating expenses at a rate greater than sales growth. Earnings per share also benefited from a decrease in the number of shares outstanding as a result of the share repurchase plan.



Unusual Items

As noted above, several unusual items are reflected in the company's operating results for 2000 and 1999. These transactions are summarized as follows (see Note 3, Note 5, and Note 13 to the consolidated financial statements for additional information):

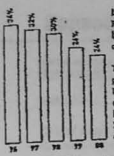
- A gain of $214.4 million on the sale of its interest in Kinetra LLC to WebMD Corporation (WebMD) and the subsequent sale of WebMD stock, which increased earnings per share by approximately $.20 in the first quarter of 2000
- Approximately $91 million in additional product sales in 1999 as a result of year-2000-related wholesaler buying that normally would have been realized during the first quarter of 2000, which increased earnings per share by approximately $.06 in the fourth quarter of 1999 and reduced earnings per share by the same amount in the first quarter of 2000
- A pretax gain of $210.0 million in settlement of litigation with Biochimica Opoi S.p.A., which increased earnings per share by approximately $.06 in the fourth quarter of 1999
- A pretax charge of $26.0 million associated with the decommissioning of manufacturing facilities and other site charges, which decreased earnings per share by approximately $.02 in the fourth quarter of 1999
- A pretax gain of $67.8 million on the sale of U.S. and Puerto Rican Lorabid marketing rights, which increased earnings per share by approximately $.05 in the third quarter of 1999
- A pretax charge of $150.0 million as the result of a contribution to Eli Lilly and Company Foundation, which decreased earnings per share by approximately $.09 in the first quarter of 1999
- A pretax charge of $61.4 million associated with the impairment of certain manufacturing assets, which decreased earnings per share by approximately $.04 in the first quarter of 1999.

Sales

The company's reported worldwide sales for 2000 increased 9 percent, to $10.86 billion. Worldwide sales for 1999 included approximately $91 million of sales relating to year-2000 wholesaler buying that normally would have been recognized in 2000. Adjusting for the impact of year-2000 wholesaler buying, sales growth for 2000 would have been 10 percent. Sales growth was led by Zyprexa, a treatment for schizophrenia and related psychoses; diabetes care products; Evista, an osteoporosis treatment and prevention agent; and Gemzar, an oncolytic product. Sales in the U.S. increased 12 percent, to $7.00 billion. Sales outside the U.S. increased 2 percent, to $3.86 billion. Worldwide sales reflected volume growth of 11 percent, partially offset by a 2 percent decrease in exchange rates while prices remained flat.

Prozac and Sarafem had combined worldwide sales of $2.57 billion, representing a decrease of 2 percent. Sarafem, launched in the U.S. in August 2000 for the treatment of premenstrual dysphoric disorder (PMDD), had sales of $14.6 million in 2000. Combined sales of Prozac, an antidepressant, and Sarafem in the U.S. increased 7 percent, to $2.23 billion. The U.S. sales comparison benefited, in part, from wholesaler inventory reductions in 1999. Prozac sales outside the U.S. decreased 35 percent,

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
ZY 9553 917
Exhibit A, Page 18 of 52
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205097
Page 18
005892

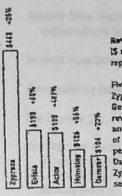


Lilly's Decreasing Dependency on Prozac

Percentages represent the Prozac share of total net sales

Through strong growth of newer products, Lilly is consistently lessening its reliance on sales of Prozac. In 2000, Prozac (including Sarafem) accounted for 24 percent of Lilly's total net sales, down from 34 percent in 1996.

to $341.0 million, primarily due to continuing generic competition in the U.K. On August 9, 2000, the Court of Appeals for the Federal Circuit affirmed a lower court decision upholding the company's February 2002 U.S. patent on Prozac but ruled that the company's December 2003 patent is invalid. Reference is made to the discussion of the Prozac patent litigation under "Legal and Environmental Matters." For additional information on the expected financial impact of the ruling, see the "Financial Expectations for 2001" section below.



Revenue Growth of Newer Products

$ millions; growth percentages represent change from 1999

Five of the company's newer products—Zyprexa, Evista, Actos, Humalog, and Gemzar—generated $4.0 billion in revenues in 2000. These newer products and ReoPro now represent 21 percent of total net sales compared with 14 percent in 1999 and 26 percent in 1998. During the fourth quarter of 2000, Zyprexa became the company's top-selling product.

Zyprexa had worldwide sales of $2.35 billion in 2000, representing an increase of 25 percent. Sales in the U.S. increased 23 percent, to $1.69 billion. Sales in 2000 benefited from the U.S. Food and Drug Administration (FDA) approval of Zyprexa for the treatment of acute mania associated with bipolar disorder in the first quarter of 2000. Sales outside the U.S. increased 28 percent, to $659.3 million.

Gemzar had worldwide sales of $559.3 million in 2000, representing an increase of 23 percent. Sales in the U.S. increased 20 percent, to $315.9 million. Sales outside the U.S. increased 27 percent, to $243.3 million.

Evista had worldwide sales of $521.5 million in 2000, representing an increase of 60 percent. Sales in the U.S. increased 52 percent, to $433.8 million. Increases in sales in the U.S. were due, in part, to the FDA approval of Evista for the treatment of postmenopausal osteoporosis in the U.S., which was granted in September 1999. Sales outside the U.S. increased 115 percent, to $87.7 million.

ReoPro had worldwide sales of $418.2 million in 2000, representing a decrease of 7 percent. Sales in the U.S. decreased 12 percent, to $315.1 million. Sales outside the U.S. increased 15 percent, to $102.9 million. The decline in sales was due to increased competition in the U.S.

Diabetes care products, composed primarily of Humulin, the company's biosynthetic human insulin; Humalog, the company's insulin analog; and Actos, an oral diabetes agent introduced in the U.S. in 1999, had worldwide revenues of $1.76 billion in 2000, representing an increase of 22 percent. Diabetes care revenues in the U.S. increased 21 percent, to $1.08 billion. Diabetes care revenues outside the U.S. increased 22 percent, to $685.8 million. Humulin had worldwide sales of $1.21 billion, representing an increase of 2 percent. Humulin sales in the U.S. decreased 6 percent, to $617.4 million, largely as a result of patients shifting to Humalog and Humalog mixture products. Humulin sales outside the U.S. increased 25 percent, to $497.0 million. Humalog had worldwide sales of $350.2 million, representing an increase of 56 percent. Sales of Humalog benefited from the U.S. launch of Humalog Mix75/25™ Pen in the first quarter of 2000. The company received service revenues of $223.0 million in 2000 relating to sales of Actos. Actos, an oral agent for the treatment of type 2 diabetes, was introduced to the U.S. diabetes market in the third quarter of 1999. Actos is manufactured and sold in the U.S. by Takeda Chemical Industries, Ltd., and is copromoted by Takeda and the company.

Anti-infectives had worldwide sales of $894.3 million in 2000, representing a decrease of 13 percent, due to continuing competitive pressures. Cefaclor and Lorabid accounted for the majority of the decline. Sales in the U.S. decreased 12 percent, to $189.4 million. Sales outside the U.S. decreased 13 percent, to $702.9 million.

Animal health products had worldwide sales of $668.5 million in 2000, representing an increase of 6 percent. Sales in the U.S. increased 8 percent, to $307.5 million. Sales outside the U.S. increased 5 percent, to $360.9 million. The increases were balanced across the product line.

The company's payments under federally mandated Medicaid rebate programs reduced 2000 sales by approximately $464.0 million compared with approximately $352.5 million in 1999.

Gross Margin, Costs, and Expenses

The 2000 gross margin improved to 81.1 percent of sales compared with 79.0 percent for 1999. This increase was attributed primarily to favorable changes in product mix due to growth in sales of newer products and, to a lesser extent, increased production volume.

Operating expenses (the aggregate of research

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
Exhibit A, Page 18 of 52
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205098
Page 19

005893

Consolidated Statements of Income

Eli Lilly and Company and Subsidiaries (Dollars in millions, except per-share data) Year Ended December 31	2000	1999	1998
Net sales	$10,862.2	$10,002.9	$9,236.8
Cost of sales	2,055.7	2,098.0	2,015.1
Research and development	2,018.5	1,783.6	1,738.9
Marketing and administrative	3,228.3	2,757.6	2,658.3
Acquired in-process technology (Note 3)	—	—	127.5
Asset impairment and other site charges (Note 5)	—	87.4	—
Interest expense	182.3	183.8	181.3
Other income—net	(481.3)	(152.9)	(149.3)
	7,003.5	6,757.5	6,571.8
Income from continuing operations before income taxes and extraordinary item	3,858.7	3,245.4	2,665.0
Income taxes (Note 11)	800.9	698.7	568.7
Income from continuing operations before extraordinary item	3,057.8	2,546.7	2,096.3
Income from discontinued operations, net of tax (Note 4)	—	174.3	8.8
Extraordinary item, net of tax (Note 7)	—	—	(7.2)
Net income	$ 3,057.8	$ 2,721.0	$2,097.9
Earnings per share—basic (Note 20):			
Income from continuing operations before extraordinary item	$ 2.83	$ 2.34	$ 1.91
Income from discontinued operations	—	.16	.01
Extraordinary item	—	—	(.01)
Net income	$ 2.83	$ 2.50	$ 1.91
Earnings per share—diluted (Note 20):			
Income from continuing operations before extraordinary item	$ 2.79	$ 2.30	$ 1.87
Income from discontinued operations	—	.16	.01
Extraordinary item	—	—	(.01)
Net income	$ 2.79	$ 2.46	$ 1.87

See notes to consolidated financial statements.

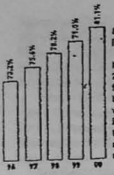
ZY 9553 919

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 20 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205099
Page 20

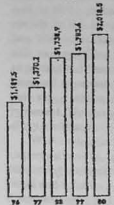
005894



Gross Margin
(as a percent of total net sales)

In 2000, gross margin improved by 2.1 percentage points, primarily due to favorable changes in product mix and, to a lesser extent, increased production volume. This continuous improvement in gross margin has enabled the company to aggressively fund investments in research and development, sales, and marketing.

and development and marketing and administrative expenses) increased 16 percent in 2000. Research and development expenses increased 13 percent, to $2.02 billion, in 2000 as the company continued to invest in both the early and late stages of its internal product pipeline and external collaborations. Marketing and administrative expenses increased 17 percent primarily due to sales force expansions and increased marketing efforts to support the company's newer products.



Research and Development
($ millions)

Worldwide research and development expenditures increased 13 percent in 2000 in support of the company's strong pipeline. Research and development expenditures represented 19 percent of total net sales in 2000 compared with 18 percent in 1999. The late-stage pipeline includes 10 new products for a wide range of serious, unmet medical needs that are expected to be launched during the period from 2001 to 2004.

Net other income for 2000 was $267.9 million, an increase of $142.8 million, excluding the gain on the sale of Xinetra LLC in 2000 and the gains from the litigation settlement and the sale of Lorabid marketing rights and a charge for the contribution to Eli Lilly and Company Foundation in 1999. The increase was primarily due to an increase in interest income.

The company's effective tax rate for 2000 was 20.8 percent compared with 21.5 percent for 1999. Excluding the unusual items discussed previously, the effective tax rate for both 2000 and 1999 was 22.0 percent. See Note 12 to the consolidated financial statements for additional information.

Operating Results From Continuing Operations—1999

Summary

Income from continuing operations was $2.55 billion, or $2.30 per share, in 1999 and $2.10 billion, or $1.87 per share, in 1998 (before the 1998 extraordinary charge of $7.2 million, or $.01 per share). Comparisons between 1999 and 1998 are made difficult by the impact of several unusual items that are reflected in the company's operating results for both years. Excluding these unusual items, which are discussed further below, income from continuing operations before extraordinary item for 1999 and 1998 would have been $2.52 billion, or $2.28 per share, and $2.17 billion, or $1.94 per share, respectively. This represents an increase in net income and earnings per share of 16 percent and 18 percent, respectively. The 1999 increases are attributed to increased sales, improved gross margin, and increases in operating expenses at a rate less than sales growth. Earnings per share also benefited from a decrease in the number of shares outstanding as a result of the share repurchase plan.

Unusual Items

As noted above, several unusual items are reflected in the company's operating results for 1999 and 1998. The unusual items relating to 1999 are summarized under Operating Results From Continuing Operations—2000. During 1998, the company recognized a pretax charge of $227.5 million for acquired in-process technology associated with a collaboration with ICOS Corporation, which reduced earnings per share by approximately $.07 net of tax. See Note 3 to the consolidated financial statements for additional information.

Sales

The company's reported worldwide sales for 1999 increased 8 percent, to $10.0 billion. Approximately $91 million of worldwide sales were related to year-2000 wholesaler buying. Sales growth was led by Zyprexa, Evista, Gemzar, diabetes care products, and ReoPro. Sales in the U.S. were $6.23 billion, a 7 percent increase, while sales outside the U.S. were $3.77 billion, an 11 percent increase. Worldwide sales reflected volume growth of 9 percent and a 1 percent increase in prices, partially offset by a 2 percent decrease in exchange rates.

Worldwide sales of Prozac in 1999 were $2.61 billion, representing a decrease of 7 percent. Approximately $12 million of worldwide Prozac sales were related to year-2000 wholesaler buying. Prozac sales in the U.S. decreased 8 percent, to $2.09 billion. Sales of Prozac outside the U.S. decreased 3 percent, to $525.1 million. The decline in U.S. sales was largely caused by wholesaler stocking that occurred during 1998, creating a significant adverse impact on sales comparisons in 1999. Prozac sales in the U.S. were also adversely affected by increased competition from new antidepressants.

Zyprexa posted worldwide sales of $1.89 billion in 1999, representing an increase of 31 percent.

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
Exhibit A, Page 21 of 52
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205100
Page 21
005895

Approximately $17 million of worldwide Zyprexa sales were related to year-2000 wholesaler buying. U.S. sales of Zyprexa increased 22 percent, to $1.37 billion. Sales outside the U.S. increased 62 percent, to $513.9 million.

Worldwide Gemzar sales of $455.8 million in 1999 reflected an increase of 49 percent. Sales in the U.S. increased 57 percent, to $264.2 million, and sales outside the U.S. increased 38 percent, to $191.6 million.

Worldwide ReoPro sales of $447.3 million in 1999 reflected an increase of 22 percent. U.S. sales of ReoPro increased 18 percent, to $357.5 million. ReoPro sales outside the U.S. increased 43 percent, to $89.8 million.

Worldwide diabetes care revenues, composed of Humulin, Humalog, Iletin, and Actos, increased 19 percent, to $1.38 billion, in 1999. Approximately $23 million of worldwide diabetes care revenues were related to year-2000 wholesaler buying. Diabetes care revenue in the U.S. increased 18 percent, to $827.7 million. Diabetes care revenue outside the U.S. increased 21 percent, to $547.5 million. Worldwide Humulin sales increased 13 percent, to $1.09 billion. U.S. Humulin sales increased 12 percent and Humulin sales outside the U.S. increased 15 percent. Worldwide Humalog sales were $224.5 million, representing an increase of 73 percent. The company received service revenues of $37.9 million in 1999 relating to sales of Actos.

Worldwide sales of anti-infectives decreased 12 percent in 1999, to $1.02 billion, as a result of continuing competitive pressures. U.S. and international anti-infectives sales declined 22 percent and 8 percent, respectively. Cefaclor and Lorabid accounted for the majority of the decline in anti-infectives sales, offsetting growth in Vancocin® outside the U.S.

Evista sales increased $182.0 million, or 126 percent, to $326.1 million in 1999. Evista was launched in the first quarter of 1998 in the U.S. for the prevention of osteoporosis in postmenopausal women. During 1999, the company received approval from the FDA to promote Evista for the treatment of postmenopausal osteoporosis. While most of the sales dollar growth for Evista occurred in the U.S., international Evista sales reflected strong percentage growth.

Worldwide sales of animal health products of $627.8 million in 1999 reflected a 2 percent increase. Sales were flat in the U.S. and increased 4 percent outside the U.S.

The company's payments under federally mandated Medicaid rebate programs reduced 1999 sales by approximately $352.5 million compared with approximately $278.6 million in 1998.

Gross Margin, Costs, and Expenses

The 1999 gross margin improved to 79.0 percent of sales compared with 78.2 percent for 1998. This increase was attributed primarily to production efficiencies and, to a lesser extent, favorable changes in product mix, as well as the expiration of Humulin and Humalog royalties in August 1998.

Operating expenses (the aggregate of research and development and marketing and administrative expenses) increased 3 percent in 1999. Research and development investments increased 3 percent, to $1.78 billion, in 1999 as the company continued to build internal and external capabilities. Reduced incentive compensation significantly offset the expense growth. In addition, Phase III clinical trials for certain compounds were discontinued in the first half of 1999, which contributed to the reduction in the growth rate. Marketing and administrative expenses increased 4 percent due to increased spending to support new product launches around the world and enhancements in the company's global information technology systems, including year-2000 readiness efforts. However, the impact of these increases was mitigated by expense management initiatives and reduced incentive compensation.

Excluding the gains from the litigation settlement, the sale of Lorabid marketing rights, and the charge for the contribution to Eli Lilly and Company Foundation, net other income for 1999 was $125.1 million, which represents a decrease of $24.2 million. Other income in 1998 benefited from gains generated from the sale of investments.

The company's effective tax rate for 1999 was 21.5 percent compared with 21.3 percent for 1998. Excluding the unusual items discussed previously, the effective tax rates for 1999 and 1998 were 22.0 percent and 22.2 percent, respectively.

Discontinued Operations

Discontinued operations consist of the company's PCS health-care-management business. In November 1998, the company entered into an agreement to sell PCS for $1.60 billion in cash. The sale was closed in January 1999 and the resulting net gain on disposal of $174.3 million, net of $8.7 million tax benefit, was recognized in the first quarter of 1999. See Note 4 to the consolidated financial statements for further information.

Financial Condition

As of December 31, 2000, cash, cash equivalents, and short-term investments totaled approximately $4.62 billion compared with $3.84 billion at December 31, 1999. The increase in cash was primarily due to cash generated from operations, partially offset by dividends paid, share repurchases, and

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
ZY 9553 921
Exhibit A, Page 22 of 52
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205101
Page 22
005896

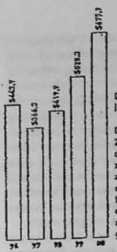
capital expenditures. The company acquired approximately 14.8 million shares, for approximately $1.09 billion, during 2000 pursuant to its previously announced $3 billion share repurchase program. Total debt at December 31, 2000, was $2.82 billion, a decrease of $235.4 million. The company believes that cash generated from operations, along with available cash and cash equivalents, will be sufficient to fund essentially all the company's operating needs, including debt service, capital expenditures, and dividends in 2001.

The company believes that amounts available through existing commercial paper programs should be adequate to fund maturities of short-term borrowings. The company's commercial paper program is also backed by $2.02 billion of committed bank credit facilities.

In the normal course of business, operations of the company are exposed to fluctuations in interest rates. These fluctuations can vary the costs of financing, investing, and operating. The company addresses a portion of these risks through a controlled program of risk management that includes the use of derivative financial instruments. The objective of controlling these risks is to limit the impact on earnings of fluctuations in interest rates. All derivative activities are for purposes other than trading.

The company's primary interest rate risk exposure results from changes in short-term U.S. dollar interest rates. In an effort to manage interest rate exposures, the company strives to achieve an acceptable balance between fixed and floating rate debt positions and may enter into interest rate swaps to help maintain that balance. Based on the company's overall interest rate exposure at December 31, 2000, including derivatives and other interest rate risk sensitive instruments, a hypothetical 10 percent change in interest rates applied to the fair value of the instruments as of December 31, 2000, would have no material impact on earnings, cash flows, or fair values of interest rate risk sensitive instruments over a one-year period. Similarly, a hypothetical 10 percent change in interest rates from 1999 applied to the fair value of the instruments as of December 31, 1999, would have had no material impact on earnings, cash flows, or fair values of interest rate risk sensitive instruments during 2000.

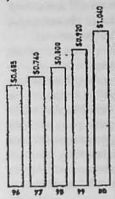
Capital expenditures of $677.9 million during 2000 were $249.6 million more than in 1999 as the company continued to invest in manufacturing and research and development initiatives and related infrastructure. The company expects near-term capital expenditures to increase from 2000 levels. Sufficient cash flows exist to meet these near-term requirements.



Capital Expenditures
($ millions)

Capital expenditures increased 28 percent from the 1999 level, primarily due to the increased support of various manufacturing and research initiatives and related infrastructure. The company expects near-term capital expenditures to increase from 2000 levels due to continuing investment in research and manufacturing capacity to support its growing portfolio.

Dividends of $1.04 per share were paid in 2000, an increase of 13 percent from the $.92 per share paid in 1999. In the fourth quarter of 2000, effective for the first-quarter dividend in 2001, the quarterly dividend was increased to $.28 per share (8 percent), resulting in an indicated annual rate for 2001 of $1.12 per share. The year 2000 was the 116th consecutive year in which the company made dividend payments and the 33rd consecutive year in which dividends have been increased.



Dividends Paid per Share
(dollars)

Dividends paid during 2000 increased 13 percent over 1999. The year 2000 became the 33rd consecutive year in which dividends were increased. The continued earnings growth in 2000 enabled the company to declare a first-quarter 2001 dividend of $.28 per share, an 8 percent increase over 2000. The increase reflects the company's continued commitment to delivering shareholder value.

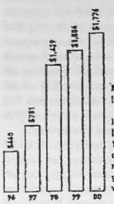
Euro Conversion

On January 1, 1999, 11 European nations adopted a common currency, the euro, and formed the European Economic and Monetary Union (EMU). For a three-year transition period, both the euro and individual participants' currencies will remain in circulation. After July 1, 2002, at the latest, the euro will be the sole legal tender for EMU countries. Greece has joined the original 11 countries adopting the euro in 2002. The adoption of the euro affects a multitude of financial systems and business applications as the commerce of these nations is transacted in the euro and the existing national currency.

The company has created the capability to transact in both the euro and the legacy currency and has converted the underlying information systems within the EMU countries from the legacy currencies to the euro. The company will continue

ZY 9553 922
Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
Exhibit A, Page 23 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205102
Page 23
005897

to address euro-related issues and their impact on information systems, currency exchange rate risk, taxation, contracts, competition, and pricing. Action plans currently being implemented are expected to result in compliance with all laws and regulations; however, there can be no certainty that such plans will be successfully implemented or that external factors will not have an adverse effect on the company's operations. Any costs of compliance associated with the adoption of the euro are expensed as incurred and the company does not expect these costs to be material to its results of operations, financial condition, or liquidity.



Economic Value Added
($ millions)

In 2000, Lilly's Economic Value Added (EVA) was $1.8 billion, an increase of 12 percent, reflecting the company's commitment to effective asset management and focus on earnings growth in order to deliver shareholder value.

Financial Expectations for 2001

As noted above, a federal appeals court has upheld the company's February 2001 U.S. Prozac patent but ruled that the 2003 patent is invalid. In addition, the FDA has granted the company an additional six months of market exclusivity for Prozac under a federal statute encouraging pediatric studies of certain medicines, extending market exclusivity for Prozac to August 2, 2001, assuming the 2003 Prozac patent ruling is not overturned. The company expects a very substantial decline in Prozac sales in the U.S. in the 12 months following the entry of generic fluoxetine in the U.S. market. Prozac sales in the U.S. represent a significant portion of the company's overall sales, accounting for approximately 20 percent of the company's consolidated worldwide sales in 2000.

As a result of the above, excluding any unusual items, the company anticipates earnings per share for 2001 to be in the range of $2.75 to $2.85, assuming the entry of generic fluoxetine in the U.S. in August 2001. Strong earnings growth in the first half of 2001 is expected to more than offset declines in the second half, resulting in single-digit earnings growth for the full year compared with 2000 earnings per share of $2.65, excluding unusual items.

In addition, excluding any unusual items, the company expects to post single-digit sales growth in 2001. Excluding worldwide sales of Prozac, the company expects sales to grow in the mid-teens for 2001. Several key products are expected to contribute to this growth, including Zyprexa; Evista; Gemzar; diabetes care products; and drotrecogin alfa (activated), also known by the proposed trade name Zovant, a therapy for sepsis, which was submitted for regulatory approval in early 2001 and is expected to launch in the second half of 2001. The growth in these products is anticipated to more than offset the very substantial expected decline of Prozac sales and continuing decreases in sales of anti-infectives and ReoPro.

Gross margins as a percent of sales are expected to decline in 2001 in the range of .5 to 1.0 percentage points as a result of the decline in Prozac sales. The company anticipates marketing and administrative expenses will grow in the low-to-mid single digits. Underlying marketing expenses for continuing products, excluding Prozac, are expected to grow in the double digits as the company continues to invest in sales force expansions and increased marketing efforts. Research and development expenses are expected to grow in the low double digits, demonstrating the company's continued commitment to invest in scientific innovation. The tax rate is expected to remain at approximately 22 percent for the full year.

The company believes that the loss of Prozac market exclusivity will not have a material adverse effect on the company's consolidated financial position or liquidity. The actual impact will depend on, among other things, the outcome of the appeal of the Federal Circuit ruling; the timing, number of entrants, and pricing strategies of generic competitors; the continuing growth of the company's other currently marketed products; developments with competitive products; the timing of regulatory approvals; and the expected introduction of new products.

Legal and Environmental Matters

Barr Laboratories, Inc. (Barr), and Geneva Pharmaceuticals, Inc. (Geneva), have each submitted an Abbreviated New Drug Application (ANDA) seeking FDA approval to market generic forms of Prozac before the expiration of the company's patents. The ANDAs assert that two U.S. patents held by Lilly covering Prozac are invalid and unenforceable. The company filed suit against Barr and Geneva in federal court in Indianapolis seeking a ruling that Barr's challenge to Lilly's patents is without merit. In January 1999, the trial court granted summary judgment in favor of Lilly on two of the four claims raised by Barr and Geneva against Lilly's patents. That decision was appealed to the Court of Appeals for the Federal Circuit. Barr and Geneva dismissed their other two claims in exchange for a $4 million

ZY 9553 923

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 24 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205103
Page 24

005898

payment. On August 9, 2000, the Court of Appeals upheld the 2001 compound patent but held that the 2003 method of use patent was invalid. The company has filed a petition requesting a rehearing by the Court of Appeals.

Several other generic manufacturers have also filed ANDAs for generic forms of Prozac, challenging one or both of the patents. In late 1998, Zenith Goldline Pharmaceuticals, Inc.; Teva Pharmaceuticals USA (Teva); and Cheminor Drugs, Ltd., together with one of its subsidiaries (Cheminor), notified the company that they had filed ANDAs challenging the 2003 patent. Also in 1998, Novex Pharma, a division of Apotex, Inc., notified the company that it had filed an ANDA challenging both patents. In 1999, Cheminor notified the company that it had filed an ANDA for a different dosage form. In 2000, Barr and Teva both notified the company that they had filed additional ANDAs for the different dosage form, and Alphapharm Pty. Ltd. also notified the company that it had filed ANDAs for two dosage forms.

The company has filed lawsuits in the United States District Court of the Southern District of Indiana seeking rulings that all these challenges to the patent(s) are without merit. The cases are awaiting resolution of the petition for rehearing by the Court of Appeals in the original Barr case.

For additional information on the impact of the Prozac patent litigation, see the "Financial Expectations for 2003" section above.

In addition, the company is a defendant in numerous product liability suits involving primarily two products, diethylstilbestrol (DES) and Prozac. See Note 13 to the consolidated financial statements for further information on those matters.

The company's worldwide operations are subject to complex and changing environmental and health and safety laws and regulations, which will continue to require capital investment and operational expenses. The company has also been designated a potentially responsible party with respect to fewer than 10 sites under the federal environmental law commonly known as Superfund. For more information on those matters, see Note 13 to the consolidated financial statements.

While it is not possible to predict or determine the outcome of the patent, product liability, or other legal actions brought against the company or the ultimate cost of environmental matters, the company believes that, except as noted above with respect to the Prozac patent litigation, the costs associated with all such matters will not have a material adverse effect on its consolidated financial position or liquidity but could possibly be material to the consolidated results of operations in any one accounting period.

Other Matters

On October 28, 2000, President Clinton signed the Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act for fiscal year 2001. This legislation includes a provision that repeals the federal ban on the reimportation of most prescription drugs by anyone other than the manufacturer. Consequently, under the new law, wholesalers and pharmacists may be permitted to reimport certain drugs approved for sale in the U.S. and originally sold abroad, subject to several conditions. The law authorizes reimportation from select jurisdictions, including Australia, Canada, the European Union, Israel, Japan, New Zealand, South Africa, and Switzerland.

Before the law takes effect, the secretary of Health and Human Services (HHS) must "demonstrate" to Congress that the law poses no additional risk to public health and safety and will result in significant reductions in drug costs for American consumers. If HHS can make that demonstration, then the FDA must draft regulations prior to implementing the law. In December 2000, the secretary of HHS stated that she would be unable to make the demonstration required by the law. It is uncertain what action, if any, may be taken on this bill by the incoming secretary of HHS or whether Congress will modify the legislation.

The company cannot predict at this time the extent to which it will be affected by this legislation or potential future legislative or regulatory developments in this area. However, if widespread reimportation of the company's products were to occur, this could have a material adverse effect on the company's results of operations.

Private Securities Litigation Reform Act of 1995—A Caution Concerning Forward-Looking Statements

Under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, the company cautions investors that any forward-looking statements or projections made by the company, including those made in this document, are based on management's expectations at the time they are made, but they are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Economic, competitive, governmental, technological, and other factors that may affect the company's operations and prospects are discussed in Exhibit 99 to the company's most recent report on Forms 10-Q and 10-K filed with the Securities and Exchange Commission.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
Exhibit-A, Page 25 of 62
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205104
Page 25
005899

Consolidated Balance Sheets

Eli Lilly and Company and Subsidiaries (Dollars in millions) December 31	2000	1999
Assets		
Current Assets		
Cash and cash equivalents	$ 4,214.9	$ 3,700.4
Short-term investments	593.3	135.6
Accounts receivable, net of allowances of $215.3 (2000) and $79.9 (1999)	1,630.7	1,443.2
Other receivables	335.4	399.6
Inventories	883.1	899.6
Deferred income taxes (Note 11)	269.5	240.3
Prepaid expenses	206.1	236.8
Total current assets	7,943.0	7,055.5
Other Assets		
Prepaid retirement (Note 12)	1,032.5	741.2
Investments	395.7	180.3
Sundry	1,143.0	866.8
	2,571.2	1,788.2
Property and Equipment	4,176.6	3,981.5
	$14,690.8	$12,825.2

ZY 9553 925

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 26 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205105
Page 26

005900

(Dollars in millions) December 31	2000	1999
Liabilities and Shareholders' Equity		
Current Liabilities		
Short-term borrowings (Note 7)	$ 184.3	$ 241.5
Accounts payable	661.9	445.5
Employee compensation	468.3	489.3
Dividends payable	315.4	283.0
Income taxes payable (Note 11)	2,200.2	1,445.3
Other liabilities	1,130.6	1,030.8
Total current liabilities	4,960.7	3,935.4
Other Liabilities		
Long-term debt (Note 7)	2,633.7	2,811.9
Deferred income taxes (Note 11)	91.6	137.0
Retiree medical benefit obligation (Note 12)	83.3	115.7
Other noncurrent liabilities	874.6	812.2
	3,683.2	3,876.8
Commitments and contingencies (Note 13)	—	—
Shareholders' Equity (Notes 8 and 9)		
Common stock—no par value		
Authorized shares: 3,200,000,000		
Issued shares: 1,126,567,407 (2000) and 1,091,226,806 (1999)	704.4	682.0
Additional paid-in capital	2,610.0	—
Retained earnings	6,223.2	4,985.6
Employee benefit trust	(2,635.0)	—
Deferred costs—ESOP	(235.0)	(139.9)
Accumulated other comprehensive income (Note 14)	(611.2)	(406.4)
	6,156.4	5,121.3
Less cost of common stock in treasury: 2000—1,007,235 shares 1999—988,902 shares	109.5	108.3
	6,046.9	5,013.0
	$14,690.8	$12,825.2

See notes to consolidated financial statements.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
Exhibit A, Page 27 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205106
Page 27
005901

Consolidated Statements of Cash Flows

Eli Lilly and Company and Subsidiaries (Dollars in millions) Year Ended December 31	2000	1999	1998
Cash Flows From Operating Activities			
Net income	$ 3,057.8	$ 2,721.0	$ 2,097.9
Adjustments To Reconcile Net Income to Cash Flows From Operating Activities			
Depreciation and amortization	435.8	439.7	490.4
Change in deferred taxes	(442.7)	27.1	25.4
Gain on sale of Kinetra, net of tax	(214.4)	—	—
Gain on sale of PCS, net of tax	—	(374.3)	—
Asset impairment and other site charges, net of tax	—	58.1	—
Other, net	127.3	96.6	153.5
	2,953.8	3,168.2	2,767.2
Changes in operating assets and liabilities:			
Receivables—increase	(165.4)	(179.0)	(403.6)
Inventories—(increase) decrease	9.8	16.9	(55.6)
Other assets—increase	(210.5)	(88.8)	(81.1)
Accounts payable and other liabilities—increase (decrease)	1,143.8	(174.9)	649.4
	777.7	(425.8)	109.1
Net Cash Provided by Operating Activities	3,731.5	2,742.4	2,876.3
Cash Flows From Investing Activities			
Purchase of property and equipment	(677.9)	(528.3)	(419.9)
Disposals of property and equipment	5.1	78.3	30.6
Proceeds from sale of investments	983.9	216.1	273.1
Purchase of investments	(1,233.2)	(262.8)	(57.6)
Proceeds from sale of PCS	—	1,600.0	—
Other, net	(134.4)	(116.6)	(195.1)
Net Cash Provided by (Used in) Investing Activities	(1,056.5)	1,086.7	(368.9)
Cash Flows From Financing Activities			
Dividends paid	(1,226.0)	(1,000.5)	(877.7)
Purchase of common stock and other capital transactions	(1,052.8)	(1,453.0)	(1,999.8)
Issuances under stock plans	278.4	187.5	242.5
Redemption of subsidiary stock	—	—	(172.8)
Net change in short-term borrowings	(203.0)	(339.4)	(170.0)
Proceeds from issuance of long-term debt	1.1	843.5	23.8
Repayments of long-term debt	(27.2)	(13.5)	(30.2)
Net Cash Used for Financing Activities	(2,229.5)	(1,575.4)	(2,984.2)
Effect of exchange rate changes on cash	(31.0)	(49.0)	25.0
Net increase (decrease) in cash and cash equivalents	414.5	2,204.7	(451.8)
Cash and cash equivalents at beginning of year	3,700.4	1,495.7	1,947.5
Cash and cash equivalents at end of year	$ 4,114.9	$ 3,700.4	$ 1,495.7

See notes to consolidated financial statements.

ZY 9553 927

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 28 of 52
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205107
Page 28

005902

Segment Information

The company operates in one significant business segment—pharmaceutical products. Operations of the animal health business segment are not material and share many of the same economic and operating characteristics as pharmaceutical products. Therefore, they are included with pharmaceutical products for purposes of segment reporting.

Eli Lilly and Company and Subsidiaries (Dollars in millions) Year Ended December 31	2000	1999	1998
Net sales—to unaffiliated customers			
Neurosciences	$ 5,157.6	$ 4,729.3	$4,487.8
Endocrinology	2,583.5	2,075.5	1,626.6
Anti-infectives	894.3	1,022.3	1,160.9
Animal health	668.5	627.8	614.4
Cardiovascular	587.9	637.6	536.9
Oncology	580.5	486.1	339.2
Gastrointestinal	321.4	354.7	418.0
Other pharmaceutical	68.5	69.6	53.0
Net sales	$10,862.2	$10,002.9	$9,236.8
Geographic Information			
Net sales—to unaffiliated customers[1]:			
United States	$ 7,002.9	$ 6,226.4	$5,836.2
Western Europe	1,773.9	1,888.0	1,692.3
Other foreign countries	2,085.4	1,888.5	1,708.3
	$10,862.2	$10,002.9	$9,236.8
Long-lived assets:			
United States	$ 3,621.0	$ 3,416.8	$3,363.5
Western Europe	735.3	744.2	808.4
Other foreign countries	472.1	470.3	459.3
	$ 4,828.4	$ 4,631.3	$4,631.2

[1]Net sales are attributed to the countries based on the location of the subsidiary making the sale.

The largest category of products is the neurosciences group, which includes Prozac, Zyprexa, Permax®, and Darvon®. Endocrinology products consist primarily of Humulin, Evista, Humalog, Humatrope®, and Actos. Anti-infectives include primarily Ceclor®, Vancocin, Keflex®, Nebcin®, and Lorabid. Cardiovascular products consist primarily of ReoPro and Dobutrex®. The gastrointestinal category is entirely composed of Axid®. Oncology products consist primarily of Gemzar. Animal health products include Tylan®, Rumensin®, Micotil®, Surmax®, Coban®, and other products for livestock and poultry. The other pharmaceutical product group includes other miscellaneous pharmaceutical products and services.

Most of the pharmaceutical products are distributed through wholesalers that serve physicians and other health care professionals, pharmacies, and hospitals. In 2000, the company's three largest wholesalers each accounted for between 14 percent and 18 percent of consolidated net sales. Animal health products are sold primarily to wholesale distributors.

The company's business segments are distinguished by the ultimate end user of the product: humans or animals. Performance is evaluated based on profit or loss from operations before income taxes. The accounting policies of the individual segments are substantially the same as those described in the summary of significant accounting policies in Note 1. Income before taxes for the animal health business was approximately $180.0 million, $165.0 million, and $141.0 million in 2000, 1999, and 1998, respectively. The assets of the animal health business are intermixed with those of the pharmaceutical products business and are not separately determinable. Long-lived assets disclosed above consist of property and equipment and certain sundry assets of the continuing operations.

The company is exposed to the risk of changes in social, political, and economic conditions inherent in foreign operations, and the company's results of operations and the value of its foreign assets are affected by fluctuations in foreign currency exchange rates.

ZY 9553 928

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 29 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205108
Page 29

005903

Consolidated Statements of Comprehensive Income

Eli Lilly and Company and Subsidiaries (Dollars in millions) Year Ended December 31	2000	1999	1998
Net income	$3,057.8	$2,721.0	$2,097.9
Other comprehensive income (loss):			
Foreign currency translation adjustments	(170.7)	(177.7)	69.2
Net unrealized gains (losses) on securities (Note 14)	(20.5)	27.8	(2.6)
Minimum pension liability adjustment	(33.6)	(26.7)	(30.8)
Other comprehensive income (loss) before income taxes	(224.8)	(176.6)	35.8
Provision for income taxes related to other comprehensive income items	20.0	—	15.6
Other comprehensive income (loss)	(204.8)	(176.6)	51.4
Comprehensive income	$2,853.0	$2,544.4	$2,149.3

See notes to consolidated financial statements.

ZY 9553 929

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 30 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205109
Page 30

005904

Selected Quarterly Data (unaudited)

Eli Lilly and Company and Subsidiaries
(Dollars in millions, except per-share data)

2000	Fourth	Third	Second	First
Net sales	$2,977.7	$2,811.9	$2,621.5	$2,451.1
Cost of sales	565.2	490.1	491.7	508.7
Operating expenses	1,489.4	1,306.4	1,304.2	1,146.8
Other (income) expense—net	(60.6)	17.0	(28.5)	(226.9)
Income before income taxes	983.7	998.4	854.1	1,022.5
Net income	767.3	778.8	666.2	845.5
Earnings per share—basic	.71	.72	.62	.78
Earnings per share—diluted	.70	.71	.61	.77
Dividends paid per share	.26	.26	.26	.26
Common stock prices:				
High	94.50	108.24	101.33	70.86
Low	80.64	67.18	64.13	54.34

1999	Fourth	Third	Second	First
Net sales	$2,820.5	$2,585.2	$2,341.6	$2,255.6
Cost of sales	565.2	548.2	491.1	493.5
Operating expenses	1,285.8	1,139.3	1,110.1	1,006.0
Asset impairment and other site charges	26.0	—	—	61.4
Other (income) expense—net	(80.2)	(42.5)	1.4	151.2
Income from continuing operations before income taxes	1,023.7	939.2	739.0	543.5
Income from: Continuing operations	786.3	732.6	576.4	451.4
Discontinued operations	—	—	—	174.3
Net income	786.3	732.6	576.4	625.7
Earnings per share—basic:				
Continuing operations	.73	.68	.53	.43
Discontinued operations	—	—	—	.16
Net income	.73	.68	.53	.57
Earnings per share—diluted:				
Continuing operations	.72	.67	.52	.40
Discontinued operations	—	—	—	.16
Net income	.72	.67	.52	.56
Dividends paid per share	.23	.23	.23	.23
Common stock prices:				
High	77.38	77.19	90.25	97.44
Low	64.13	61.50	65.19	76.19

The company's common stock is listed on the New York, London, Tokyo, and other stock exchanges.

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29

Selected Financial Data (unaudited)

Eli Lilly and Company and Subsidiaries (Dollars in millions, except per-share data)	2000	1999	1998	1997	1996
Operations					
Net sales	$10,862.2	$10,002.9	$9,236.8	$7,987.7	$6,998.3
Research and development	2,018.5	1,783.6	1,738.9	1,370.2	1,189.5
Other costs and expenses	4,985.0	4,973.9	4,832.9	4,348.2	3,677.5
Gain on sale of DowElanco	—	—	—	(631.8)	—
Income from continuing operations before taxes and extraordinary item	3,858.7	3,245.4	2,665.0	2,901.1	2,231.3
Income taxes	800.9	698.7	568.7	885.2	505.6
Income (loss) from:					
Continuing operations before extraordinary item	3,057.8	2,546.7	2,096.3	2,015.9	1,625.7
Discontinued operations	—	174.3	8.8	(2,401.0)	(102.2)
Net income (loss)	3,057.8	2,721.0	2,097.9[2]	(385.1)	1,523.5
Income from continuing operations before extraordinary item as a percent of sales	28.2%	25.5%	22.7%	25.2%	23.2%
Per-share data—diluted:					
Income (loss) from:					
Continuing operations before extraordinary item	$ 2.79	$ 2.30	$ 1.87	$ 1.78	$ 1.45
Discontinued operations	—	.16	.01	(2.12)	(.09)
Net income (loss)	2.79	2.46	1.87[2]	(.34)	1.36
Dividends declared per share	1.06	.95	.83	.76	.694
Weighted-average number of shares outstanding—diluted (thousands)	1,097,725	1,106,055	1,121,486	1,130,579	1,117,110
Financial Position					
Current assets	$ 7,943.0	$ 7,055.5	$ 5,406.8	$ 5,320.7	$ 3,891.3
Current liabilities	4,960.7	3,935.4	4,607.2	4,191.6	4,222.2
Property and equipment—net	4,176.6	3,981.5	4,096.3	4,101.7	4,307.0
Total assets	14,690.8	12,825.2	12,595.5	12,577.4	14,307.2
Long-term debt	2,633.7	2,811.9	2,185.5	2,326.1	2,576.5
Shareholders' equity	6,046.9	5,013.0	4,429.6	4,645.6	6,100.1
Supplementary Data[1]					
Return on shareholders' equity	55.3%	53.9%	46.2%	37.5%	28.2%
Return on assets	22.9%	21.3%	17.0%	15.4%	11.4%
Capital expenditures	$ 677.9	$ 528.3	$ 419.9	$ 366.3	$ 443.9
Depreciation and amortization	435.8	439.7	490.4	509.8	543.5
Effective tax rate	20.8%	21.5%	22.3%	30.5%[3]	23.7%
Number of employees	35,700	31,300	29,800	28,900	27,400
Number of shareholders of record	59,290	62,300	62,300	58,200	54,500

1 All supplementary financial data have been computed using income from continuing operations except for capital expenditures and depreciation and amortization, which include amounts from discontinued operations. The number of employees reflects continuing operations, including controlled joint ventures.

2 Reflects the impact of an extraordinary item (see Note 7).

3 Excluding the impacts of the unusual transactions reflected in 1997, the effective tax rate would have been 24.2 percent.

ZY 9553 931

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
Exhibit A, Page 32 of 62
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205111
Page 32
005906

Notes to Consolidated Financial Statements

Eli Lilly and Company and Subsidiaries
(Dollars in millions, except per-share data)

Note 1: Summary of Significant Accounting Policies

Basis of presentation: The accounts of all wholly owned and majority-owned subsidiaries are included in the consolidated financial statements. All intercompany balances and transactions have been eliminated.

The preparation of financial statements in conformity with generally accepted accounting principles requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenues, expenses, and related disclosures at the date of the financial statements and during the reporting period. Actual results could differ from those estimates.

All per-share amounts, unless otherwise noted in the footnotes, are presented on a diluted basis, that is, based on the weighted-average number of outstanding common shares and the effect of all potentially dilutive common shares (primarily unexercised stock options).

Reclassifications: Certain reclassifications have been made to prior-year amounts to conform with current-year presentation.

Cash equivalents: The company considers all highly liquid investments, generally with a maturity of three months or less, to be cash equivalents. The cost of these investments approximates fair value.

Inventories: The company states all its inventories at the lower of cost or market. The company uses the last-in, first-out (LIFO) method for substantially all its inventories located in the continental United States, or approximately 60 percent of its total inventories. Other inventories are valued by the first-in, first-out (FIFO) method. Inventories at December 31 consisted of the following:

	2000	1999
Finished products	$284.3	$295.1
Work in process	380.6	372.7
Raw materials and supplies	230.1	224.7
	895.0	892.5
Increase (decrease) to LIFO cost	(11.9)	7.1
	$883.1	$899.6

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Investments: All short-term debt securities are classified as held-to-maturity because the company has the positive intent and ability to hold the securities to maturity. Held-to-maturity securities are stated at amortized cost, adjusted for amortization of premiums and accretion of discounts to maturity. Substantially all long-term debt and marketable equity securities are classified as available-for-sale. Available-for-sale securities are carried at fair value, with the unrealized gains and losses, net of tax, reported in other comprehensive income. Realized gains and losses on sales of available-for-sale securities are computed based upon initial cost adjusted for any other than temporary declines in fair value. The company owns no investments that are considered to be trading securities.

Derivative financial instruments: The company's derivative activities, all of which are for purposes other than trading, are initiated within the guidelines of documented corporate risk-management policies and do not create additional risk because gains and losses on derivative contracts offset losses and gains on the assets, liabilities, and transactions being hedged. As derivative contracts are initiated, the company designates the instruments individually as hedges of underlying financial instruments or anticipated transactions (i.e., underlying exposures). Management reviews the correlation and effectiveness of its derivatives on a periodic basis. Derivative contracts that do not qualify for deferral hedge accounting are marked to market.

For terminations of derivatives receiving deferral accounting, gains and losses are deferred when the related underlying exposures remain outstanding and are included in the measurement of the related transaction or balance. In addition, upon termination of the underlying exposures, the derivative is marked to market and the resulting gain or loss is included with the gain or loss on the related transaction. The company may redesignate the remaining derivative instruments as hedges of other underlying exposures.

The company enters into foreign currency forward and option contracts to reduce the effect of fluctuating currency exchange rates (principally the Japanese yen and the euro). Generally, foreign currency derivatives used for hedging are put in place using the same or like currencies and duration as

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
Exhibit A, Page 33 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205112
Page 33
005907

the underlying exposures. Forward contracts are principally used to manage exposures arising from affiliate foreign currency balances. These contracts are marked to market with gains and losses recognized currently in income to offset the respective losses and gains recognized on the underlying exposures. The company also enters into purchased option contracts to hedge anticipated foreign currency transactions, primarily intercompany inventory activities expected to occur within the next year, and foreign currency forward contracts and currency swaps to hedge firm commitments. The contracts are designated and effective as hedges of those future transactions. Gains and losses on these contracts that qualify as hedges are deferred and recognized as an adjustment of the subsequent transaction when it occurs. Forward and option contracts generally have maturities not exceeding 12 months.

The company also enters into interest rate swaps to manage interest rate exposures. The company designates the interest rate swaps as hedges of the underlying debt. Interest expense on the debt is adjusted to include the payments made or received under the swap agreements.

Goodwill and other intangibles: Goodwill and other intangibles arising from acquisitions and research alliances are amortized over their estimated useful lives, ranging from 5-25 years, using the straight-line method. Goodwill and other intangibles are reviewed to assess recoverability when impairment indicators are present. Assets are considered to be impaired and are written down to fair value if expected future operating cash flows of the related assets are less than their carrying amounts. Fair value is the present value of the expected future cash flows of the related assets using a discount rate commensurate with the risk involved. Assets are grouped at the lowest level for which there are identifiable cash flows for purposes of impairment testing. Goodwill and other intangibles and the related allowances for amortization were $233.2 million and $217.8 million, respectively, at December 31, 2000, and $226.2 million and $107.6 million, respectively, at December 31, 1999, and are included in sundry assets in the consolidated balance sheets.

Property and equipment: Property and equipment is stated on the basis of cost. Provisions for depreciation of buildings and equipment are computed generally by the straight-line method at rates based on their estimated useful lives (generally 12 to 50 years for buildings and 5 to 18 years for equipment). At December 31, property and equipment consisted of the following:

	2000	1999
Land	$ 103.5	$ 104.6
Buildings	2,395.1	2,255.8
Equipment	4,638.5	4,458.9
Construction in progress	647.6	528.0
	7,784.7	7,347.3
Less allowances for depreciation	3,608.1	3,365.8
	$4,176.6	$3,981.5

Depreciation expense related to continuing operations for 2000, 1999, and 1998 was $393.5 million, $406.7 million, and $393.4 million, respectively. Approximately $43.1 million, $29.0 million, and $17.0 million of interest costs were capitalized as part of property and equipment in 2000, 1999, and 1998, respectively. Total rental expense for all leases related to continuing operations, including contingent rentals (not material), amounted to approximately $172.3 million for 2000, $154.9 million for 1999, and $134.8 million for 1998. Capital leases included in property and equipment in the consolidated balance sheets, capital lease obligations entered into, and future minimum rental commitments are not material.

Revenue recognition: Revenue from sales of products is recognized at the time title of goods passes to the buyer and the buyer assumes the risks and rewards of ownership. This is generally at the time products are shipped to the customer. Revenue from copromotion services is recognized at the time the copromotion partner records sales.

Income taxes: Deferred taxes are recognized for the future tax effects of temporary differences between financial and income tax reporting based on enacted tax laws and rates. Federal income taxes are provided on the portion of the income of foreign subsidiaries that is expected to be remitted to the United States and be taxable.

Earnings per share: Basic earnings per share are calculated based on the weighted-average number of outstanding common shares and incremental shares. Diluted earnings per share are calculated based on the weighted-average number of outstanding common shares plus the effect of dilutive stock options and other incremental shares.

ZY 9553 933

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 34 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205113
Page 34

005908

Note 2: Implementation of New Financial Accounting Pronouncements

In June 1998, Statement of Financial Accounting Standards (SFAS) No. 133, "Accounting for Derivative Instruments and Hedging Activities," was issued. Statement 133 was amended in June 1999 and is now required to be adopted in years beginning after June 15, 2000. The company will adopt Statement 133 effective as of January 1, 2001. The statement will require the company to recognize all derivatives on the balance sheet at fair value. Derivatives that are not hedges must be adjusted to fair value through income. If the derivative is a hedge, depending on the nature of the hedge, changes in the fair value of derivatives will either be offset against the change in fair value of the hedged assets, liabilities, or firm commitments through earnings or recognized in other comprehensive income until the hedged item is recognized in earnings. Hedge ineffectiveness, the amount by which the change in the value of a hedge does not exactly offset the change in the value of the hedged item, will be immediately recognized in earnings. The company estimates that the adoption of Statement 133 will not have a material effect on the consolidated results of operations or financial position of the company.

Note 3: Collaboration and Dispositions

During the first quarter of 2000, the company sold its interest in Kinetra LLC, a joint venture between the company and EDS, to WebMD Corporation (WebMD) in exchange for shares of WebMD common stock. A gain of $214.4 million was recognized on the combined effect of the transaction and the subsequent sale of the majority of those shares of WebMD stock. The gain is included in other income in the consolidated statements of income.

During 1999, the company recognized a pretax gain of $67.8 million on the sale of the U.S. and Puerto Rican marketing rights of Lorabid, an antibiotic used in the treatment of bacterial infections, to King Pharmaceuticals, Inc. The gain has been included in other income in the consolidated statements of income. The company has an opportunity to receive additional payments if certain sales performance milestones are achieved.

During 1998, the company announced a collaboration with ICOS Corporation to jointly develop and globally commercialize a phosphodiesterase type 5 (PDE5) inhibitor as an oral therapeutic agent for the treatment of male erectile dysfunction and female sexual dysfunction. The compound was in the development phase (Phase II clinical trials) and no alternative future uses were identified. As with many Phase II compounds, launch of the product, if successful, was not expected in the near term. The company's payments to acquire rights to this compound were required to be charged as an expense of $127.5 million.

Note 4: Discontinued Operations

In January 1999, the company sold PCS, its health-care-management subsidiary, to Rite Aid Corporation for $1.6 billion in cash. The transaction generated a gain of $274.3 million ($.16 per share), net of $8.7 million tax benefit, in the first quarter of 1999.

The results of operations of PCS have been classified as discontinued operations in the consolidated statements of income. Selected 1998 income statement information for PCS follows:

Revenues	$814.5
Income tax expense	32.2
Income from discontinued operations	8.8

Note 5: Asset Impairment and Other Site Charges

The company recognized two separate asset impairments and other site charges totaling $87.4 million in 1999 ($61.4 million and $26.0 million in the first and fourth quarters, respectively). The impairment charges were necessary to adjust the carrying value of certain manufacturing assets to fair value. The major portion of the charges ($75.0 million) related to the decommissioning of manufacturing buildings and the related equipment, which resulted from the consolidation of certain manufacturing processes. The company plans to continue ownership of the vacated buildings although no planned future uses have been identified. The fair values of the facilities were estimated based upon anticipated future cash flows, discounted at a rate commensurate with the risk involved.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
Exhibit A, Page 35 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205114
Page 35
005909

Note 6: Financial Instruments

Risk-Management Instruments and Off-Balance-Sheet Risk

In the normal course of business, operations of the company are exposed to fluctuations in currency values and interest rates. These fluctuations can vary the costs of financing, investing, and operating. The company addresses a portion of these risks through a controlled program of risk management that includes the use of derivative financial instruments.

The notional amounts of derivatives summarized in the following paragraphs do not represent amounts exchanged by the parties and thus are not a measure of the exposure of the company through its use of derivatives. The company is exposed to credit-related losses in the event of nonperformance by counterparties to financial instruments, but it does not expect any counterparties to fail to meet their obligations given their high credit ratings.

At December 31, the stated, or notional, amounts of the company's outstanding derivative financial instruments were as follows:

	2000	1999
Forward exchange contracts	$1,384.9	$608.7
Foreign currency options—purchased	639.8	756.0
Interest rate swaps	445.0	295.0

Financial instruments that potentially subject the company to credit risk consist principally of trade receivables and interest-bearing investments. Wholesale distributors of life-sciences products and managed care organizations account for a substantial portion of trade receivables; collateral is generally not required. The risk associated with this concentration is mitigated by the company's ongoing credit review procedures. The company places substantially all its interest-bearing investments with major financial institutions, in U.S. government securities, or with top-rated corporate issuers. In accordance with documented corporate policies, the company limits the amount of credit exposure to any one financial institution.

Fair Value of Financial Instruments

A summary of the company's outstanding financial instruments at December 31 follows. As summarized, "cost" relates to investments while "carrying amount" relates to long-term debt.

	2000		1999	
	Cost/ Carrying Amount	Fair Value	Cost/ Carrying Amount	Fair Value
Short-term investments:				
Debt securities	$ 503.3	$ 504.3	$ 235.6	$ 236.0
Noncurrent investments:				
Marketable equity	79.8	90.1	63.9	96.8
Debt securities	266.2	271.2	35.6	35.6
Nonmarketable equity	7.5	7.5	14.9	14.9
Long-term debt, including current portion	2,796.6	2,861.7	3,026.7	2,990.6

The company determines fair values based on quoted market values where available or discounted cash flow analyses (principally long-term debt). The fair values of nonmarketable equity securities, which represent either equity investments in start-up technology companies or partnerships that invest in start-up technology companies, are estimated based on the fair value information provided by these ventures. The fair value and carrying amount of risk-management instruments were not material at December 31, 2000 and 1999.

At December 31, 2000 and 1999, the gross unrealized holding gains on available-for-sale securities were $24.3 million and $42.5 million, respectively, and the gross unrealized holding losses were $14.9 million and $12.6 million, respectively. Substantially all these gains and losses are associated with the marketable equity securities. The proceeds from sales of available-for-sale securities totaled $773.8 million, $56.2 million, and $36.3 million in 2000, 1999, and 1998, respectively. Purchases of available-for-sale securities totaled $443.0 million in 2000 and were not material in 1999 and 1998. Realized gains on sales of available-for-sale securities were $71.6 million, $25.0 million, and $20.6 million in 2000, 1999, and 1998, respectively. Realized losses on sales of available-for-sale securities were $16.5 million, negligible, and $2.5 million in 2000, 1999, and 1998, respectively. The net adjustment to unrealized gains and losses on available-for-sale

ZY 9553 935

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 36 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205115
Page 36

005910

securities decreased other comprehensive income by $12.3 million in 2000 and increased other comprehensive income by $18.6 million in 1999.

Note 7: Borrowings

Long-term debt at December 31 consisted of the following:

	2000	1999
6.57 to 7.13 percent notes (due 2016–2036)	$1,000.0	$1,000.0
6.25 to 8.38 percent notes (due 2001–2006)	650.0	650.0
Floating rate capital securities (due 2029)	525.0	525.0
8.38 percent eurodollar bonds (due 2005)	350.0	350.0
Resettable coupon capital securities (due 2029)	300.0	300.0
6.55 percent ESOP debentures (due 2017)	97.6	98.6
Other, including capitalized leases	74.0	103.1
	2,796.6	3,026.7
Less current portion	162.9	214.8
	$2,633.7	$2,811.9

On August 5, 1999, the company issued $525.0 million floating rate capital securities and $300.0 million adjustable rate capital securities. These capital securities are subordinated to the notes, bonds, and debentures listed above. The floating rate capital securities pay cumulative interest at an annual rate equal to LIBOR plus a predetermined spread, reset quarterly. The rates at December 31, 2000 and 1999, were 7.951 percent and 7.355 percent, respectively. The securities may be redeemed any time on or after August 5, 2004, for a defined redemption price. The resettable coupon capital securities pay cumulative interest at an annual rate of 7.717 percent until August 1, 2004. At this date and every fifth anniversary thereafter, the interest rate will be reset equal to the weekly average interest rate of U.S. treasury securities having an index maturity of five years for the week immediately preceding the reset date plus a predetermined spread. The securities may be redeemed on August 1, 2004, and anytime thereafter for a defined redemption price.

The 6.55 percent Employee Stock Ownership Plan (ESOP) debentures are obligations of the ESOP but are shown on the consolidated balance sheet because they are guaranteed by the company. The principal and interest on the debt are funded by contributions from the company and by dividends received on certain shares held by the ESOP. Because of the amortizing feature of the ESOP debt, bondholders will receive both interest and principal payments each quarter. These debentures replaced other ESOP debentures pursuant to a refinancing in March 1998. An extraordinary charge of $7.2 million, net of a $4.8 million income tax benefit, was recorded as a result of this refinancing.

The aggregate amounts of maturities on long-term debt for the next five years are as follows: 2001, $162.9 million; 2002, $13.5 million; 2003, $212.0 million; 2004, $8.8 million; and 2005, $157.9 million.

At December 31, 2000 and 1999, short-term borrowings included $21.4 million and $26.7 million, respectively, of notes payable to banks. At December 31, 2000, unused committed lines of credit totaled approximately $2.01 billion. Compensating balances and commitment fees are not material, and there are no conditions that are probable of occurring under which the lines may be withdrawn.

Cash payments of interest on borrowings totaled $195.9 million, $170.6 million, and $188.2 million in 2000, 1999, and 1998, respectively.

Note 8: Stock Plans

Stock options are granted to employees at exercise prices equal to the fair market value of the company's stock at the dates of grant. Generally, options vest 100 percent three years from the grant date and have a term of 10 years. Performance awards are granted to officers and key employees and are payable in shares of the company's common stock. The number of performance award shares actually issued varies depending upon the achievement of certain earnings targets. In general, performance awards vest 100 percent at the end of the second fiscal year following the grant date.

In 1999, the company issued its third grant under the GlobalShares program. Essentially all employees were given an option to buy 100 shares of the company's stock at a price equal to the fair market value of the company's stock on the date of the grant. Options to purchase approximately 2.8 million shares were granted as part of the program. Individual grants generally become exercisable on or after the third anniversary of the grant date and have a term of 10 years.

ZY 9553 936

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A Page 37 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205116
Page 37

005911

The company has elected to follow Accounting Principles Board Opinion (APB) No. 25, "Accounting for Stock Issued to Employees" and related interpretations in accounting for its stock options and performance awards. Under APB No. 25, because the exercise price of the company's employee stock options equals the market price of the underlying stock on the date of grant, no compensation expense is recognized. Total compensation expense for stock-based performance awards reflected in income on a pretax basis was $88.3 million, $117.1 million, and $257.8 million in 2000, 1999, and 1998, respectively. However, SFAS No. 123, "Accounting for Stock-Based Compensation," requires presentation of pro forma information as if the company had accounted for its employee stock options and performance awards granted subsequent to December 31, 1994, under the fair value method of that statement. For purposes of pro forma disclosure, the estimated fair value of the options and performance awards at the date of the grant is amortized to expense over the vesting period. Under the fair value method, the company's net income and earnings per share would have been as follows:

	2000	1999	1998
Net income	$2,969.3	$2,639.6	$2,120.9
Earnings per share—diluted	2.70	2.39	1.89

The weighted-average per-share fair value of the individual options and performance awards granted during 2000, 1999, and 1998 were as follows on the date of grant:

	2000	1999	1998
Employee stock options	$29.25	$20.27	$16.64
Performance awards	93.06	66.50	88.88

The fair values of the options were determined using a Black-Scholes option-pricing model with the following assumptions:

	2000	1999	1998
Dividend yield	2.26%	2.73%	2.96%
Volatility	32.7%	25.2%	23.5%
Risk-free interest rate	5.02%	6.15%	4.29%
Forfeiture rate	0	0	0
Expected life	7 years	7 years	7 years

Stock option activity during 1998-2000 is summarized below:

	Shares of Common Stock Attributable to Options (in thousands)	Weighted-Average Exercise Price of Options
Unexercised at January 1, 1998	60,894	$24.05
Granted	6,803	74.18
Exercised	(13,697)	16.88
Forfeited	(1,047)	24.29
Unexercised at December 31, 1998	52,953	32.35
Granted	12,494	68.22
Exercised	(10,849)	19.04
Forfeited	(875)	50.46
Unexercised at December 31, 1999	53,723	43.08
Granted	1,315	86.75
Exercised	(9,242)	22.33
Forfeited	(671)	64.97
Unexercised at December 31, 2000	45,125	48.28

The following table summarizes information concerning outstanding and exercisable options at December 31, 2000 (shares in millions, contractual life in years):

	Options Outstanding			Options Exercisable	
Range of Exercise Prices	Number Outstanding	Weighted-Average Remaining Contractual Life	Weighted-Average Exercise Price	Number Exercisable	Weighted-Average Exercise Price
$10–$25	16.27	2.82	13.56	16.27	13.56
$25–$65	9.13	5.55	38.23	9.04	38.11
$65–$95	19.73	8.50	71.39	.82	71.97

ZY 9553 937

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 38 of 52
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205117
Page 38

005912

Shares exercisable at December 31, 2000, were 26.1 million (1999—29.9 million shares, 1998—35.8 million shares).

As noted above, the number of shares ultimately issued pursuant to the performance award program is dependent upon the earnings achieved during the vesting period. Pursuant to this plan, approximately 1.2 million shares, 2.2 million shares, and 1.5 million shares were issued in 2000, 1999, and 1998, respectively. At December 31, 2000, plan participants had the right to receive up to 4.1 million additional shares (reduced to the extent necessary to satisfy payroll tax withholdings), contingent upon earnings achieved.

At December 31, 2000, additional options, performance awards, or restricted stock grants may be granted under the 1998 Lilly Stock Plan and the Lilly GlobalShares Stock Plan, for not more than 32.8 million shares and 7.9 million shares, respectively.

Note 9: Shareholders' Equity

Changes in certain components of shareholders' equity were as follows:

	Additional Paid-in Capital	Retained Earnings	Deferred Costs—ESOP	Common Stock in Treasury Shares (in thousands)	Common Stock in Treasury Amount
Balance at January 1, 1998	$ —	$4,497.3	$(155.7)	1,000	$ 109.5
Net income		2,097.9			
Cash dividends declared per share: $.83		(908.9)			
Retirement of treasury shares	(2,035.2)			(29,020)	(2,053.3)
Purchase for treasury				28,350	2,005.8
Issuance of stock under employee stock plans	558.7			660	47.5
ESOP transactions	23.6		8.8		
Other	5.4	(10.0)		(5)	(0.5)
Reclassification	1,447.5	(1,447.5)			
Balance at December 31, 1998	—	4,228.8	(146.9)	995	109.0
Net income		2,721.0			
Cash dividends declared per share: $.95		(1,030.5)			
Retirement of treasury shares	(1,488.4)			(19,689)	(1,500.8)
Purchase for treasury				19,147	1,455.1
Issuance of stock under employee stock plans	530.6			542	45.7
ESOP transactions	20.8		7.0		
Other	3.3			(6)	(0.7)
Reclassification	933.7	(933.7)			
Balance at December 31, 1999	—	4,985.6	(139.9)	989	108.3
Net income		3,057.8			
Cash dividends declared per share: $1.06		(1,158.4)			
Retirement of treasury shares	(1,117.6)			(15,256)	(1,126.9)
Purchase for treasury				14,794	1,089.8
Issuance of stock under employee stock plans	405.6			494	39.8
Issuance of stock for employee benefit trust	2,610.0				
ESOP transactions	16.7		4.9		
Other	33.7	(0.2)		(14)	(1.5)
Reclassification	661.6	(661.6)			
Balance at December 31, 2000	$2,610.0	$6,223.2	$(135.0)	2,007	$ 209.5

As shown above, the company completed $1.09 billion of its announced $3.0 billion share repurchase program in 2000. A $1.5 billion share repurchase program was completed in 1999. The company acquired approximately 14.8 million and 19.1 million shares in 2000 and 1999, respectively, pursuant to these programs.

ZY 9553 938

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A-Page 39 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205118
Page 39

005913

In connection with the share repurchase program, the company has entered into agreements to purchase shares of the company's stock. As of December 31, 2000, the company has agreements to purchase up to approximately 4.0 million shares of company stock from an independent third party at various times through the expiration of the agreements in December 2002, at prices ranging from $83 to $100 per share. The number of shares to be purchased will be reduced ratably each quarter through the expiration of the agreements. In addition, as of December 31, 2000, written equity put options, purchased call options, and other derivative contracts, which provide for purchase of a total of approximately 4.6 million shares, remain outstanding at prices ranging from $69 to $98 per share with expiration dates ranging from February 2001 to November 2002. If the options are exercised, the contracts allow the company, at its option, to repurchase the shares for cash or deliver to the holder cash or shares for the difference between the contractual exercise price and the market price of the company's stock. The company's objective with the above agreements is to reduce the average price of repurchased shares.

During the second quarter of 2000, the company funded an employee benefit trust with 40 million shares of Lilly common stock to provide a source of funds to assist the company in meeting its obligations under various employee benefit plans. The funding had no net impact on shareholders' equity as the employee benefit trust is consolidated with the company. The cost basis of the shares held in the trust was $2.64 billion and is shown as a reduction in shareholders' equity, which offsets the resulting increases of $2.61 billion in additional paid-in capital and $25 million in common stock. Any dividend transactions between the company and the trust are eliminated. Stock held by the trust is not considered outstanding in the computation of earnings per share.

The company has an ESOP as a funding vehicle for the existing employee savings plan. The ESOP used the proceeds of a loan from the company to purchase shares of common stock from the treasury. The ESOP issued $200 million of third-party debt, repayment of which was guaranteed by the company (see Note 7). The proceeds were used to purchase shares of the company's common stock on the open market. Shares of common stock held by the ESOP will be allocated to participating employees annually through 2017 as part of the company's savings plan contribution. The fair value of shares allocated each period is recognized as compensation expense.

Under a Shareholder Rights Plan adopted by the company's board of directors in 1998, all shareholders receive along with each common share owned a preferred stock purchase right entitling them to purchase from the company one one-thousandth of a share of Series B Junior Participating Preferred Stock (the "Preferred Stock") at a price of $325. The rights are not exercisable until after the "Distribution Date," which is generally the 10th business day after the date of a public announcement that a person (the "Acquiring Person") has acquired ownership of 15 percent or more of the company's common stock. The company may redeem the rights for $.005 per right up to and including the Distribution Date. The rights will expire on July 28, 2008, unless redeemed earlier by the company.

The plan provides that, if an Acquiring Person acquires 15 percent or more of the outstanding common stock of the company and the company's redemption right has expired, generally each holder of a right (other than the Acquiring Person) will have the right to purchase at the exercise price the number of shares of common stock of the company as have a value of two times the exercise price.

Alternatively, if, in a transaction not approved by the board of directors, the company is acquired in a business combination transaction or sells 50 percent or more of its assets or earning power after a Distribution Date, generally each holder of a right (other than the Acquiring Person) will have the right to purchase at the exercise price the number of shares of common stock of the acquiring company as have a value of two times the exercise price.

At any time after an Acquiring Person has acquired 15 percent or more but less than 50 percent of the company's outstanding common stock, the board of directors may exchange the rights (other than those owned by the Acquiring Person) for company common stock or Preferred Stock at an exchange ratio of one common share (or one one-thousandth of a share of Preferred Stock) per right.

ZY 9553 939

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 40 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205119
Page 40

005914

Note 10: Earnings per Share

The following is a reconciliation of the numerators and denominators used in computing earnings per share from continuing operations before extraordinary item:

(Shares in thousands)	2000	1999	1998
Income from continuing operations before extraordinary item available to common shareholders:			
Income from continuing operations before extraordinary item	$3,057.8	$2,546.7	$2,096.3
Preferred stock dividends	—	(0.2)	(1.7)
Income from continuing operations before extraordinary item available to common shareholders	$3,057.8	$2,546.6	$2,094.6
Basic earnings per share:			
Weighted-average number of common shares outstanding, including incremental shares	1,081,559	1,087,652	1,095,834
Basic earnings per share from continuing operations before extraordinary item	$2.83	$2.34	$1.91
Diluted earnings per share:			
Weighted-average number of common shares outstanding	1,081,409	1,087,368	1,095,537
Stock options and other incremental shares	16,316	18,687	25,949
Weighted-average number of common shares outstanding—diluted	1,097,725	1,106,055	1,121,486
Diluted earnings per share from continuing operations before extraordinary item	$2.79	$2.30	$1.87

Note 11: Income Taxes

Following is the composition of income taxes attributable to continuing operations before extraordinary item:

	2000	1999	1998
Current:			
Federal	$ 928.4	$439.2	$322.1
Foreign	322.4	260.4	238.9
State	(7.2)	(4.9)	(8.9)
	1,243.6	694.7	552.1
Deferred:			
Federal	(81.2)	104.0	36.3
Foreign	(58.6)	22.4	9.4
State	.9	2.7	9.6
	(138.9)	129.1	55.3
Utilization of capital loss carryforwards	(303.8)	(125.1)	(38.7)
Income taxes	$ 800.9	$698.7	$568.7

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 41 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205120
Page 41

005915

Significant components of the company's deferred tax assets and liabilities as of December 31 are as follows:

	2000	1999
Deferred tax assets:		
Tax credit carryforwards and carrybacks	$ 734.5	$ 496.0
Other carryforwards	450.4	243.9
Sale of intangibles	230.6	76.5
Capital loss carryforward	158.8	561.7
Compensation and benefits	109.0	188.8
Inventory	70.2	172.9
Other	378.6	300.4
	2,132.1	2,040.2
Valuation allowances	(408.0)	(703.4)
Total deferred tax assets	1,724.1	1,336.8
Deferred tax liabilities:		
Property and equipment	(527.7)	(527.2)
Prepaid employee benefits	(429.2)	(257.4)
Unremitted earnings	(182.0)	(381.9)
Other	(29.2)	(65.1)
Total deferred tax liabilities	(1,168.1)	(1,231.6)
Deferred tax assets—net	$ 556.0	$ 105.2

At December 31, 2000, the company had capital loss and other carryforwards for income tax purposes of $694.7 million: $643.4 million will expire within five years and $43.9 million thereafter; $7.4 million of the carryforwards will never expire. The company also has tax credit carryforwards of $734.5 million available to reduce future income taxes: $495.1 million will expire within five years and $183.2 million thereafter; $56.2 million of the tax credit carryforwards will never expire.

As discussed in Note 4, the company sold its PCS health-care-management subsidiary in January 1999. As a consequence of the sale, the company recorded a deferred tax asset of $655.3 million for the tax capital loss that resulted from this transaction. A portion of this loss carryforward has been used; the remainder can be carried forward four more years. A valuation allowance was established for this asset due to the uncertain realization of the benefit.

Domestic and Puerto Rican companies contributed approximately 56 percent, 56 percent, and 60 percent in 2000, 1999, and 1998, respectively, to consolidated income from continuing operations before income taxes and extraordinary item. Unremitted earnings of foreign subsidiaries that have been, or are intended to be, permanently reinvested for continued use in foreign operations and that, if distributed, would result in taxes at approximately the U.S. statutory rate aggregated $5.2 billion at December 31, 2000. Cash payments of income taxes totaled $294.0 million, $252.0 million, and $273.0 million in 2000, 1999, and 1998, respectively.

Following is a reconciliation of the effective income tax rate applicable to income from continuing operations:

	2000	1999	1998
United States federal statutory tax rate	35.0%	35.0%	35.0%
Add (deduct):			
International operations, including Puerto Rico	(12.9)	(7.5)	(10.5)
General business credits	(1.2)	(2.6)	(2.4)
Sundry	(0.1)	(4.4)	(0.8)
Effective income tax rate	20.8%	21.5%	21.3%

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 42 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205121
Page 42

005916

Note 12: Retirement Benefits

The change in benefit obligation, change in plan assets, funded status, and amounts recognized in the consolidated balance sheets at December 31 for the company's defined benefit pension and retiree health benefit plans were as follows:

	Defined Benefit Pension Plans		Retiree Health Benefits	
	2000	1999	2000	1999
Change in benefit obligation:				
Benefit obligation at beginning of year	$3,004.4	$2,898.8	$687.6	$622.5
Service cost	130.1	127.7	23.2	26.8
Interest cost	219.6	193.7	49.6	41.5
Actuarial loss	144.3	16.5	52.4	60.5
Benefits paid	(179.8)	(175.0)	(61.5)	(48.5)
Foreign currency exchange rate changes and other adjustments	61.5	(57.3)	1.0	(4.2)
Benefit obligation at end of year	3,380.1	3,004.4	752.3	687.6
Change in plan assets:				
Fair value of plan assets at beginning of year	3,532.0	3,069.6	332.1	252.5
Actual return on plan assets	238.7	543.6	(16.4)	80.4
Employer contribution	270.0	122.1	95.0	47.7
Benefits paid	(179.8)	(175.0)	(61.5)	(48.5)
Foreign currency exchange rate changes and other adjustments	(28.8)	(28.3)	—	—
Fair value of plan assets at end of year	3,732.1	3,532.0	349.2	332.1
Funded status	352.0	527.6	(402.1)	(355.5)
Unrecognized net actuarial (gain) loss	298.8	(36.0)	317.1	240.9
Unrecognized prior service cost (benefit)	227.2	119.3	(.1)	(.1)
Unrecognized net obligation at January 1, 1986	1.7	2.0	2.8	—
Net amount recognized	$ 879.7	$ 612.9	$ (83.3)	$(115.7)
Amounts recognized in the consolidated balance sheet consisted of:				
Prepaid benefit cost	$1,032.5	$ 741.1	$ —	$ —
Accrued benefit liability	(302.9)	(237.6)	(83.3)	(115.7)
Intangible asset	42.1	34.0	—	—
Accumulated other comprehensive income before income taxes	109.0	75.4	—	—
Net amount recognized	$ 879.7	$ 612.9	$ (83.3)	$(115.7)

[Percents]	Defined Benefit Pension Plans		Retiree Health Benefits	
	2000	1999	2000	1999
Weighted-average assumptions as of December 31:				
Discount rate	7.4	7.4	7.5	7.5
Expected return on plan assets	10.5	10.5	10.5	10.5
Rate of compensation increase	3.5–8.0	3.5–8.0	—	—

Health-care-cost trend rates were assumed to increase at an annual rate of 6.5 percent in 2001 for participants under age 65, decreasing one-half percent to 6.0 percent in 2002 and thereafter. For participants over age 65, the rate was assumed to increase 6.0 percent in 2001 and thereafter.

The projected benefit obligation, accumulated benefit obligation, and fair value of the plan assets for the defined benefit pension plans with projected benefit obligations in excess of plan assets were $736.8 million, $616.8 million, and $381.6 million, respectively, as of December 31, 2000, and $637.1 million, $539.0 million, and $364.5 million, respectively, as of December 31, 1999.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 43 of 52
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205122
Page 43

005917

Net pension and retiree health benefit expense included the following components related to continuing operations:

	Defined Benefit Pension Plans			Retiree Health Benefits		
	2000	1999	1998	2000	1999	1998
Components of net periodic benefit cost:						
Service cost	$130.1	$127.7	$112.9	$ 23.2	$ 16.8	$ 12.8
Interest cost	219.6	193.7	184.2	49.6	42.5	34.3
Expected return on plan assets	(341.0)	(295.1)	(277.1)	(30.1)	(24.2)	(23.0)
Amortization of prior service cost (benefit)	16.9	11.5	9.7	.1	—	(3.3)
Recognized actuarial loss	5.9	3.7	3.4	21.9	17.6	7.3
Net periodic benefit cost	$ 31.5	$ 41.5	$ 33.1	$ 64.7	$ 52.7	$ 28.1

The assumed health-care-cost trend rates have a significant effect on the amounts reported. If these trend rates were to be increased by one percentage point each future year, the December 31, 2000, accumulated postretirement benefit obligation would increase by 13 percent and the aggregate of the service cost and interest cost components of 2000 annual expense would increase by 15 percent. A one-percentage-point decrease in these rates would decrease the December 31, 2000, accumulated postretirement benefit obligation by 12 percent and the aggregate of the 2000 service cost and interest cost by 13 percent.

The company has defined contribution savings plans that cover its eligible employees worldwide. The purpose of these defined contribution plans is generally to provide additional financial security during retirement by providing employees with an incentive to make regular savings. Company contributions to the plan are based on employee contributions and the level of company match. Expenses under the plans related to continuing operations totaled $65.2 million, $56.4 million, and $50.3 million for the years 2000, 1999, and 1998, respectively.

The company provides certain other postemployment benefits primarily related to disability benefits and accrues for the related cost over the service lives of the employees. Expenses associated with these benefit plans in 2000, 1999, and 1998 were not significant.

Note 13: Contingencies

Barr Laboratories, Inc. (Barr), and Geneva Pharmaceuticals, Inc. (Geneva), have each submitted an Abbreviated New Drug Application (ANDA) seeking FDA approval to market generic forms of Prozac before the expiration of the company's patents. The ANDAs assert that two U.S. patents held by Lilly covering Prozac are invalid and unenforceable. The company filed suit against Barr and Geneva in federal court in Indianapolis seeking a ruling that Barr's challenge to Lilly's patents is without merit. In January 1999, the trial court granted summary judgment in favor of Lilly on two of the four claims raised by Barr and Geneva against Lilly's patents. That decision was appealed to the Court of Appeals for the Federal Circuit. Barr and Geneva dismissed their other two claims in exchange for a $4 million payment. On August 9, 2000, the Court of Appeals upheld the 2001 compound patent but held that the 2003 method of use patent was invalid. The company has filed a petition requesting a rehearing by the Court of Appeals.

Several other generic manufacturers have also filed ANDAs for generic forms of Prozac, challenging one or both of the patents. In late 1998, Zenith Goldline Pharmaceuticals, Inc.; Teva Pharmaceuticals USA (Teva); and Cheminor Drugs, Ltd., together with one of its subsidiaries (Cheminor), notified the company that they had filed ANDAs challenging the 2003 patent. Also in 1998, Novex Pharma, a division of Apotex, Inc., notified the company that it had filed an ANDA challenging both patents. In 1999, Cheminor notified the company that it had filed an ANDA for a different dosage form. In 2000, Barr and Teva both notified the company that they had filed additional ANDAs for the different dosage form, and Alphapharm Pty. Ltd. also notified the company that it had filed ANDAs for two dosage forms.

The company has filed lawsuits in the United States District Court of the Southern District of Indiana seeking rulings that all these challenges to the patent(s) are without merit. The cases are awaiting resolution of the petition for rehearing by the Court of Appeals in the original Barr case.

Assuming the Prozac patent ruling is not overturned, the company expects a very substantial decline in Prozac sales in the U.S. in the 12 months following the entry of generic fluoxetine in the U.S. market in August 2001. Prozac sales in the U.S. represent a significant portion of the company's overall sales, accounting for approximately 20 percent of the company's consolidated worldwide sales in 2000. The company believes that the Prozac patent litigation will not have a material adverse effect on the company's consolidated financial position or liquidity.

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 44 of 52
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205123
Page 44

005918

The company has been named as a defendant in numerous product liability lawsuits involving primarily two products, diethylstilbestrol (DES) and Prozac. The company has accrued for its estimated exposure with respect to all current product liability claims. In addition, the company has accrued for certain claims incurred, but not filed, to the extent the company can formulate a reasonable estimate of their costs. The company's estimates of these expenses are based primarily on historical claims experience and data regarding product usage. The company expects the cash amounts related to the accruals to be paid out over the next several years. The majority of costs associated with defending and disposing of these suits are covered by insurance. The company's estimate of insurance recoverables is based on existing deductibles, coverage limits, and the existing and projected future level of insolvencies among its insurance carriers.

Under the Comprehensive Environmental Response, Compensation, and Liability Act, commonly known as Superfund, the company has been designated as one of several potentially responsible parties with respect to fewer than 10 sites. Under Superfund, each responsible party may be jointly and severally liable for the entire amount of the cleanup. The company also continues remediation of certain of its own sites. The company has accrued for estimated Superfund cleanup costs, remediation, and certain other environmental matters, taking into account, as applicable, available information regarding site conditions, potential cleanup methods, estimated costs, and the extent to which other parties can be expected to contribute to payment of those costs. The company has reached a settlement with its primary liability insurance carrier and certain excess carriers providing for coverage for certain environmental liabilities. Litigation seeking coverage from certain other excess carriers is ongoing.

The environmental liabilities and litigation accruals have been reflected in the company's consolidated balance sheet at the gross amount of approximately $138.9 million at December 31, 2000. Estimated insurance recoverables of approximately $74.1 million at December 31, 2000, have been reflected as assets in the consolidated balance sheet.

The company recognized a pretax gain of $110.0 million as a result of a cash payment received in settlement of litigation with Biochimica Opos S.p.A. relating to the manufacture, sale, or distribution of cefaclor and certain other products made by Biochimica Opos S.p.A. The gain, which was recorded in other income, increased earnings per share by approximately $.06 in the fourth quarter of 1999.

While it is not possible to predict or determine the outcome of the patent, product liability, or other legal actions brought against the company or the ultimate cost of environmental matters, the company believes that, except as noted above with respect to the Prozac patent litigation, the costs associated with all such matters will not have a material adverse effect on its consolidated financial position or liquidity but could possibly be material to the consolidated results of operations in any one accounting period.

Note 14: Other Comprehensive Income

The accumulated balances related to each component of other comprehensive income were as follows:

	Foreign Currency Translation	Unrealized Gains (Losses) on Securities	Minimum Pension Liability	Accumulated Other Comprehensive Income
Beginning balance at January 1, 2000	$(375.6)	$ 20.1	$(50.9)	$(406.4)
Other comprehensive income (loss)	(170.7)	(12.3)	(21.8)	(204.8)
Balance at December 31, 2000	$(546.3)	$ 7.8	$(72.7)	$(611.2)

The amounts above are net of income taxes. The income taxes related to other comprehensive income were not significant as income taxes were generally not provided for foreign currency translation.

The unrealized gains (losses) on securities is net of reclassification adjustments of $43.9 million, $8.5 million, and $4.8 million, net of tax, in 2000, 1999, and 1998, respectively, for realized gains and losses on sales of securities included in net income.

Generally, the assets and liabilities of foreign operations are translated into U.S. dollars using the current exchange rate. For those operations, changes in exchange rates generally do not affect cash flows; therefore, resulting translation adjustments are made to shareholders' equity rather than to income.

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
Exhibit A, Page 45 of 52
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205124
Page 45
005919

Responsibility for Financial Statements

Eli Lilly and Company and Subsidiaries

The consolidated financial statements and related notes have been prepared by management, who are responsible for their integrity and objectivity. The statements have been prepared in accordance with generally accepted accounting principles and include amounts based on judgments and estimates by management. The other financial information in this annual report is consistent with that in the financial statements.

The company maintains internal accounting control systems that are designed to provide reasonable assurance that assets are safeguarded, that transactions are executed in accordance with management's authorization and are properly recorded, and that accounting records are adequate for preparation of financial statements and other financial information. The design, monitoring, and revision of internal accounting control systems involve, among other things, management's judgments with respect to the relative cost and expected benefits of specific control measures. A staff of internal auditors regularly monitors, on a worldwide basis, the adequacy and effectiveness of internal accounting controls.

In addition to the system of internal accounting controls, the company maintains guidelines of company policy emphasizing proper overall business conduct, possible conflicts of interest, compliance with laws, and confidentiality of proprietary information. The guidelines are reviewed on a periodic basis with employees worldwide.

The financial statements have been audited by Ernst & Young LLP, independent auditors. Their responsibility is to examine the company's financial statements in accordance with generally accepted auditing standards and to express their opinion with respect to the fairness of presentation of the statements.

The members of the audit committee of the board of directors, none of whom are employees of the company, recommend independent auditors for appointment by the board of directors, review the services performed by the independent auditors, and receive and review the reports submitted by them. The audit committee meets several times during the year with management, the internal auditors, and the independent auditors to discuss audit activities, internal controls, and financial reporting matters. The internal auditors and the independent auditors have full and free access to the committee.

Sidney Taurel, Chairman of the Board, President, and Chief Executive Officer

Charles E. Golden, Executive Vice President and Chief Financial Officer

January 29, 2001

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 46 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205125
Page 46

005920

Report of Independent Auditors

Board of Directors and Shareholders
Eli Lilly and Company

We have audited the accompanying consolidated balance sheets of Eli Lilly and Company and subsidiaries as of December 31, 2000 and 1999, and the related consolidated statements of income, cash flows, and comprehensive income for each of the three years in the period ended December 31, 2000. These financial statements are the responsibility of the company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

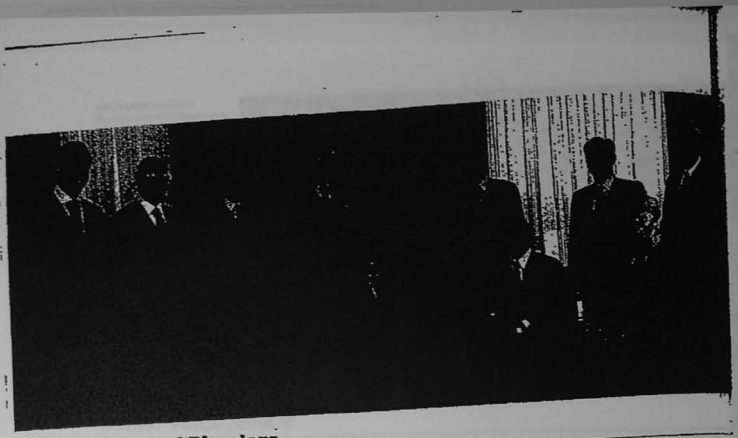
We conducted our audits in accordance with auditing standards generally accepted in the United States. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Eli Lilly and Company and subsidiaries at December 31, 2000 and 1999, and the consolidated results of their operations and their cash flows for each of the three years in the period ended December 31, 2000, in conformity with accounting principles generally accepted in the United States.

Ernst & Young LLP

Indianapolis, Indiana
January 29, 2001

Exhibit A, Page 47 of 52
Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
SOA Request for Clarification of the Court's Order re: Other Drugs Case No. 3AN-06-5630 CI
ZY1 00205126
Page 47
005921



Board of Directors

Sidney Taurel
Chairman of the Board, President, and Chief Executive Officer

Steven C. Beering, M.D. [2,5,6]
President Emeritus, Purdue University

Sir Winfried F. W. Bischoff [2,3]
Chairman, Citigroup Europe

George M. C. Fisher [2,6]
Retired Chairman of the Board and Chief Executive Officer, Eastman Kodak Company

Alfred G. Gilman, M.D., Ph.D. [2,4]
Regental Professor and Chairman, Department of Pharmacology, The University of Texas Southwestern Medical Center

Charles E. Golden [4]
Executive Vice President and Chief Financial Officer

Karen N. Horn, Ph.D. [2,4,5]
President, Marsh Private Client Services, Marsh, Inc.

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Edmond and Marion Guggenheim Professor of Biochemistry and Molecular Biology and Director, Mayo Clinic Cancer Center

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Executive Vice President, Kimberly-Clark Corporation

August M. Watanabe, M.D. [4]
Executive Vice President, Science and Technology

Alva O.Way [1,2,5]
Chairman of the Board, IBJ Whitehall Bank & Trust Company

Board Committees
1 Audit Committee
2 Compensation Committee
3 Public Policy Committee
4 Finance Committee
5 Directors and Corporate Governance Committee
6 Science and Technology Committee

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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 48 of 52
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205127
Page 48

005922

LEFT: BOARD OF DIRECTORS
[Standing, left to right] Sidney Taurel; Steven C. Beering, M.D.; Alfred G. Gilman, M.D., Ph.D.; Sir Winfried F. W. Bischof; Kathi P. Seifert; Kenneth L. Lay, Ph.D.; August M. Watanabe, M.D.; Franklyn B. Prendergast, M.D., Ph.D. [Seated, left to right] Alva O. Way; Charles E. Golden; Georges M. C. Fisher; Karen N. Horn, Ph.D.

RIGHT: POLICY COMMITTEE
[Standing, left to right] Sidney Taurel; August M. Watanabe, M.D.; John C. Lechleiter, Ph.D.; Rebecca O. Kendall. [Seated, left to right] Gerhard N. Mayr; Pedro P. Granadillo; Charles E. Golden.

Senior Management

Sidney Taurel [A,B]
Chairman of the Board, President, and Chief Executive Officer

Charles E. Golden [A,B]
Executive Vice President and Chief Financial Officer

Pedro P. Granadillo [A,B]
Senior Vice President, Human Resources and Manufacturing

Rebecca O. Kendall [A,B]
Senior Vice President and General Counsel

John C. Lechleiter, Ph.D. [A,B]
Executive Vice President, Pharmaceutical Products and Corporate Development

Gerhard N. Mayr [A,B]
Executive Vice President, Pharmaceutical Operations

August M. Watanabe, M.D. [A,B]
Executive Vice President, Science and Technology

Bryce D. Carmine [B]
President, Primary Care Products

Newton F. Crenshaw [B]
Vice President, eLilly

Richard D. DiMarchi, Ph.D. [B]
Group Vice President, Research Technologies and Product Development

W. Roy Dunbar [B]
Vice President and Chief Information Officer

Michael L. Eagle [B]
Vice President, Manufacturing

Brendan P. Fox, D.V.M. [B]
President, Elanco Animal Health

James A. Harper [B]
Group Vice President, Global Marketing and Sales

Elizabeth H. Klimes [B]
President, Diabetes and Growth Disorders Products

Steven M. Paul, M.D. [B]
Group Vice President, Therapeutic Area Discovery Research and Clinical Investigation

Richard D. Pilnik [B]
President, European Operations

Gino Santini [B]
President, U.S. Operations

Lorenzo Tallarigo, M.D. [B]
President, Intercontinental Operations

Albertus J. van den Bergh [B]
President, Neuroscience Products

Alfonzo M. G. Zulueta [B]
President, Oncology and Critical Care Products

Senior Management Committees
A Policy Committee
Establishes corporate strategy and policy and ensures compliance
B Senior Management Forum
Implements corporate strategies and ensures corporate performance, identifies issues and opportunities, and facilitates communication and learning

Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY1 00205128
Page 49
005923

Corporate Information

Annual meeting
The annual meeting of shareholders will be held at the Hilbert Circle Theatre, 45 Monument Circle, Indianapolis, Indiana, on Monday, April 16, 2001. Formal notice of the meeting, together with the proxy statement and form of proxy, is sent to each holder of common stock.

10-K and 10-Q reports
The company's Annual Report to the Securities and Exchange Commission on Form 10-K will be available in April. Quarterly reports on Form 10-Q are also available upon request. Anyone wishing to receive copies of the company's 10-K or 10-Q reports may send a written request to:

Eli Lilly and Company
P.O. Box 88665
Indianapolis, Indiana 46208-0665

or access these reports electronically on the Internet. Lilly's address on the Internet is http://www.lilly.com

Stock listings
Eli Lilly and Company common stock is listed on the U.S. New York and Pacific stock exchanges and the London, Tokyo, and Swiss stock exchanges. NYSE ticker symbol: LLY

Transfer agent and registrar
Wells Fargo Shareowner Services
Mailing address:
Shareowner Relations Department
P.O. Box 64854
St. Paul, Minnesota 55164-0854
Overnight address:
161 North Concord Exchange
South St. Paul, Minnesota 55075
Telephone: 1-800-833-8699
E-mail: stocktransfer@wellsfargo.com
Internet: http://www.wellsfargo.com/com/shareowner_services

Environmental report
Eli Lilly and Company's Environmental, Health and Safety Report, which summarizes the company's efforts in these areas, is available on the Internet. The address is http://www.lilly.com/environment

Dividend reinvestment and stock purchase plan
Wells Fargo Shareowner Services administers the Shareowner Service Plus Plan, which allows registered shareholders to purchase additional shares of Lilly common stock through the automatic investment of dividends. The plan also allows registered shareholders and new investors to purchase shares with cash payments, either by check or by automatic deductions from checking or savings accounts. The minimum initial investment for new investors is $1,000. Subsequent investments must be at least $50. The maximum cash investment during any calendar year is $150,000.

Please direct inquiries concerning the Shareowner Service Plus Plan to:

Wells Fargo Shareowner Services
Shareowner Relations Department
P.O. Box 64854
St. Paul, Minnesota 55164-0854
Telephone: 1-800-833-8699

Online delivery of proxy materials
Registered shareholders may now elect to receive annual reports and proxy materials online. This reduces paper mailed to the shareholder's home and saves the company printing and mailing costs. To enroll, go to http://proxyonline.lilly.com and follow the directions provided.

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Actos® (pioglitazone, Takeda), Takeda
Alimta™ (multitargeted antifolate, Lilly)
Axid® (nizatidine, Lilly), Reliant Pharmaceuticals LLC
Ceclor® (cefaclor, Lilly)
Cialis™ (IC351), Lilly-ICOS LLC
Coban® (monensin sodium, Elanco)
Darvon® (propoxyphene hydrochloride, Lilly)
Debutrex® (dobutamine hydrochloride, Lilly)
Evista® (raloxifene hydrochloride, Lilly)
Forteo™ (teriparatide, Lilly)
Gemzar® (gemcitabine hydrochloride, Lilly)
Humalog® (insulin lispro injection of recombinant DNA origin, Lilly)
Humalog® Mix75/25™ (75% insulin lispro protamine suspension 25% insulin lispro injection of recombinant DNA origin, Lilly)
Humatrope® (somatropin of recombinant DNA origin, Lilly)
Humulin® (human insulin of recombinant DNA origin, Lilly)
Iletin® (insulin, Lilly)
Keflex® (cephalexin, Dista)
Lorabid® (loracarbef, Lilly), Xing Pharmaceuticals, Inc
Micotil® (tilmicosin, Lilly)
Nebcin® (tobramycin sulfate, Lilly)
Permax® (pergolide mesylate, Lilly)
Prozac® (fluoxetine hydrochloride, Dista)
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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Exhibit A, Page 50 of 52
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

ZY1 00205129
Page 50

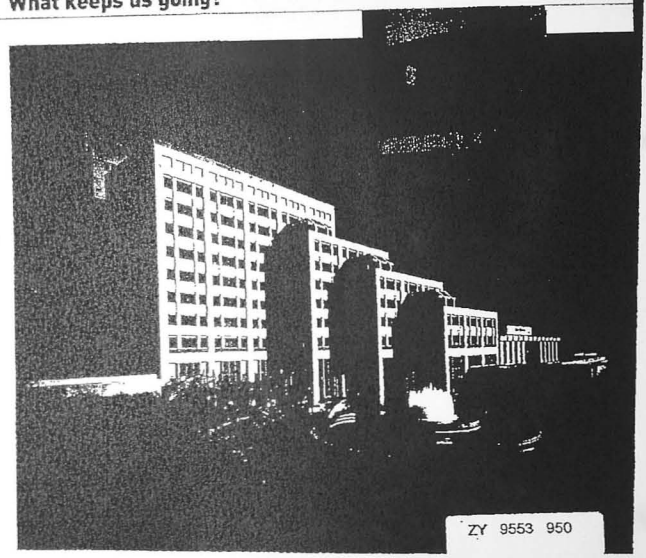
005924

Our people do. There were only four of them when Lilly opened its doors on Pearl Street in Indianapolis in 1876. Today, as we celebrate our 125th year in business, they number more than 35,700 worldwide.

With passion for their work and for the welfare of patients, Lilly employees have exemplified the company's values and driven its success. They have been steadfast in their commitment through the ups and downs of external history and the rewards and pain of internal expansion and culture change. They are, indeed, the source of all that we are and all that we have achieved for the advance of medicine.

The people of Eli Lilly and Company have brought us this far, and it's Lilly people who will take us forward over the next 125 years.

What keeps us going?



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Zyprexa MDL 1596
Zyprexa MDL Plaintiffs' Exhibit No.05913

Lilly

Answers That Matter.

Eli Lilly and Company
Lilly Corporate Center
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Kellogg
Graduate School of Management

Eli Lilly & Company: Part A

Sidney Taurel was deep in thought as he strolled across Eli Lilly's downtown Indianapolis campus on an unusually warm day in the early spring of 2002. The CEO of the $11 billion pharmaceutical giant was on his way to a meeting with his senior executives; on the agenda was a review of the progress of the recommendations made at Leadership V 2001, held in April of the previous year. In response to changes in the landscape of the pharmaceutical industry over the past several years, Taurel and his senior staff had recognized the increasing importance of the customer and the urgent need to become a truly customer-centric organization – a daunting task in a company and industry where science and "the molecule" is king. In response, the focus of Leadership V in 2001 revolved around generating strategies to establish the 125 year-old company as the preeminent customer-focused pharmaceutical company. In addition to the recommendations made at Leadership V, Lilly had several other initiatives – including a large customer relationship management (CRM) project and the Lilly Center for Women's Health – that looked promising in bringing the company closer to its goals. However, Mr. Taurel worried that even the best laid strategies and tactics would not be enough to transform a company that had had a century and a quarter to establish its culture and practices.

INDUSTRY BACKGROUND

The pharmaceutical industry as it exists today began to develop during the 1920s and 1930s with the discovery of compounds such as sulfa antibacterials, penicillin and other antibiotics. During World War II, pharmaceutical production increased significantly due to demand for penicillin and other anti-infectives to treat wounded soldiers and civilians. After the war ended, the industry as a whole increasingly invested in research and development (R&D). This led to significant scientific breakthroughs in a number of therapeutic areas.

Because demand for medicine is correlated with a population's health, the pharmaceutical industry is relatively immune to fluctuations in the economy. U.S. pharmaceutical companies sold approximately $165 billion worth of prescription drugs in 2000, of which approximately 68% was sold to U.S. consumers. Worldwide, North America, Europe, and Japan accounted for 88% of all pharmaceutical consumption in 2000, with North America representing 48% of global retail sales. Europe ranked second, accounting for 24% of the total market in 2000. As a whole, the European market is comparable in size to the U.S. market; however, because of the government-controlled healthcare systems, which regulate which drugs are eligible for reimbursement, Europe is well below the U.S. in profitability and growth[1].

This case was researched and written by Professor Ranjay Gulati and Research Fellow Sarah Huffman as the basis of class discussion rather than to illustrate either effective or ineffective handling of an administrative situation. Some facts within the case have been altered for confidentiality reasons.

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[1] Standard & Poor's Industry Surveys, Healthcare: Pharmaceuticals

Exhibit B, Page 1 of 14
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY202166113
Page 1

Zyprexa MDL Plaintiffs' Exhibit No.09070
9070-001 / 1
9070-001
005927

U.S. pharmaceutical sales were expected to grow at a compound annual rate of about 12% between 2000-2005. This level of growth was attributed to several factors: an aging population requiring an increasing number of prescriptions; strong R&D productivity at U.S. drug companies; and the increase in aggressive direct-to-consumer advertising. Comparably, the U.K. is expected to have growth rates of about 8%[2].

Demographic trends contributing to the estimated increase in demand for pharmaceuticals over the next several decades include an aging population and the lengthening of the average lifespan. The World Health Organization predicts that close to two billion people will be over the age of 60 by 2050, compared to approximately 606 million in 2000. In the U.S., the over-65 age group is expected to expand by 53% from 2001 through 2020, compared to a 17% increase in all Americans over the same period. In 2001, people age 65 and older accounted for almost one-third of all prescriptions written, even though they made up only 16 percent of the total U.S. population[3].

Pharmaceutical companies have one of the highest levels of research and development spending relative to sales than any other industry. R&D spending as percent of sales has increased steadily, rising from 11.9 percent in 1980 to 18.5 percent in 2001. Pharmaceutical companies invested $30.5 billion in R&D during 2001, up 18.7 percent from 2000. The most money was invested in research focusing on diseases affecting neoplasms, the endocrine system and metabolic diseases, followed by those affecting the central nervous system and sense organs (Exhibit 1). The mapping of the human genome in 2001 contributed to the rise in spending, and R&D costs are expected to continue to rise over the next several years. Although drug output from advances in genomics is not expected for at least five to fifteen years, once realized, productivity gains are expected to be significant. It is estimated that a cost savings of almost $300 million and a times savings of two years per drug is possible with genomics technology. These savings, resulting primarily from efficiency gains, correspond to potentially a 35 percent reduction in R&D costs and a 15 percent reduction in time[4].

Although the pharmaceutical industry was virtually immune from fluctuations in the overall economy and enjoyed significant gains throughout the 1990s, by 2002 drug makers faced other significant challenges including patent expirations and decreased R&D productivity. Over the next four years, drugs that generated approximately $30 billion in U.S. sales were expected to lose their patent protection. Without patent protection, generic drug manufacturers – who could sell the same drug at a fraction of the price of the branded drug – were certain to squeeze market share from the major pharmaceutical companies.

Compounding the predicted losses from generic sales drug makers were facing a "drought" and were not able to efficiently and successfully bring new drugs to market despite a dramatic increase in R&D spending. Although R&D spending tripled between 1990 and 2001 – swelling from $8.4 billion to $30.3 – billion, only 52 new drugs were approved by the FDA in 2001 compared to 64 in 1990[5]. Factors contributing to the slowdown: traditional methods of drug development were less productive than in the past, and the payoff from genomics technology was taking longer than anticipated.

In 2002, major U.S. pharmaceutical stocks as a group under performed the S&P 500 through the first quarter of 2002; however, individual company performance varied significantly across the group, with Wyeth, Pfizer and Pharmacia all outperforming the index. The erosion in earnings growth has been attributed in part to patent expirations and the ensuing generic competition.

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[2] Ibid
[3] Ibid
[4] *Chemical Market Reporter*, January 7, 2002
[5] *Business Week*, May 6, 2002: "No Quick Cure" (p. 30-33).

Exhibit B, Page 2 of 14
SOA Request for Clarification of
the Court's Order re: Other Drugs ZY202166114
Case No. 3AN-06-5630 CI
Page 2

Zyprexa MDL Plaintiffs' Exhibit No.09070
9070-001 / 2
9070-002
005928

AN EVOLVING INDUSTRY

By the late 1990s, the pharmaceutical industry found itself in the midst of dramatic changes – both in the general healthcare industry as well as their own – that would force them to reevaluate their role in the marketplace and in the eyes of their consumers. One critical factor was the increasing influence and control of patients over their own healthcare. Patients were increasingly paying a higher percentage of their total healthcare costs, and as a result began to demand more information and have insisted on being more actively involved in healthcare decisions. In addition, as patients began to be more proactive about their health concerns, primary care physicians were progressively losing control because of pressure from managed care organizations. Managed care was putting pressure on physician incomes by dictating how much they would reimburse. Many doctors were being forced to spend less time with patients, just as the patients were demanding more time from them. Government also began to play a more influential role as the national cost of healthcare continued to expand. Budget pressures, as well as pressure from the public, pushed the government to act more intrusively in an attempt to stem rising healthcare costs. Physician attitudes towards the pharmaceutical industry were also a factor. Industry marketing practices – viewed as "marketing ploys" – became increasingly resented, especially given the rising cost of healthcare in general and prescription medications in general. In 1990 the Pharmaceutical Research and Manufacturers of America (PhRMA) adopted the American Medical Association's (AMA) definition of "acceptable gifts" to physicians; however, despite industry self-regulation, many critics argued that pharmaceutical companies continued to use excessive gifts, entertainment and travel to influence physicians.

The pharmaceutical industry was far from immune from the consequences of climbing healthcare costs. Managed care companies were not only limiting how much they would reimburse physicians, but were beginning to put pricing pressures on pharmaceutical companies as well. Managed care companies and pharmacy benefit managers (PBMs) were increasingly restricting the use of expensive drugs if a cheaper alternative was available. In addition, many employers were switching to three-tiered prescription benefit programs, under which expensive brands might have a co-pay of $15 dollars, compared to $10 for a moderately priced brand and $5 for a generic. Because more of the cost had been shifted to them, consumers were more likely to request a generic if it was available.

The use of technology in the healthcare industry has also increased across all players. In particular, the Internet has evolved as a valuable tool with implications for patients, providers, and pharmaceutical companies, and is accelerating the transformation of the healthcare industry toward a more efficient and customer-driven healthcare system. By 2001, nearly 70 percent of Americans had used the Internet to search for medical information. In fact, it was the second most common reason that people access the web. The Internet has allowed consumers' access to a wealth of information regarding health issues from a variety of sources online, including company and product websites, online support groups and chat rooms for specific conditions, self-diagnostic tools, physician referrals, medical research information, to name a few. The Internet has been used to facilitate communication between patient and providers, as well as streamlined clinical trial data collection and dissemination.

Pharmaceutical companies were also utilizing the Internet on several levels. In 2001 Cap Gemini Ernst & Young surveyed over 100 senior managers at 42 pharmaceutical companies, including the top ten 10, and found that 77 percent had a separate group to handle e-business, with most investing between one-half and one percent of their sales on Internet initiatives – with an industry total of over $2 billion annually. Over half of that money was spent on online sales and marketing, particularly on e-detailing. E-detailing allows for real-time, face-to-face interactions between sales reps and physicians on demand; one-third of the study participants reported that their companies had initiated e-detailing pilots[6].

[6] Sellers, L.J. "Pharma's Quantum Shuffle," *Pharmaceutical Executive*, August 2001, p. 70.

Zyprexa MDL Plaintiffs' Exhibit No.09070
9070-001 / 3
9070-003
005929
Exhibit B, Page 3 of 14
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY202166115
Page 3

The Internet has also been increasingly used by pharmaceutical companies in clinical trials, with most companies in the Cap Gemini Ernst & Young survey indicating that they were planning to use the Internet to accelerate the clinical trials. The Internet was being used to capture data and recruit patients for clinical trials, and companies reported that Web-enabled processes could reduce the time it takes to move from clinical trials to regulatory submission by 40 percent.

Similar to companies in most other industries, pharmaceutical companies have increasingly utilized the Internet as a marketing tool. Numerous companies have created websites beyond "corporate" websites that just provide company information and statistics. Pharmaceutical companies have developed product-focused websites that provide information about a specific drug (such as Lilly's prozac.com) and disease-specific websites that provides information about a certain condition (such as Aventis' www.RAwatch.com designed to help patients manage rheumatoid arthritis). In addition, several companies have launched websites geared towards specific populations, such as women and senior citizens. These websites offer a host of information about health issues that are of specific concern to these groups.

Pharmaceutical Marketing

One of the most profound changes to hit the industry in recent years has been the way in which pharmaceutical companies marketed their products. Marketing in the pharmaceutical industry has traditionally been very different from marketing in most other industries, and as a result drugmakers have been faced with unique challenges in promoting their products. First, "defining the customer" has long been an issue, because the prescription decision often involves more than one party. Second, more so than any other industry, pharmaceutical companies are subject to stringent monitoring and regulation by government agencies, particularly the Food & Drug Administration (FDA). In recent years, some marketing restrictions have been relaxed, giving pharmaceutical companies greater access to the end-user of their products – the patient.

In most industries – particularly consumer products – the target of marketing and promotional messages is the end user of that product. In the pharmaceutical industry, however, the end-user of the product – the patient – is often only one of several constituents involved in the decision-making process. The pharmaceutical industry can have several customers for one product, each with different needs and roles in the purchase decision process. Doctors, patients, payers such as HMOs, and the government can all play a role in the decision of whether or not a particular drug is prescribed.

Mark Kershisnik, executive director of Global Marketing Planning at Eli Lilly, described marketing in the toy industry as being the closest comparison to marketing in the pharmaceutical industry, because the person who ultimately decides what to purchase (the parent) is different from the end user (the child). He explained the conundrum faced by pharmaceutical companies:

> Proximity to customers is a challenge in or business. Who IS the customer? The end user (the patient) is a very important customer. But the physician, because he or she is the gatekeeper, is the customer because without them there would not be a transaction. Now, direct to consumer (DTC) marketing as well as lifestyle pharmaceuticals (such as Viagra and Prozac) has changed that because they are driven by consumer pull demand – probably more so than the physician prescribing them. Then we have pure physician-driven drugs, like sepsis and oncology treatments. So there we are a B2B business rather than a B2C business.

Because they typically foot the bill for much of the nation's prescription drug costs and had steadily gained power in dictating prices, managed care organizations (MCOs) and government agencies such as Medicare and Medicaid have become an increasingly important audiences for the pharmaceutical industry. In 2000, MCOs accounted for over 70 percent of all retail prescriptions; Medicaid accounted

Exhibit B, Page 4 of 14
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY202166116
Page 4

Zyprexa MDL Plaintiffs' Exhibit No.09070
9070-001 / 4
9070-004
005930

for 11 percent[7]. Pharmaceutical companies must convince these gatekeepers why their drugs should be included in the managed care organization's drug formulary.

Historically, due to stringent regulations regarding pharmaceutical marketing, the patient was rarely the focus of marketing and promotion by the drug companies. Regulations required that that advertising for specific products contain extremely detailed information of relevant safety and dosage information for that product. Conveying this substantial amount of information through traditional communications -- particularly television and radio advertising -- was impractical given the prohibitive expenses, and as a result direct-to-consumer (DTC) marketing was minimal. Instead, pharmaceutical companies focused the majority of their promotion activities on the physician, who was in essence the "gatekeeper"

However, in 1997, the FDA relaxed its rules regarding the advertising of prescription drugs, heralding a dramatic change in the way the industry markets drugs to consumers. Under the revised rules, pharmaceutical companies were permitted to identify a product by name and describe its use; however, key side effects had to be described and directions to either a print ad or website with more detailed information was required. Perfunctory mention of indications and benefits were permitted, with an emphasis on serious side effects. All ads had to include the statement "be sure to consult your doctor before taking this and all prescription medications."

The relaxed guidelines led to an explosion in DTC advertising, which quickly became the fastest-growing portion of the pharmaceutical industry's promotional budget. Spending reached $2.5 billion in 2000, up 34% from 1999. Pharmaceutical advertising was the fourth largest advertising category in the U.S. after cars and trucks, restaurants, and movies in 2000. Pharmaceutical companies, which initially only advertised treatments for common chronic ailments such as allergies, soon branched out into more "taboo" areas, including erectile dysfunction, contraception, and herpes. The number of brands promoted via DTC campaigns went up from 59 in 1998 to 92 in 1999[8].

And it seemed to work: Several reports indicated that DTC advertising did in fact influence consumers and drive demand. An IMS Health survey conducted in 2000 found that over one-third of respondents had a conversation with their doctor as a result of seeing a pharmaceutical advertisement. A similar survey by the FDA indicated that 27 percent of respondents who had seen a doctor in the previous three months were prompted by an advertisement to talk to their doctor about a condition they had not previously discussed. These conversations often led to a prescription: one-quarter of the IMS survey respondents requested a prescription, with the doctor prescribing the exact brand requested two-thirds of the time. Reasons for not prescribing the desired drug included the patient being given another drug, the prescription was not indicated for the condition, or there were possible drug interactions[9].

Although it was coup for the pharmaceutical companies, the massive increase in DTC advertising ignited a firestorm of controversy, particularly among physicians. Many physicians feared that patients' requests for particular medications would undermine their authority and are not in the best interest of patients. In addition, many felt that DTC advertising – although in many cases can increase doctor-patient communication, has led to inappropriate or unnecessary prescriptions. Physicians began to feel increasing pressure from patients who come to them and demand specific drugs, which can drive a wedge into the doctor-patient relationship. A survey by IMS Health indicated that 64 percent of physicians would like to see fewer or no DTC ads at all. Although sixteen percent of physicians reported that they believed that DTC ads offered some educational value, 38 percent

[7] Standard & Poor's Industry Surveys, Healthcare: Pharmaceuticals
[8] Blankenhorn, K., Duckwitz, N., & Sherr, "Power to the People: Reaching the Smart Market of Empowered Consumers," *MM&M*, August 2001.
[9] Ibid.

Zyprexa MDL Plaintiffs' Exhibit No.09070
9070-001 / 5
9070-005
005931
Exhibit B, Page 5 of 14
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY202156117
Page 5

believed pharmaceutical ads confused patients. Critics also argued that excessive marketing and advertising budgets would unnecessarily drive up the cost of prescription drugs.

Proponents of DTC advertising maintained that marketing directly to the consumer had significant benefits for consumers. They argued that DTC ads inform patients about various diseases and conditions, prompted them to seek help, promoted dialogue between patient and doctor, and reached populations typically underserved by traditional healthcare education. A study conducted by RxRemedy indicated that DTC advertising of prescription drugs allowed patients to more actively participate in their health care, thus increasing the likelihood that they would follow their treatment regimen. The study – which analyzed arthritis, depression, nasal allergies, diabetes, and high blood pressure – found that compliance was highest among patients who asked for a drug because they were prompted by seeing a DTC advertisement[10].

ELI LILLY & COMPANY

Eli Lilly & Company was founded in 1876 by a 38-year old pharmaceutical chemist and Civil War veteran, Colonel Eli Lilly, who was frustrated by medications that were poorly prepared. Colonel Lilly, who started the Indianapolis, Indiana-based company with $1,300, pledged to "manufacture pharmaceutical products of the highest quality" that were "based on the best science of the day" (lilly.com). Eli Lilly emphasized research from early in its history and became one of the first in the pharmaceutical industry to establish a full-fledged research program. Colonel Lilly hired the company's first scientist – Ernest Eberhard, a chemist and recent graduate of the pharmacy at Purdue University – in 1886. This laid the foundation for Eli Lilly's commitment to quality and the discovery and development of new pharmaceuticals. Today, although the company pursues innovation and opportunities in a number of areas and embraces a philosophy of "research without walls," Lilly's products and primary research efforts are focused on five key therapeutic areas: neuroscience, endocrinology, infectious diseases, oncology, and cardiovascular diseases. In addition, the company markets several animal health products. Lilly's largest product category is the neuroscience group (Exhibit 2).

One of the company's earliest breakthroughs came during the 1920s, when Lilly scientists partnered with researchers at the University of Toronto to develop a treatment for diabetes, which at the time was a fatal disease with no treatment options. The process involved extracting insulin from the pancreases of hogs and cattle – 6,000 cattle or 24,000 hog glands produced one ounce of insulin. Their work in isolating and purifying insulin resulted in the development of Iletin, the first commercially available insulin treatment in the world. Lilly's groundbreaking research in diabetes treatment continued, and culminated in 1982 with the introduction of Humulin, an insulin identical to that produced by the human body. Humulin was the first human healthcare product that was created by using recombinant DNA technology, a technology that was eventually used in a new therapy called Humatrope used to treat growth hormone deficiency in children.

Also during the 1920s and 30s, Lilly introduced the antiseptic Merthiolate, sedative Seconal, and treatments for heart disease and anemia. Lilly scientists, along with researchers from Harvard, developed a therapy for life-threatening pernicious anemia using a liver-extract product. This therapy, which for many years was the primary treatment for pernicious anemia, led to a Nobel Prize.

Since the 1940s, Lilly played an important role in the development and delivery of antibiotic treatments. The company was one of the first to mass-produce penicillin – the world's first antibiotic. In 1952, Lilly researchers launched both erythromycin, a powerful antibiotic from a species of mold found in the Philippines that expanded options for patients allergic to penicillin; and vancomycin, a powerful antibiotic used to treat patients suffering from serious hospital infections. During the 1960s,

[10] Ibid.

Exhibit B, Page 6 of 14
SOA Request for Clarification of
the Court's Order re: Other Drugs ZY202186118
Case No. 3AN-06-5630 CI Page 6

Zyprexa MDL Plaintiffs' Exhibit No.09070

9070-001 / 6

9070-006

005932

Lilly launched a new class of oral and injectable antibiotics called cephalosporins. The first in a long line of this class of antibiotics, over the next twenty years scientists at Lilly discovered several breakthroughs that allowed for the large scale production of these products including Keflex and Kefzol. A member of this class of antibiotics – Ceclor – became the world's top-selling antibiotic in the 1970s.

Developing new treatments for cancer has been a priority for Lilly since the 1960s, when it introduced vinca alkaloid anticancer drugs derived from the rosy periwinkle plant. Other treatments include Gemzar, a product that analysts expect will grow by 36% over the next several years. In addition, Lilly is in the late-stage development phase of a treatment for non-small-cell lung cancer.

Lilly is perhaps best known for its contributions in the area of neuroscience, particularly drugs that treat psychiatric conditions. One of its biggest and most profitable drugs was Prozac, used for the treatment of depression and other related mental illnesses. Prozac, an antidepressant in the serotonin reuptake inhibitor class (SSRI) was introduced in 1986 and was an almost immediate blockbuster and provided relief for millions suffering from depression. By 2000, there were some 40 million user of the drug, accounting for a quarter of Lilly's $10.8 billion in sales that year and more than a third of a $3 billion profit. Over a thirteen year period the drug earned Lilly $23 billion – some years accounting for one-third of the company's revenue.

Despite its many successes in research and development, the company faced its share of legal challenges over the years, including lawsuits over product side effects and patent issues. In 1971, it was discovered that DES – a drug used to prevent miscarriages that was introduced by the company in 1947 – caused a rare form cervical cancer in the daughters of women who had used the drug during pregnancy. This discovery led to a number of lawsuits that continued into the 1990s. More recently, in 1999 a federal court ruled that Lilly had been illegally promoting its osteoporosis drug, Evista, as preventing breast cancer similar to the drug Nolvadex, produced by competitor AstraZeneca. Also in 1999, the deaths of 53 patients led the company to cease testing its variation of the heart drug Moxonidine.

Lilly has established a significant global presence since its founding: In addition to marketing its products in 158 countries, Lilly operates research and development facilities around the globe, including Australia, Belgium, Canada, England, Germany, Japan, Singapore, Spain and the United States. Clinical research is conducted in approximately 70 countries worldwide. Manufacturing facilities are located in Australia, Brazil, China, Egypt, England, France, Germany, Ireland, Italy, Japan, Korea, Mexico, Pakistan, Puerto Rico, Taiwan and the United States.

By 2001, Lilly had achieved sales of over $11.5 billion and employed approximately 41,000 people (Exhibit 3; see Appendix A for financial comparison of Lilly and top competitors). Twelve Lilly products had sales of over $200 billion (Exhibit 4). The company continued to be a leader in the pharmaceutical industry in R&D investment, spending $216.6 million, or 19% of sales. Over the last five years, Lilly's total R&D investments from continuing operations topped $9 billion. Lilly was also committed to providing human capital investment: In 2001, over 7,000 employees, or 18 percent of the company's workforce, were engaged in research activities.

Shifting Priorities

Although it was one of the most significant and profitable achievements in Lilly's history, the Prozac era came to an end when the company lost its patent for the drug in 2001. In August 2000 a U.S. Court of Appeals ruled that the company would have to cede its Prozac patent in 2001 rather than in late 2003, more than two years earlier than expected. After the news of the ruling, Lilly's stock plunged by almost one-third in a day, to $75, wiping out $36.8 billion in equity. The stock bottomed out the following month at $66 (but later rebounded to more than $80). Lilly appealed to the Supreme Court, but despite briefs filed in support of Lilly by the Pharmaceutical Research and Manufacturers

Exhibit B, Page 7 of 14
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY202166119
Page 7

Zyprexa MDL Plaintiffs' Exhibit No.09070
9070-001 / 7
9070-007
005933

of America (PhRMA) and the Biotechnology Industry Organization, the justices declined to hear the case and upheld the lower court's ruling. When the Prozac patent expired a year later, in August 2001, 80% of U.S. patients who used the drug switched to the cheaper generics, making Prozac the biggest-selling drug ever to come off patent. Sales of the molecule dropped faster than the company had expected, and by the fourth quarter of 2001 sales declined 66 percent. This brought the total sales for the year down 23 percent to $2 billion.

Anticipating the challenges that the Prozac patent loss would undoubtedly bring, the company ensured that it had a comprehensive plan in place to create and capitalize on other opportunities. The company increased its support for five medications that became the primary sources of growth in recent years (Exhibit 5). Zyprexa, which is used to treat schizophrenia and bipolar disorder, reached sales of $3.1 billion in 2001 – making it both the first Lilly product and the first product for treating mental illness to achieve over $3 billion in sales in one year. During the second quarter of 2002, Zyprexa worldwide sales increased 23% to $907 million for that quarter – ahead of analyst estimates. Zyprexa's prescription market share stood at 30.9% in June 2002, and the drug retained the highest U.S. cash share of the anti-psychotic market with 44%. The company hoped to expand the brand by extending Zyprexa into the bipolar depression market. Lilly planned to conduct additional research on Zyprexa as a therapy for bipolar depression, with an expected FDA submission in early 2004.

Another promising product in the Lilly portfolio in 2001 was the cancer agent Gemzar – its growth rate increased from 23 percent to 29 percent and achieved sales of $723 million. Three other products that enjoyed significant growth were Evista for the treatment of osteoporosis and Humalog and Actos, both treatments for diabetes. Humalog sales increased by 79 percent, which helped propel a 16 percent increase in global insulin revenues for Lilly.

Another vital strategy that the company took was to expand opportunities by increasing research and development expenditures and ramping up its efforts in bringing promising molecules to market. In 2001, Lilly had increased its R&D expenditures by over $216 million from the previous year and submitted more New Drug Applications for novel products than the company has ever had in a single year. The company had built up what was cited by some analysts as the best pipeline in the industry: Lilly planned to launch at least 10 or more new products over the next four or five years (Exhibit 6); in contrast, Lilly brought just 14 drugs to market over the past two decades. According to the 2001 annual report, Lilly was poised to triple the size of its product line over the next five or so years. In a July 2002 report, Credit Suisse First Boston analysts echoed this sentiment: "Lilly's emerging pipeline characteristics and strong proprietary patent positioning provide an excellent growth platform for the 2003-2006 period[11].

One potential blockbuster – Xigris for severe sepsis – received FDA approval in 2001. The condition, which is the body's overreaction to infection triggered by trauma, surgery, burns, or illnesses such as pneumonia and cancer, claims the lives of 1,400 people every day. As the first drug approved to treat severe sepsis, some analysts predicted that Xigris had the potential to become a multi-billion dollar product. Initial sales of the drug through December 31st, 2001 were $21.2 million. The drug's uptake into the critical care markets was slower than analyst expectations, due largely to physician conservatism and skepticism over the benefits associated with initiating therapy. Lilly planned to expand its marketing efforts by emphasizing broader critical care and oncology audiences and increasing "peer-to-peer" educational programs. In July 2002, Lilly scientists received the 2002 Inventor of the Year Award for Xigris. The award, given annually by the Intellectual Property Owners Association (IPO), ranks as one of the nation's most prestigious awards for breakthrough inventions.

[11] Credit Suisse First Boston Equity Research earnings report, July 19, 2002.

Exhibit B, Page 8 of 14
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY202166120
Page 8

Zyprexa MDL Plaintiffs' Exhibit No.09070
9070-001 / 8
9070-008
005934

Other potential winners targeted for launch in 2002 include Forteo, Cialis, Atomoxetine and Duloxetine. Forteo, an osteoporosis agent that is awaiting marketing approval from the FDA, differs from other therapies in that it stimulates the formation of new bone rather than simply slowing or stopping bone loss. Cialis, which was developed in collaboration with ICOS Corporation, is a treatment for male erectile dysfunction. Lilly hoped to capture a significant share of the market dominated by Pfizer's Viagra. Atomoxetine and Duloxetine, both neuroscience drugs, offered hope for people suffering from attention deficit hyperactivity disorder (ADHD) and treatment-resistant depression, respectively. The launch of atomoxetine was particularly anticipated, as it is the first non-stimulant treatment for ADHD.

Leveraging Technology

In addition to developing new blockbusters, Lilly is hopeful that its increased use of new technologies will also help propel the company's continued success and provide a competitive advantage. In early 2001, Eli Lilly announced the launch of e-Lilly, the company's new venture fund. With an investment of $50 million, the fund backs early-stage start-up companies developing innovative e-business solutions for the research and development of new drugs, increasing research productivity, reducing clinical trial costs, and developing new ways to connect to the customer. Said Newt Crenshaw, vice president of e-Lilly:

> The vision for e-Lilly was to create a competitive advantage for Lilly by defining and implementing new business models that leverage technology and put the customer back in to the center of what we do. From the very beginning we felt that the customer was number one, and that technology is just a means to an end.

E-Lilly provides a platform – separate from Eli Lilly – to make riskier investments. Although e-Lilly avoids angel and seed rounds because of the risks involved with developing those kinds of companies, the company invests early in order to have access to innovative business models. The goal of the fund is to make investments that can be connected back to Eli Lilly, either by integrating the new technology or by building a business model that benefits both companies.

The venture fund has both an external and internal focus. Externally, e-Lilly has invested in several companies that own promising technologies that are aligned with Lilly's customer focused objectives. In addition, in order to build a more market-based approach and free flow of capital ideas and talents within Lilly, e-Lilly also makes significant investments internally. As of 2002, the group had helped implement over forty ventures or projects inside the walls of Lilly. For example, e-Lilly has been responsible for the company's customer relationship management initiatives.

Sheri Morin, Director, Product Team e-Lilly Strategy, described the value of the e-Lilly function within the company:

> E-Lilly provides funding for projects that would not normally get funding through Lilly corporate. Because this arm is separate, you are allowed to fail. We have always been a culture that is afraid to fail so we might not take enough risks. With e-Lilly, failure is accepted – you can be recognized if you take a high risk even if you fail, and it is still seen as an accomplishment because it was justified.

Emphasis at e-Lilly is placed primarily on projects related to research and development and sales and marketing; projects such as software and enterprise issues were not undertaken. "We have fundamentally wanted to look at the value drivers of the business so we have unashamedly focused on R&D and sales marketing, and said no to the other things like software and enterprise," said Crenshaw. Finding ways to better connect with physicians and patients have been particularly emphasized. Because a continuing issue in the pharmaceutical industry is access to physicians, e-Lilly has been investing in projects that promote multi-channel access to physicians. E-Lilly has also been

Zyprexa MDL Plaintiffs' Exhibit No.09370
9070-001 / 9
9070-009
005935
Exhibit B, Page 9 of 14
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY202166121
Page 9

investigating ways in which to better connect with patients, particularly at the point of decision for treatment and providing rich information about disease states and Lilly product information.

One example of a technology initiative that e-Lilly has invested in is XigrisMobile, a program that would provide physicians with selected information about Xigris and sepsis via any wireless Internet accessible devise, including wireless laptops, hand-held prescribing devices, and PDAs. Physicians would be able to access needed information anywhere in the hospital – such as at the patient's bedside – where it would have immediate impact and would not disrupt treatment methodology.

Utilizing the Internet to facilitate clinical trials has been a particularly promising technology development at Lilly. Called "e-Clinical," Internet applications were being piloted for use at all stages of a clinical trial, from study design through start-up and execution, to study reporting. One example is the "Virtual Clinical Trials Tool Chest SM" (VCTTC), a set of clinical trial management tools to virtually conduct clinical trial start-up meetings and regulatory readiness at investigative sites. In addition, the VCTTC could be used for affiliate training meetings as well as internal staff training at the study sites. Benefits of VCTTS include decreased travel and travel costs, increased quality, flexibility, and consistency in training, and decreased study start-up delays. By 2002, 30 Virtual Startups had been completed.

MARKETING AT LILLY

Today, marketing responsibilities fall onto three axis at Lilly, each with specific roles and responsibilities in the marketing function: the product teams, the affiliates, and the Global Marketing and Sales Organization (GMSO). Each different molecule, or brand, at Lilly is the responsibility of an individual product team; these product teams are responsible for developing the overall global product strategy. Each affiliate represents a specific geographic region in the world and is responsible for tailoring and implementing the product strategy. The GMSO is a corporate-level function that is responsible for developing marketing capabilities and ensuring best practices within the organization.

This structure was developed in the late 1990s, when Lilly recognized that its marketing practices were not as efficient or effective as they needed to be in the ever-changing pharmaceutical industry. Like most companies in the pharmaceutical industry, Lilly was a primarily science-driven organization, where the "molecule was king," and little emphasis was placed on marketing or branding. Science came first, and marketing consisted mainly of brochures about a product for the sales reps to give to physicians.

Remarked Chad McBride, manager of marketing, GMSO:

> We were very much a "you either work for the white coats or the suits" type of company – either research or sales. Marketing were the people who would produce the detail work that would go to the sales force.

Although Lilly had had some success developing individual product brands, individual efforts – rather than well-defined processes – were credited with those successes. There were no processes in place nor was there an organized discipline of sharing knowledge. James Harper, group vice president of GMSO, explained how marketing capabilities were basically owned by individuals and were not necessarily disseminated throughout the organization:

> People who do it really well and spend a lot of time focusing on the customer do it because they like it in terms of developing a relationship with the customers. They carry a lot of this stuff in their heads, and could provide a lot more insight and a lot more meaningful direction in terms of what our marketing plans should be, what clinical trials should look like, etc. When you see the potential impact of that kind of knowledge, it seems to me that it should be

Exhibit B, Page 10 of 14
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY202166122
Page 10

Zyprexa MDL Plaintiffs' Exhibit No.09070
9070-001 / 10
9070-010
005936

> much more systematic and planned and organized than just allowing it to be randomly determined by people who have the aptitude for it.

The lack of defined processes often resulted in redundant efforts, and management believed that Lilly brands could be made stronger with the implementation of standardized processes. In response to the concern that no one was ultimately responsible for marketing expertise, the Global Marketing and Sales Organization (GMSO) was established in 1998 to bring marketing capabilities together under into one functional home.

In addition to the creation of the GMSO, Lilly restructured the products organization and developed the product team format. Before the restructuring, several different molecules were housed under one business unit – one business unit was responsible for developing the long-term strategic direction for several molecules, on both the medical and the marketing side. Under the new structure, product teams had similar responsibilities to the business units; however, now each product team is responsible for one molecule.

Chad McBride described the evolution of the role of marketing at Lilly:

> That is where we have come from in the past seven years. We have since developed marketing capabilities and consistent processes and have made people understand the importance.

Product Teams

Currently, the pharmaceutical products organization consists of four distinct product groups that address specific disease states (Exhibit 7). The four product groups include Primary Care Products, Neuroscience Products, Oncology/Critical Care Products, and Diabetes/Growth Disorders Products. Within each product group are the individual product teams; i.e. the Prozac team is part of the Neuroscience group. As of 2002 there were twenty product teams using the product team model.

Product teams consist of both medical and marketing personnel, with each team having a Clinical Team and a Global Marketing Team. The clinical team is responsible for the scientific aspects of the molecule, including early research through post-marketing clinical trials. It includes researchers, physicians, statisticians, and other clinical and operations personnel. The medical staff reports to both the product team as well as to Lilly Research Labs, the research and development function at Lilly. The marketing team is responsible for the marketing activities that revolve around the product, including developing the brand, brand positioning, and developing the core brand message. The ratio of clinical to marketing personnel varies widely depending on the life stage of a product – in the early research stages, the product team largely consists of clinical personnel such as research scientists, whereas at a later stage in a product's life the team consists of a greater percentage of marketers.

The core product team leadership consists of a Team Leader, who has overall responsibility for the product team, a Medical Director, and a Marketing Director. In addition, each team has a Chief Operating Officer who is responsible for functions such as finance and human resources. The medical and marketing directors jointly develop the strategy for developing and marketing the molecule. The product teams are fully integrated, matrixed groups with reporting responsibilities, performance appraisals, etc. managed by the product team leader. The core product team works directly with the affiliates and development and manufacturing organizations (Exhibit 8).

The product team is formed when the decision has been made to move ahead and commercialize the molecule, in the third phase of clinical trials (see Appendix B for description of clinical trial phases). The product team, in essence, is responsible for mapping out the lifecycle of the drug. They develop an Integrated Product Plan (IPP) for a molecule – a 5-year cross-functional lifecycle plan that includes the global marketing and clinical plans as well label needs and wants, two-year budgets and 5-year

Zyprexa MDL Plaintiffs' Exhibit No.09070
9070-001 / 11
9070-011
005937
Exhibit B, Page 11 of 14
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY202166123
Page 11

forecasts. The product team also develops the product's brand position and creates and updates the Brand Book. The Brand Book outlines all aspects of the branding elements for the molecule. In addition, the product team crafts the core message of the brand to be used to develop global communication plans.

Other product team responsibilities include developing and implementing late-stage, human clinical trials (known as Phase III and IV clinical trials. (See Appendix for description of clinical trial phases). The team is also responsible for any new indications or any line extensions, as well as the scientific content of the molecule. Said Baluch, "You look at the label: How do you strengthen the label? How do you defend the label? That is the responsibility of the product team."

Global Affiliates

Once the overall global strategy is developed for a product, implementing that strategy becomes the responsibility of each of the global affiliates. Each affiliate is essentially an individual unit, and is responsible for sales in its particular geographic region. Although the product teams develop the overall strategy and brand for a particular drug, the affiliate is responsible for tailoring it to meet the individual and unique needs of its location.

Whereas the product team is responsible for the long-term success of the product, the affiliate has P&L responsibility and is held accountable for delivering quarterly results. Baluch described the distinction between the two entities' responsibilities:

> If at the end of the year, every affiliate is below their target, the finger gets pointed at the product team. If you happen to have two or three or half a dozen below their targets, then the finger is pointed at the affiliates.

Overall, there are 130 affiliates worldwide; however, the top 10 affiliates drive 70 to 80 percent of the value of a molecule. Several of the top affiliates include the U.S., Europe, Japan, Canada and Mexico. Because they drive the majority of revenues, marketing plans and strategies are typically developed based on the needs of the top affiliates. The product teams interact with these affiliates to understand their market and specific needs.

Global Marketing and Sales Organization (GMSO)

The overarching objective of the Global Marketing and Sales organization (GMSO) – led by Jim Harper – is to provide marketing expertise for the product teams, who in a sense are GMSO's "clients." GMSO provides the product teams and affiliates with the tools necessary to develop and implement the marketing plans for each product. As described in the "Roles and Responsibilities" document – developed in 2001 by the Sales and Marketing Executive Committee to define accountabilities for marketing work – GMSO "maintains process integrity, skills and capability training and quality control for the marketing process."

The GMSO is considered to be a "center of excellence" that serves as the functional home for marketing core competencies. GMSO is responsible for corporate-wide branding, but product branding is the responsibility of the individual teams. Sheri Morin described the relationship between the product teams and GMSO:

> GMSO provides capabilities, tools, processes and guidelines, but they do not do the end work on the product – that is left up to the product team. GMSO will tell you how to do it, because they have set the best practices standards, but the people on the product team who know the product and who work directly with the affiliate has the end decision.

Whereas the product team has responsibility for developing the Integrated Product plan and the 5-year forecast, GMSO is responsible for models, analysis, and review of the 5-year sales forecast. GMSO

Zyprexa MDL Plaintiffs' Exhibit No.09070
9070-001 / 12
005938
9070-012
Exhibit B, Page 12 of 14
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5830 CI
ZY202166124
Page 12

also owns the bulk of marketing research responsibilities within Lilly. They provide a common protocol and analysis reporting system to track the progress of a product after it has been launched. GMSO develops pricing strategy and conducts payor and pricing research, as well as maintains a global pricing database.

One of GMSO's core responsibilities is marketing and sales training. For the product teams, GMSO both develops and delivers training. It also develops training for the sales force; however, the affiliates are responsible for implementing the training. GMSO also develops disease and product training to be delivered by the affiliates.

Corporate e-business is under the jurisdiction of GMSO as well, with GMSO developing the corporate e-commerce strategy. It develops and maintains global web standards and adapts product branding to the web "look and feel." In addition, GMSO oversees affiliate e-commerce deployment.

Bridging the Gap: Brand Council/Marketing Planning Process

Recognizing the importance of utilizing the expertise and knowledge of both the product team and the affiliates in developing and marketing a product in 2001 Lilly established the Brand Council process – formalized input and review teams for developing marketing plans. They were established to ensure that the marketing plans that are developed are world-class and meet the needs of the U.S. and top ten worldwide affiliates. The process incorporates input from all parties involved with a brand and provides a "checks and balances" structure. Chad McBride described the Brand Council process as "a mechanism to ensure global coordination between our product teams and our top affiliates."

The Brand Council involves three meetings per year, with the first meeting in January. The first meeting is an input meeting, where the top ten affiliates bring information to the product teams about what they need to understand about the product. The affiliates present the needs of their customers to the product teams, so the product teams can address these needs as they are writing their global marketing plans from a medical and marketing perspective. Said McBride, It really focuses on putting the customer first. 75 percent of the time is spent listening to what the affiliates are saying." At this time, product team marketing and medical activities are prioritized, and "Global Core Marketing Elements" (GCME) – patient segmentation, product position, and brand character – are aligned. During the sixteen weeks after Brand Council 1, product team marketing and medical plans are developed. At the second Brand Council meeting, the product teams meet with the same affiliates and the plans are refined. From this, the affiliate marketing and medical plans are developed. Finally, at the third Brand Council meeting, the top ten affiliates come back and report what they have been doing from a strategic and practical perspective based on the plans laid out at the previous meetings.

Zyprexa MDL Plaintiffs' Exhibit No.09070
9070-001 / 13
005939
9070-013
Exhibit B, Page 13 of 14
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
ZY202166125
Page 13

Exhibit B, Page 14 of 14
SOA Request for Clarification of
the Court's Order re: Other Drugs ZY202166126
Case No. 3AN-06-5630 CI
Page 14

Zyprexa MDL Plaintiffs' Exhibit No.09070
9070-001 / 14
9070-014
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SUPERIOR COURT FOR THE
STATE OF ALASKA
THIRD JUDICIAL DISTRICT OF ANCHORAGE

STATE OF ALASKA	:	Case Number
v.	:	
ELI LILLY & COMPANY	:	3 AN 065630 CIV

- - -

CONFIDENTIAL

- - -

September 19, 2007

- - -

Videotape deposition of SIDNEY TAUREL, held in the offices of Ice Miller, One American Square, Indianapolis, Indiana 46282-0200, commencing at 8:34 a.m., on the above date, before Linda L. Golkow, a Federally-Approved Registered Diplomate Reporter and Certified Shorthand Reporter.

- - -

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deps@golkow.com - 877.370.3377

Page 202

Q. Were you ever advised of that recommendation of the advisory board?

MS. GUSSACK: Objection.

THE WITNESS: Again, I was not aware there was a meeting of the advisory board and, therefore, I could not be aware of that specific recommendation. But they are referring here to the issue of impaired glucose tolerance, and I believe that we conducted something called clamp studies, don't ask me more details about that because I'm not a physician, but this was geared at understanding whether there was a direct correlation between impaired glucose tolerance and Zyprexa. And those studies were conducted later on and did not show the correlation.

MR. SUGGS: Move to strike as nonresponsive.

Page 203

BY MR. SUGGS:

Q. They were clearly saying, "Don't get too aggressive about denial, blaming it on schizophrenia, or claiming no worse than other agents until we are sure of the facts," correct?

A. That's what it says here.

Q. Now, this meeting occurred in October of 2000 about two months after the Federal Appeals Court had denied your patent in that litigation, correct?

A. Which patent?

Q. The Zyprexa patent.

MR. ALLEN: Prozac.

MS. GUSSACK: Objection.

BY MR. SUGGS:

Q. I'm sorry. I misspoke. This meeting in October of 2000 occurred several months after the Federal Appeals Court held that the Zy – pardon me, that the Prozac patent was to expire in 2001, correct?

A. Yes.

Q. Okay.

Page 204

That legal decision had a profound impact on Lilly's financial well-being, didn't it, sir?

MS. GUSSACK: Objection.

THE WITNESS: I think we talked about that earlier. It's a decision for which we had been prepared and which led us to the development of several new products and licensing of others and so on.

BY MR. SUGGS:

Q. Sir, do you recall that the day that that Federal Court ruling was announced publicly that Lilly's stock plunged by almost one-third in a day, wiping out over $36 billion in equity?

A. I sure do. I still have the scar tissue.

Q. I'll bet you do.

MR. SUGGS: I'll show – have marked as Taurel Exhibit 4 –

MS. GUSSACK: After this

Page 205

exhibit, David, would it be appropriate for a lunch break?

MR. SUGGS: Sure.

- - -

(Whereupon, Deposition Exhibit Taurel-4, Wall Street Journal Online Excerpt (1 page), was marked for identification.)

- - -

BY MR. SUGGS:

Q. I went on Wall Street Journal online and had a chart drawn of Lilly's stock between the dates of August 1, 2000 and August 10, 2000, August 10, 2000 being the date of the outside advisory board meeting that we had referred to in the prior exhibits. And it indicates that there was a quite dramatic drop in the stock price in early August there on the day of the announcement from, it looks like something – the stock value is something over $105 per share, dropping down to about $75 per share. Is that accurate?

Chairman **Sidney Taurel** presented the company's 2002 priorities to the global management team on December 14, stressing their importance as Lilly works to become "the pharmaceutical growth company of the decade."

Taurel emphasized that to weather Year X and outgrow its competition, Lilly must:

- Maximize sales of Zyprexa® – redacted

redacted

- Speed late-stage molecules to market and further strengthen the pipeline by increasing internal R&D productivity.
- Maximize partnering effectiveness.
- Make plan.

He also stressed that Lilly must work to implement the company's strategic initiatives:

- Build a winning culture.
- Fulfill the brand promise – Answers That Matter.
- Capitalize on e-business.
- Realize the full potential of GBIP.

Referring to in-licensing and out-licensing agreements, Taurel called 2001 "a banner year for our business development area," adding, "In 2002, we need to make sure we make the business development deals we struck in 2001 work."

DAT priorities are:

redacted

Support for Japan Market

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: MDL-1596

ZYPREXA PRODUCTS
LIABILITY LITIGATION
THIS DOCUMENT RELATES TO:
ALL CASES

SHAFIQA WARDAK	:	LOS ANGELES
	:	COUNTY,
V.	:	CALIFORNIA
ELI LILLY, et al.	:	BC348211

JOEL ALGARIO	:	LOS ANGELES
	:	COUNTY,
V.	:	CALIFORNIA
ELI LILLY, et al.	:	BC347855

PATRICIA GODLEY,	:	LOS ANGELES
et al.	:	COUNTY,
V.	:	CALIFORNIA
ELI LILLY, et al.	:	BC347856

- - -

March 28, 2007

- - -

C O N F I D E N T I A L

- - -

Videotape deposition of JOHN C.

LECHLEITER, Ph.D.

- - -

GOLKOW TECHNOLOGIES, INC.
1880 John F. Kennedy Boulevard
Suite 760
Philadelphia, Pennsylvania 19103

marked for identification.)

- - -

BY MR. ALLEN:

Q. Sir, I've handed you what's been marked as Deposition Exhibit Number 6. This is an on line document I got from the Wall Street Journal's web page concerning stock prices. Particularly I was looking at the stock price of Eli Lilly in the year 2000 from August 1st to October 10th. On August the 1st, Eli Lilly's stock price was somewhere near $110 per share. And before the end of August, it had dropped to $75 a share in August of 2000. What happened --

MR. LEHNER: Object to the form.

BY MR. ALLEN:

Q. -- to cause this stock price fall?

A. Stock price is generally responsive to -- can be responsive to external events. In this case, we were surprised to receive, I believe, in early

August, at about the time that you point to this stock price decline, word that was quite unexpected that a three-judge panel had reversed an earlier court's decision about the validity of our Prozac patent.

Q. Yes. And, in fact, Prozac had been the number one selling drug product for Eli Lilly up until August of 2000, had it not?

A. I'm not certain about that. It's possible that Zyprexa sales were larger than Prozac sales at that time. I'm not certain.

Q. Nevertheless, you know if you take the number of share prices or the share price, that Eli Lilly stock after Prozac lost its patent rights in August of 2000 lost $36 billion worth of equity. Did you know that?

MR. LEHNER: Object to the form.

THE WITNESS: Sir, it's not unusual when a company receives

this kind of news that tells investors that a key patent may be jeopardized or may be revoked sooner than the market had anticipated for the market to react this way based on their estimate of revenues, in this case, Prozac revenues, that would not be incurred.

MR. SUGGS: Objection, nonresponsive.

BY MR. ALLEN:

Q. My only question to you was, sir, the stock capitalization of Eli Lilly lost $36 billion in August of 2000 when this -- when your stock fell. Is that correct?

A. I don't have a basis for saying that. This simply shows me that the stock fell. I don't know what the valuation numbers were at that time.

- - -

(Whereupon, Deposition Exhibit Lechleiter-7 (Zyprexa MDL

Plaintiff's Exhibit No. 09070) "Eli Lilly & Company: Part A" (Gulati) 2002 ZY202166113 - ZY202166126, was marked for identification.)

- - -

BY MR. ALLEN:

Q. I'm going to hand you what I marked as Exhibit Number 7. Particularly I'm going to point to Page 7 and part of Page 8, I've highlighted it for you, so we can know what we're going to talk about. I've given this to your lawyer before the deposition.

This is a report that was contained in Kellogg Graduate School of Management, Northwestern's University's graduate school, contained in your files and produced in this litigation. If we turn to Page 7, the highlighted language.

MR. SUGGS: Excuse me, can you also point out this is also Zyprexa MDL Plaintiff's Exhibit 9070.

Page 118

with the annual report?
A. Yes, I am.
Q. Publicly-held corporations such as Eli Lilly issue these every year?
A. Yes, we do.
Q. You issue it in the following year -- does your annual report come out in March or April?
A. It comes out in March generally.
Q. Is the one for 2006 out yet?
A. Yes, it is.
Q. When did it come out?
A. It would have come out about two to three weeks ago.
Q. I'm going to have to talk to somebody.
But anyhow, so, the 2000 annual report would have come out in March of 2001; is that correct?
A. That's right.
Q. Okay.
If we -- there's a lot I'd like to read, we don't have time, but if

Page 119

we look at the 2000 annual report, it says, "No company would relish losing the patent on its biggest product three years early. We certainly don't." You're talking about Prozac, are you not, what happened with Prozac? Doesn't it say that -- it's right there. Page 6. Right in the middle of the page it says, "What happened with Prozac?"
A. Yes. I'm sorry. I was looking to see if it was a continuation, but it's not. It starts right there.
Q. Yes, sir. I'm trying to be fair.
Now, it says, "What happened with Prozac?"
It says, "No company would relish losing the patent on its biggest product three years early. We certainly don't."
A. That's what it says.
Q. Now, you didn't expect this, to lose this patent. You were surprised to have lost this patent?

Page 120

A. Sir, we were surprised, but we were prepared.
Q. You were not only surprised, your report says you were "very surprised and disappointed by the judicial ruling." Is that correct?
A. That's correct.
Q. So, this loss of the Prozac patent that caused your company to lose over $36 billion in market cap came as a big surprise to Eli Lilly, did it not?
A. We were surprised at the ruling by the three judge panel.
Q. Yes, sir. I'm sorry. I didn't use the word -- I'm trying to find where I put it. Here it is. Y'all used the word. I didn't.
You not only were surprised, you were "very" surprised. Is that true?
A. Our analysis of the arguments that had held sway going into that appeal and the strength of those arguments led us to believe that the earlier decision would be upheld. So,

Page 121

naturally when the judges reversed that decision, we were surprised.
Q. Very surprised, right?
A. Sir, I said "surprised." It says "very surprised" here. I didn't write this piece, so it's difficult for me to characterize the distinction.
Q. Going on down, it's on the screen, sir, it says, what did y'all do? "We've significantly increased the size of our global sales force and will continue to do so in order to have the 'firepower' we need to successfully launch and sell the next wave of products from our pipeline."
Did you consider your global sales force fire power, sir?
MR. LEHNER: Object to the form.
THE WITNESS: Sir, our global sales force is the main way in which we engage our customers and help physicians make the right decisions for patients.

Golkow Technologies, Inc. - 1.877.370.DEPS
005946
Exhibit E, Page 3 of 5
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5[illegible]30 CI

BY MR. ALLEN:
Q. And what it says here is you "significantly increased the size" of the global sales force in response to Prozac losing its patent protection, correct?
A. That's not what that statement means. This refers to the fact that we had in our pipeline at that point in time, at the point at which this document was written, nine new molecules, new drugs that we intended to launch in the succeeding years, and that actually began in 2001. This refers to the commitment of resources that were going to be necessary to launch nine new products, which was more than anybody else in our industry launched during that time.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. Go ahead and skip to Page 9, and we'll talk about this blockbuster term that we discussed earlier which is

used by your company regarding Zyprexa.
Page 9. We're on the topic of "So, what now?" That's on Page 8. Do you see where it says "So, what now?"
A. Yes. There's some kind of photograph, and I can't make that out. I can just see the words "So, what now" on this page.
Q. Yes, sir. And I don't have the photograph. This is the best copy I have available.
"So, what now?" Your company says, "Our newer products will stand as our front line against inevitable generic competition for Prozac. Introduced throughout the last half of the 1990s" -- that would be Prozac, right? I mean, excuse me, Zyprexa was introduced in the last half of the '90s, right?
A. Yes. Zyprexa would be one of several products introduced through the last half of the '90s.
Q. -- "they'll be the key to

our ability to produce earnings growth during that time and resume our strong performance thereafter."
The number one product you list, it's number one, and not in the alphabet, it's number 26 in the alphabet, is Zyprexa; is that correct?
A. Zyprexa is next in the text here, yes.
Q. Yes. I take it it's because it's the number one product that y'all are going to have replace Prozac; correct?
MR. LEHNER: Object to the form.
BY MR. ALLEN:
Q. It's certainly not in alphabetical order, is it?
MR. LEHNER: Compound, object to the form.
THE WITNESS: I have no information, since I didn't put this report together, about why Zyprexa is listed first among this

group of products. It includes Evista, insulins and Actos.
BY MR. ALLEN:
Q. Sure does. Actos, which starts with the A, is last, and Evista is in the middle.
Let's go to Zyprexa. "Zyprexa is a genuine" -- can you read that word out loud for me, sir?
A. "Blockbuster."
Q. And so, "blockbuster" is not a term Scott Allen created. It's actually one that Eli Lilly uses itself in its annual reports, right?
A. "Blockbuster" is a term that is used generically and ubiquitously throughout our industry to denote a product, as I said earlier, in general that exceeds a billion dollars in sales.
Q. "Zyprexa is a genuine blockbuster, surpassing the $2 billion sales mark in 2000 and becoming Lilly's number-one-selling product in the fourth quarter. Just as Prozac changed the

Page 126

treatment of depression, Zyprexa has redefined the standard of care for schizophrenia, a devastating disease that ravages the mind and has been called the 'cancer of mental illness.'" Did I read that correctly?

A. Yes.

Q. You used the term in one of your answers earlier, "the cancer of mental illness"? Correct?

A. Yes.

Q. And I used the term, is Zyprexa a "blockbuster," and now we can agree that Zyprexa was a blockbuster for Eli Lilly and was intended to help Eli Lilly resume their strong performance and produce earnings after Prozac lost its patent, correct?

MR. LEHNER: Objection to the form, compound.

THE WITNESS: Sir, all of the products listed here were intended to be important aspects of the company's performance and

Page 127

success after the Prozac patent expiration. This annual report, which was written in 2001, would have been the first annual report written after the unexpected loss of the Prozac patent, and I believe in this section management, intended to communicate to shareholders, who would have naturally been interested in this subject, what are we going to do, among many things, to help the company grow from the point at which we lost the Prozac patent, and, therefore, a substantial amount of the Prozac revenue.

BY MR. ALLEN:

Q. You at Eli Lilly -- let me break some of that down.

What you're just saying is, once Prozac came off patent, you were going to lose revenue, that's income to Eli Lilly, and Zyprexa was going to be

Page 128

one of the products that replaced Prozac's lost revenue, true?

MR. LEHNER: Object to the form.

THE WITNESS: As stated here very clearly, Zyprexa, along with Evista, insulins, Actos and these new submissions which are noted here and which I talked about earlier, were all going to be important for the company to continue its growth trajectory after the Prozac patent expired.

BY MR. ALLEN:

Q. Okay. The "growth trajectory," what does that mean?

A. Investors -- people invest in companies and expect companies to grow. So, this was about how are we going to resume growth after losing a substantial portion of sales of an important product, Prozac.

Q. Sir, I'm sorry for having to stand up. I have to go from you to the

Page 129

Elmo.

A. I understand.

- - -

(Whereupon, Deposition Exhibit Lechleiter-9 (Zyprexa MDL Plaintiffs' Exhibit No. 8584), "Zyprexa Product Team Off-Site July 25, 2001" ZY201548768 - ZY201548789, was marked for identification.)

- - -

BY MR. ALLEN:

Q. I'm going to hand you what we've marked as Exhibit Number 9. There's one for you and one for your counsel. You keep the original.

A. There are three copies here.

MR. ALLEN: Give one to Mr. Seth -- I'm sorry, Seth, what's your last name?

MR. OLTMAN: Oltman.

MR. ALLEN: Give one to Mr. Oltman. I'm sorry, Mr. Oltman.

MR. OLTMAN: That's quite

Zyprexa Product Team Off-site
July 25, 2001

Lilly

Answers That Matter.

Zyprexa MDL Plaintiffs' Exhibit No.08584

Zyprexa MDL 1596 Confidential-Subject to Protective Order
ZY20154679
Page 1

Objectives

Morning

Review Brand Architecture

Develop vision, value drivers, CSFs for Product Team

Begin identifying the culture required to achieve our vision

Discuss next steps

Afternoon

"Challenge Team" review with Working Team

Kick-off Next Steps

Agenda

8-8:30	Opening, Review of Brand Architecture and Implications
9-11	Vision, Value Drivers and CSFs
11:00-11:30	Culture Discussion (from-to)
11:30-12	Next Steps
12-1	Lunch
1-3:30	Review with Working Team
3:30-5	Kick-off Next Steps

Zyprexa MDL Plaintiffs' Exhibit No.8584

Zyprexa MDL 1596: Confidential-Subject to Protective Orde
ZY2015487
Page 2

Exhibit F, Page 3 of 22
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

The Chance to Make History

Olanzapine: the **first** team to dramatically speed time to registration ... making history and setting the new Lilly ***registration standard***

Zyprexa: the **first** team to achieve excellence in global product uptake ... making history and setting the new pharma industry ***launch standard***

Zyprexa: the **first** team with the **opportunity** to set the all industry ***commercialization standard*** for the most successful pharma brand in history

Zyprexa MDL Plaintiffs' Exhibit No.08584

Zyprexa MDL 1596: Confidential-Subject to Protective Orde
ZY2015487
Part 4

Straight Talk - What's at Stake

The company is betting the farm on Zyprexa ... the ability of Eli Lilly to remain independent and emerge as the fastest growing pharma company of the decade depends solely on our ability to achieve *world class commercialization of Zyprexa*

If we succeed, Zyprexa will be the most successful pharmaceutical product ever ... we will have made history

Zyprexa MDL Plaintiffs' Exhibit No.08554

Zyprexa MDL 1596; Confidential-Subject to Protective Order
ZY20154877;
Page 5

Exhibit F, Page 5 of 22
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

8584-001 / 5

005953

8584-005

Leadership Wish List

Vision and/or "burning platform" for team change .... In order to engage team members in the need for continued improvement

Clarity of what we mean by "world class commercialization" and what this will take

World-class integration of medical/marketing in strategy and operation

Integrated strategy-driven team decisions for aligned impact

Zyprexa MDL Plaintiffs' Exhibit No.08584

Zyprexa MDL 1596; Confidential-Subject to Protective Ord
ZY20154871
Page 1

Optimizing Our Work

What is change in the product team work?

- Zyprexa launch focus ⟶ Brand focus
- are there gaps?
- how well do work priorities match strategy?

Is there non-focus work?

Are we clear on roles?

- product team v Brand teams in 'top 10'
- product team v non-top 10 countries

How well do we do the work? (GMAP, other)

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ZY20154877
Page 7

Exhibit F, Page 7 of 22
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

8584-001 / 7

005955

8584-007

Implications of Brand Architecture

What has changed?

What has stayed the same?

What are some early thoughts on what this mean's for the work that we do today?

Visioning (the whats)

Defining success...

Who are our customers?

What would success look like to our external customers?

What would success look like to our internal partners?

How would our competition describe us?

How would we be distinguished from our competitors in the eyes of our customers?

What would our competitive advantage be? How would we build and sustain it?

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Zyprexa MDL 1596 Confidential-Subject to Protective Ord
ZY2015487
Page

Value Drivers and CSFs (the hows)

Value Drivers

What are the top key levers which will enable *us* to achieve this vision?

Critical Success Factors

What must we achieve with each of these levers in order to achieve this vision

Describing Our Culture..current and future

illustrative

FROM	TO
Beauracratic and slow	To flexible and fast
Consensus-driven	Single point of accountability

Zyprexa MDL Plaintiffs' Exhibit No.05984

Zyprexa MDL 1598: Confidential-Subject to Protective Ord
ZY20154877
Page 11

Exhibit F, Page 11 of 22
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

Components of Culture include..

Leadership and management behaviors

"Unwritten" rules

Established processes

Reward and recognition processes

Communication processes, frequency, style, etc.

Other???

Zyprexa MDL Plaintiffs' Exhibit No.08584

Zyprexa MDL 1596; Confidential-Subject to Protective Ord
ZY2015487;
Page 12

Next Steps

Agree on objectives for this afternoon's "challenge team" review

Discuss overall next steps

- Objectives
- Scope
- Timing
- Roles and responsibilities

Agenda

1-2:30	Review of Vision, Value Drivers and CSFs
2:30-3	Discuss/finalize next steps

Zyprexa MDL Plaintiffs' Exhibit No.08584

Zyprexa MDL 1596: Confidential-Subject to Protective Orde
ZY20154878
Page 1

Back-up Slides

Value Driver Team Formation

What

Who

When

Design Team

Decision Makers

Team Sponsor: Alan Breier

Team Leaders: Vin Rampey, Denice Torres

Medical: Mauricio Tohen

Project Mgr and Communications: Jennifer Beaulieu

Medical: Patrizia Cavazzoni, John Krueger

GMAP incorporation: Bill Hess

Marketing: John Bamforth, Tim Parshall

Scientific Communications: Jeff Ramsey

Marketing: Tim Parshall

Market Research: Ralph Robinson

Support

Process Owner: Karl Lyon

Process Consultant/US Integration: Mel Halkyard

Observers:

GMAP: Gayle Crick

GMSO: Chad McBride

Zyprexa MDL Plaintiffs' Exhibit No.04564

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ZY20154871
Page 1

Process Overview…its all about building capabilities…

Brand Architecture delivered positioning

↓

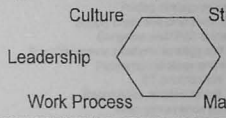
Create vision, value drivers and objectives for the product team to realize this new positioning

↓

Identify capabilities required to reach this vision

↓

Design organization required to build these capabilities



Zyprexa MDL Plaintiffs' Exhibit No.08584

Zyprexa MDL 1596; Confidential-Subject to Protective Orde
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Page 16

Expected Deliverables to include...

Identification of short and long-term priorities
Key Value Drivers
Required meeting structure
Communication processes with affiliates and within PT
PR process
Thought Leader Development Process
Best Practice ID and sharing
Issues Management Process
Review and tracking of key metrics
Marketing Planning Process
Competitive Info Collection, Analysis and Dissemination
Clearly defined roles and responsibilities
Process for budgeting and buy-up submissions
Coordination with the US
Team Building
New Marketing orientation
CT strategy, integration and management
Regulatory and label reviews
Product formulation and innovation processes
Process for reviewing promotional items
Pricing strategy process
Supply chain and production management
Congress and GMC management
Scientific communications strategy and management process
Publication strategy and execution
CT prioritization
Registration process for top 10 affiliates
Team governance structure

[redacted]

Team Charter

Draft to be determined by working team

POD Timeline and Milestones...

Phase I: Brand Architecture		**Completed**
Phase II: Celebration/Kick off of POD		**July 24**
Working Team Kick-off Meeting	**4 hours**	**July 25**
Develop Charter and Operating Principles		
Review Vision, objectives/Value Drivers		
Phase III: Working Team Meeting	**2 days**	**August 16, 17 (tbd)**
Identify/classify/assess capabilities required to achieve position		
Validation of vision/value drivers/strategies/capabilities		**August 17-September 17**
GMAP findings	**1 day**	**August 24**
Phase IV: Working Team Meeting	**2 days**	**September 16, 17**
Review/finalize capabilities Prioritize capability gaps Develop organizational design criteria Determine organizational structure option and micro design elements Develop Change Agenda		
IMPLEMENTATION		**October 1**

Zyprexa MDL Plaintiffs' Exhibit No.35524

Zyprexa MDL 1598; Confidential-Subject to Protective Orde
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Page 21

Our Operating Principles

What are our boundaries?

How will we make decisions?

How will we operate when team members are absent?

How/when will we seek approval?

How do we want to communicate with the stakeholders?

Zyprexa MDL Plaintiffs' Exhibit No.08584

Zyprexa MDL 1596: Confidential-Subject to Protective Orde
ZY2015497B
Page 22

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-520/S-012

Eli Lilly & Company
Attention: Robin Pitts Wojcieszek, R.Ph.
Associate Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Wojcieszek:

Please refer to your supplemental new drug application dated September 28, 2006, received September 29, 2006 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbyax (olanzapine/fluoxetine) 3 mg/25 mg, 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50 mg (mg equivalent olanzapine/mg equivalent fluoxetine) capsules.

We acknowledge receipt of your amendments dated November 8, 28, 2006, December 11, 14, 2006, and February 5, 20, 2007.

This supplemental new drug application provides for the use of Symbyax (olanzapine/fluoxetine) capsules for Treatment Resistant Depression (TRD).

We completed our review of this application, and it is approvable. Before the application may be approved, however, you must address the following issues:

Updated Information on Risks of Weight Gain, Hyperglycemia, and Hyperlipidemia

A primary concern with this application and the primary basis for our not taking a final action is our view that we lack important safety information needed to adequately update the labeling with all relevant risk information. In particular, we are concerned that the labeling is deficient with regard to information about weight gain, hyperglycemia, and hyperlipidemia that is associated with olanzapine use, whether taken alone or in combination with fluoxetine. You must fully address these concerns before we will be able to take a final action on this application.

Defining what your response will need to be to fully address these concerns will likely involve an interactive process with us over a period of several weeks, because we, first of all, need to fully understand the universe of relevant olanzapine and olanzapine/fluoxetine combination (OFC) studies and their characteristics. Once we better understand this set of studies and what data pertinent to our concerns were collected, we will be in a better position to provide detailed advice on what studies to pool, what data to provide, and what additional analyses to conduct. In characterizing these trials, it will be important to provide details on what data were collected (e.g., plasma glucose, HbA1c, total cholesterol, HDL, LDL, triglyceride, and urine glucose), under what conditions (e.g., fasting vs non-

EXHIBIT 6 8-1-08 Morgan

MAR 28 2007
G. Brophy

Zyprexa Plaintiff's Exhibit 10094
10094-001 / 1
005971
10094-001

fasting), the demographic characteristics of the subjects (e.g., pediatric vs adult), and at what intervals. Once we have this information, we will work with you to define what studies to pool, and what data to provide to us and in what format.

Regarding data displays, an overall strategy will be to subgroup patients on the basis of their status at baseline so that clinicians can better understand the risks associated with treatment of patients falling into different risk categories. For example, we note that your proposed Symbyax label includes information only on proportions of patients who are relatively normal at baseline with regard to random blood glucose (< 140 mg/dL), i.e., 2.9% of such patients receiving OFC had on-treatment levels ≥ 200 mg/dL compared to 0.3% of placebo-treated patients. However, we note that 46% of patients who were borderline to high at baseline (140 to 200) had such on-treatment levels compared to only 5% of placebo-treated patients. This latter finding was based on a small number of patients in the OFC program, and for this reason, we would like to see such data for the entire olanzapine program. In addition, we were troubled that this important finding was not included in your proposed label. We will want you to provide similar information based on subgroupings of patients on the basis of weight and BMI (for weight change), and lipid findings for the lipid data. We will want you to provide data both on proportions of patients meeting certain on-treatment criteria and also for mean change from baseline.

If you feel you have already aggregated and submitted data to address these concerns, then we ask that you direct us to precisely which submissions these are. If, on the other hand, you have aggregated the appropriate data for your own internal purposes but not submitted them, we ask you to submit them. Your recent February 20, 2007 response to our January 12, 2007 letter regarding the New York Times story has not been particularly helpful in addressing these concerns.

Our overall goal is to improve labeling with regard to these findings so that clinicians will be better informed on what the risks are for their patients. They cannot make reasonable treatment decisions until they have such information. We do not feel that current labeling for either Symbyax or Zyprexa, provides sufficient information on these risks, and we fully intend to insure that these labels are enhanced with the best available information to characterize these risks.

Post Marketing Commitments

Long-Term Efficacy Studies

Since TRD is a chronic illness, you are required to assess the longer-term effectiveness and safety of Symbyax in TRD. Accordingly, we ask for your commitment to submit, as a Postmarketing commitment, the results of this study to evaluate Symbyax's ability to reduce the risk of relapse in acutely remitted patients with TRD. We ask that you commit to submitting these results no later than 3 years after the date of approval of this supplemental application.

Labeling

Please submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling text for the package insert.

In addition, all previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

MAR 2 8 2007

G. Brophy

NDA 21-520/S-012
Page 3

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Foreign Regulatory Update/Labeling

We require a review of the status of all Symbyax actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If Symbyax has been approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for Symbyax along with English translations when needed.

Request for Safety Update and World Literature Update

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Prior to an approval action, we require an updated report on the world's archival literature pertaining to the safety of Symbyax. Please provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. This report should include only literature not covered in your previous submissions. We will need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Symbyax. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of

MAR 2 6 2007
G. Brophy

articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Promotional Materials

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Psychiatry Products to discuss what further steps need to be taken before the application may be approved.

If you have any questions, call LCDR Ranmeet Grewal, Pharm.D., Regulatory Project Manager, at (301) 796-1080.

Sincerely,

(See appended electronic signature page)

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

MAR 2 6 2007
G. Brophy

1

This version of labeling is based up on the version submitted with the application. We have used track changes to indicate our additions and deletions. We have added bracketed comments to explain our actions where needed.]

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Symbyax safely and effectively. See full prescribing information for Symbyax.

SYMBYAX® (olanzapine and fluoxetine HCl capsules) for oral administration
Initial U.S. Approval: 2003

WARNING

See full prescribing information for complete boxed warning.

SUICIDALITY IN CHILDREN AND ADOLESCENTS:

- Increased risk of suicidal thinking and behavior in children and adolescents taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Not approved for use in children and adolescents.

INCREASED MORTALITY IN ELDERLY PATIENTS:

- Increased mortality in elderly patients with dementia-related psychosis compared to placebo. Not approved for the treatment of patients with dementia-related psychosis.

~~SUICIDALITY IN CHILDREN AND ADOLESCENTS~~

~~Increased risk of suicidal thinking and behavior in children and adolescents taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Not approved for use in children and adolescents.~~

RECENT MAJOR CHANGES

~~Warnings and Precautions, Mortality in patients with dementia-related psychosis (5.1)~~	~~10/2005~~
Contraindications, Fluoxetine (4)	3/2006
Warnings and Precautions, Hepatobiliary events (5.14)	4/2006
Warnings and Precautions, Serotonin Syndrome (5.8)	8/2006
~~Warnings and Precautions, Weight Gain~~	
Warnings and Precautions, Risk of Glucose Dysregulation	
Warnings and Precautions, Hypercholesterolemia	

INDICATIONS AND USAGE

SYMBYAX combines olanzapine, a psychotropic agent belonging to the thienobenzodiazepine class, and fluoxetine, a selective serotonin reuptake inhibitor, indicated for treatment of:

- Depressive episodes associated with bipolar disorder (1.1)
- Treatment Resistant Depression (major depressive disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode) (1.2)

DOSAGE AND ADMINISTRATION

- Once daily in the evening, generally beginning with 6 mg/25 mg (2)
- Exercise dose cautiously in patients predisposed to hypotensive reactions, hepatic impairment, or with potential for slower metabolism (2.3)
- Dosage increase gradually (2.4)
- The safety of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical trials.

DOSAGE FORMS AND STRENGTHS

- Capsules: 3 mg/25 mg, 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50 mg (mg equivalent olanzapine/mg equivalent fluoxetine) (3)

CONTRAINDICATIONS

- Do not use with an MAOI or within 14 days of discontinuing an MAOI. At least 5 weeks should be allowed after stopping SYMBYAX before starting treatment with an MAOI (4, 7.13)
- Do not use with Pimozide (4, 7.15)
- Do not use with Thioridazine. Do not use Thioridazine within 5 weeks of discontinuing SYMBYAX (4, 7.15)

WARNINGS AND PRECAUTIONS

- Patients should be monitored for clinical worsening and suicidal thinking and behavior (5.2)
- Cerebrovascular adverse events, including fatalities were reported more commonly with olanzapine than placebo in trials of elderly patients with dementia-related psychosis (5.3)
- Neuroleptic Malignant Syndrome has been reported with atypical antipsychotics (5.4)

[See Appropriate Letter for information requested for hyperthermia section.]

- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics, including olanzapine alone as well as olanzapine taken concomitantly with fluoxetine. Diabetic patients should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Monitor all patients for symptoms of hyperglycemia. (5.5)
- Hypercholesterolemia, Hypertriglyceridemia, and Dyslipidemia, see Appropriate Letter.]
- Clinically significant weight gain may occur.
- Serotonin Syndrome may occur with SYMBYAX (5.8)
- Discontinue upon appearance of rash or allergic phenomena (5.7)
- Screen for bipolar disorder and monitor for manic/hypomanic (5.8)
- Tardive Dyskinesia may develop acutely or chronically (5.9)
- Orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some patients, syncope may occur, especially during initial dose titration. Use caution in patients with cardiovascular disease, cerebrovascular disease, and those conditions that could affect hemodynamic response (5.10)
- Use caution only in patients at risk for aspiration pneumonia due to esophageal dysmotility (5.11)
- Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold (5.12)
- Dissolution may be slower in patients with severe cirrhosis (5.13)
- Asymptomatic elevations of hepatic transaminases and alkaline phosphatase have been observed with olanzapine. Periodic assessment recommended in patients with hepatic disease (5.14)
- May increase the risk of bleeding. Use with NSAIDs or drugs that affect coagulation may potentiate the risk of gastrointestinal or other bleeding (5.15)
- Hyponatremia (some cases with serum sodium lower than 110 mmol/L) possibly associated with the syndrome of inappropriate antidiuretic hormone (SIADH) have been reported with fluoxetine (5.16)
- May impair judgment, thinking, and motor skills (5.17)
- May disrupt temperature regulation (5.18)
- Due to anticholinergic activity, use with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus or related conditions (5.19)
- Use a lower dose in patients with cirrhosis (5.19)
- May elevate prolactin levels (5.20)
- Use caution when prescribing with other products containing olanzapine, another fluoxetine or active ingredients (i.e., Zyprexa, Prozac, Sarafem) (5.21)
- Fluoxetine has a long elimination half-life (5.22)
- Monitor when discontinuing treatment since discontinuation symptoms may occur (5.23)

ADVERSE REACTIONS

Most common adverse events (25% and at least twice that for placebo) are dizziness or somnolence, dry mouth, fatigue, hypersomnia, increased appetite, peripheral edema, sedation, somnolence, tremor, vision blurred, and weight increased (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lilly at 1-800-545-5979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Antihypertensives – enhanced antihypertensive effect (7.1)
- Anti-Parkinsonian – may antagonize levodopa/dopamine agonists (7.2)

MAR 2 6 2007

G. Brophy

- Benzodiazepines – may potentiate orthostatic hypotension and sedation (7.3)
- Carbamazepine – potential for elevated carbamazepine levels (7.5)
- Clozapine – may elevate Clozapine levels (7.6).
- CNS Acting Drugs – caution should be used when taken in combination with other centrally acting drugs and alcohol (7.7)
- Ethanol – may potentiate sedation and orthostatic hypotension (7.9)
- Fluvoxamine – may double olanzapine levels (7.10)
- Haloperidol – elevated haloperidol levels have been observed (7.11)
- Lithium – monitor lithium levels (7.12)
- Phenytoin – potential for elevated phenytoin levels (7.14)
- Serotonergic drugs – potential for Serotonin Syndrome (5.6, 7.16, 7.20)
- Tricyclic antidepressants (TCAs) – monitor TCA levels (7.19)
- Warfarin – increase monitoring with SYMBYAX dose changes (7.22)
- Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.) may potentiate the risk of bleeding (7.24)
- Fluoxetine is an inhibitor of CYP450 2D6 enzyme pathway (7.25)
- Drugs tightly bound to plasma proteins, may cause shift in plasma concentrations (7.29)

USE IN SPECIFIC POPULATIONS

- Pregnancy: SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1)
- Nursing mothers: breast feeding is not recommended (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [3/2006] (BVL561JAM7)

MAR 2 8 2007
G. Brophy

FULL PRESCRIBING INFORMATION: CONTENTS*

[Section references in brackets may be rendered in robot chevrons, both here and in the body of the document.]

WARNING — INCREASED MORTALITY IN ELDERLY PATIENTS and SUICIDALITY IN CHILDREN and ADOLESCENTS
1 INDICATIONS AND USAGE
1.1 Bipolar Depression
1.2 Treatment Resistant Depression
2 DOSAGE AND ADMINISTRATION
2.1 Bipolar Depression
2.2 Treatment Resistant Depression
2.3 Special Populations
2.4 Discontinuation of Treatment with SYMBYAX
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
5.2 Clinical Worsening and Suicide Risk
5.3 Cerebrovascular Adverse Events (CVAE), including Stroke, in Elderly Patients with Dementia-Related Psychosis
5.4 Neuroleptic Malignant Syndrome (NMS)
5.5 Hyperglycemia and Diabetes Mellitus
Hyperlipidemia
Weight Gain
5.6 Serotonin Syndrome
5.7 Allergic Events and Rash
5.8 Screening Patients for Bipolar Disorder and Monitor for Mania/Hypomania
5.9 Tardive Dyskinesia
5.10 Orthostatic Hypotension
5.11 Dysphagia
5.12 Seizures
5.13 Weight Gain
5.14 Drug/Ethanol Interactions
5.15 Abnormal Bleeding
5.16 Hyponatremia
5.17 Cognitive and Motor Impairment
5.18 Body Temperature Regulation
5.19 Use in Patients with Concomitant Illness
5.20 Hyperprolactinemia
5.21 Contraindicated Use of Olanzapine and Fluoxetine Products
5.22 Long Half-Life of Fluoxetine
5.23 Discontinuation of Treatment with SYMBYAX
5.24 Laboratory Tests
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
7.1 Antihypertensive agents
7.2 Anti-Parkinsonism
7.3 Benzodiazepines
7.4 Biperiden
7.5 Carbamazepine
7.6 Cimetidine
7.7 CNS Acting Drugs
7.8 Electroconvulsive therapy (ECT)
7.9 Ethanol
7.10 Fluvoxamine
7.11 Haloperidol
7.12 Lithium
7.13 Monoamine oxidase inhibitors
7.14 Phenytoin
7.15 Pimozide
7.16 Serotonergic drugs
7.17 Theophylline
7.18 Thioridazine
7.19 Tricyclic antidepressants (TCAs)
7.20 Tryptophan
7.21 Tryptophan
7.22 Valproate
7.23 Warfarin
7.24 Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.)
7.25 Drugs metabolized by CYP2D6
7.26 Drugs metabolized by CYP3A
7.27 Effect of olanzapine on drugs metabolized by other CYP enzymes
7.28 The effect of other drugs on olanzapine
7.29 Drugs highly bound to plasma protein
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.3 Dependence
10 OVERDOSAGE
10.1 Management of Overdose
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Special Populations
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Bipolar Depression
14.2 Treatment Resistant Depression
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Information for Patients
17.2 Clinical Worsening and Suicide Risk
17.3 Serotonin Syndrome
17.4 FDA-approved Medication Guide

*Sections or subsections omitted from the full prescribing information are not listed.

MAR 9 [illegible]7
G. Brophy

4
FULL PRESCRIBING INFORMATION

WARNING

Suicidality in Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SYMBYAX or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SYMBYAX is not approved for use in pediatric patients. *[See Warnings and Precautions (5.2) and Use in Specific Populations (8.4)].*

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials. *[See Warnings and Precautions (5.2)].*

Increased Mortality in Elderly Patients — Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infections (e.g., pneumonia) in nature. SYMBYAX (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)].*

~~Suicidality in Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SYMBYAX or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SYMBYAX is not approved for use in pediatric patients. *[See Warnings and Precautions (5.2) and Use in Specific Populations (8.4)].*~~

~~Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials. *[See Warnings and Precautions (5.2)].*~~

1 INDICATIONS AND USAGE

1.1 Bipolar Depression

SYMBYAX is indicated for the treatment of depressive episodes associated with bipolar disorder.

Unlike with unipolar depression, there are no established guidelines for the length of time patients with bipolar disorder experiencing a major depressive episode should be treated with agents containing antidepressant drugs.

The effectiveness of SYMBYAX for maintaining antidepressant response in this patient population beyond 8 weeks has not been established in controlled clinical studies. Physicians who elect to use SYMBYAX for extended periods should periodically reevaluate the benefits and long-term risks of the drug for the individual patient.

1.2 Treatment Resistant Depression

SYMBYAX is indicated for treatment resistant depression (major depressive disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode) *[see Clinical Studies (14.2)]*.

The effectiveness of SYMBYAX for maintaining antidepressant response in this patient population beyond 8 weeks has not been established in controlled clinical studies. Physicians who elect to use SYMBYAX for extended periods should periodically reevaluate the benefits and long-term risks of the drug for the individual patient.

MAR 2 8 2007

G. Brophy

5

2 DOSAGE AND ADMINISTRATION

2.1 Bipolar Depression

SYMBYAX should be administered once daily in the evening, generally beginning with the 6-mg/25-mg capsule. While food has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of SYMBYAX has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with SYMBYAX in a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg *[see Clinical Studies (14)]*.

The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies.

2.2 Treatment Resistant Depression

SYMBYAX should be administered once daily in the evening, generally beginning with the 6-mg/25-mg capsule. While food has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of SYMBYAX has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with SYMBYAX in a dose range of olanzapine 6 to 18 mg and fluoxetine 25 to 50 mg *[see Clinical Studies (14)]*. The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies.

2.3 Special Populations

The starting dose of SYMBYAX 3 mg/25 - 6 mg/25 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of SYMBYAX (female gender, geriatric age, nonsmoking status) or those patients who may be pharmacodynamically sensitive to olanzapine. When indicated, dose escalation should be performed with caution in these patients. SYMBYAX has not been systematically studied in patients over 65 years of age or in patients <18 years of age *[see Warnings and Precautions (5.19), Use in Specific Populations (8.4 and 8.5), and Clinical Pharmacology (12.3)]*.

2.4 Discontinuation of Treatment with SYMBYAX

Symptoms associated with discontinuation of fluoxetine, a component of SYMBYAX, and other SSRIs and SNRIs, have been reported *[see Warnings and Precautions (5.23)]*.

3 DOSAGE FORM AND STRENGTHS

Capsules (mg equivalent olanzapine/mg equivalent fluoxetine):

- 3 mg/25 mg
- 6 mg/25 mg
- 6 mg/50 mg
- 12 mg/25 mg
- 12 mg/50 mg

4 CONTRAINDICATIONS

The use of SYMBYAX is contraindicated with the following:

- Monoamine Oxidase Inhibitors (MAOI) — *[see Drug Interactions (7.13)]*
- Pimozide — *[see Drug Interactions (7.15)]*
- Thioridazine — *[see Drug Interactions (7.18)]*

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SYMBYAX is not approved for the treatment of patients with dementia-related psychosis *[see Box Warning]*.

In olanzapine placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

5.2 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that

MAR 2 8 2007

G. Brophy

6

antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients.

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in any of these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms *[see Warnings and Precautions (5.23) and Dosage and Administration (2.4)*, for a description of the risks of discontinuation of SYMBYAX].

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for SYMBYAX should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

It should be noted that SYMBYAX is not approved for use in treating any indications in the pediatric population.

5.3 **Cerebrovascular Adverse Events (CVAE), including Stroke, in Elderly Patients with Dementia-Related Psychosis**

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine and SYMBYAX are not approved for the treatment of patients with dementia-related psychosis.

5.4 **Neuroleptic Malignant Syndrome (NMS)**

A potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or

MAR 2 9 2007

G. Brophy

7

inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If after recovering from NMS, a patient requires treatment with an antipsychotic, the patient should be carefully monitored, since recurrences of NMS have been reported.

[As noted above, we have requested additional information on treating patients with hyperglycemia in the Approvable Letter. Section 5.5 will be modified when we have reviewed the requested information. We have also grouped hyperglycemia, hypertriglyceridemia, and weight gain together (see Full Prescribing Contents section and order the appropriate sections below to correspond to these changes.)]

5.5 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

5.6 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome may occur with SYMBYAX, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of SYMBYAX with MAOIs intended to treat depression is contraindicated *[see Contraindications (4) and Drug Interactions (7.13)]*.

If concomitant treatment of SYMBYAX with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions (7.15)]*.

The concomitant use of SYMBYAX with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions (7.20)]*.

5.7 Allergic Events and Rash

In SYMBYAX premarketing controlled clinical studies, the overall incidence of rash or allergic events in SYMBYAX-treated patients [4.6% (26/571)] was similar to that of placebo [5.2% (25/477)]. The majority of the cases of rash and/or urticaria were mild; however, three patients discontinued (one due to rash, which was moderate in severity and two due to allergic events, one of which included face edema).

In fluoxetine US clinical studies, 7% of 10,782 fluoxetine-treated patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical studies, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

MAR 2 8 2007

G. Brophy

8

In fluoxetine premarketing clinical studies, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of fluoxetine, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possible allergic phenomena for which an alternative etiology cannot be identified, SYMBYAX should be discontinued.

5.8 Screening Patients for Bipolar Disorder and Monitor for Mania/Hypomania

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described for clinical worsening and suicide risk represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SYMBYAX is approved for use in treating bipolar depression.

In the two controlled bipolar depression studies there was no statistically significant difference in the incidence of manic events (manic reaction or manic depressive reaction) between SYMBYAX- and placebo-treated patients. In one of the studies, the incidence of manic events was (7% [3/43]) in SYMBYAX-treated patients compared to (3% [5/184]) in placebo-treated patients. In the other study, the incidence of manic events was (2% [1/43]) in SYMBYAX-treated patients compared to (8% [13/193]) in placebo-treated patients. This limited controlled trial experience of SYMBYAX in the treatment of bipolar depression makes it difficult to interpret these findings until additional data is obtained. Because of this and the cyclical nature of bipolar disorder, patients should be monitored closely for the development of symptoms of mania/hypomania during treatment with SYMBYAX.

5.9 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

The incidence of dyskinetic movement in SYMBYAX-treated patients was infrequent. The mean score on the Abnormal Involuntary Movement Scale (AIMS) in the SYMBYAX-controlled database across clinical studies involving SYMBYAX-treated patients decreased from baseline. Nonetheless, SYMBYAX should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on SYMBYAX, drug discontinuation should be considered. However, some patients may require treatment with SYMBYAX despite the presence of the syndrome. The need for continued treatment should be reassessed periodically.

5.10 Orthostatic Hypotension

SYMBYAX may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some patients, syncope, especially during the initial dose-titration period.

In the SYMBYAX-controlled clinical trials across all indications, there were no significant differences between SYMBYAX-treated patients and olanzapine, fluoxetine or placebo-treated patients in exposure adjusted rates of orthostatic systolic blood pressure

MAR 2 8 2007

G. Brophy

decreases of at least 30 mm Hg. Orthostatic systolic blood pressure decreases of at least 30 mm Hg occurred in 4.0% (28/705), 2.3% (19/831), 4.5% (18/399), and 1.8% (8/442) of the SYMBYAX, olanzapine, fluoxetine, and placebo groups, respectively. In this group of studies, the incidence of syncope-related adverse events (i.e., syncope and/or loss of consciousness) in SYMBYAX-treated patients was 0.4% (3/771) compared to placebo 0.2% (1/477).

In a clinical pharmacology study of SYMBYAX, three healthy subjects were discontinued from the trial after experiencing severe, but self-limited, hypotension and bradycardia that occurred 2 to 9 hours following a single 12-mg/50-mg dose of SYMBYAX. Reactions consisting of this combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in at least three other healthy subjects treated with various formulations of olanzapine (one oral, two intramuscular). In controlled clinical studies, the incidence of patients with a ≥20 bpm decrease in orthostatic pulse concomitantly with a ≥20 mm Hg decrease in orthostatic systolic blood pressure was 0.3% (2/706) in the SYMBYAX group, 0.2% (1/445) in the placebo group, 0.7% (6/837) in the olanzapine group, and 0% (0/404) in the fluoxetine group.

SYMBYAX should be used with particular caution in patients with known cerebrovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

5.11 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.12 Seizures

Seizures occurred in 0.2% (4/2547) of SYMBYAX-treated patients during open-label clinical studies. No seizures occurred in the controlled SYMBYAX studies. Seizures have also been reported with both olanzapine and fluoxetine monotherapy. SYMBYAX should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of ≥65 years of age.

[As noted, we will want the Weight Section revised with new requested information and moved to be adjacent to the hyperglycemia and hyperlipidemia sections.]

5.13 Weight Gain

In clinical studies, the mean weight increase for SYMBYAX-treated patients after 8 weeks of treatment was statistically significantly greater than placebo-treated (4.3 kg vs +0.1 kg) and fluoxetine-treated (4.3 kg vs -0.2 kg) patients, but was not statistically significantly different from olanzapine-treated patients (4.3 kg vs 4.1 kg). Thirty-five percent of SYMBYAX-treated patients met criterion for having gained >7% of their baseline weight. This was statistically significantly greater than placebo-treated (3%) and fluoxetine-treated patients (3%) but was not statistically significantly different than olanzapine-treated patients (31%).

5.14 Transaminase Elevations

As with olanzapine, asymptomatic elevations of hepatic transaminases [ALT (SGPT), AST (SGOT), and GGT] and alkaline phosphatase have been observed with SYMBYAX. In the SYMBYAX-controlled database, ALT (SGPT) elevations (normal baseline and ≥3 times the upper limit of the normal range post-baseline) were observed in 3.4% (20/586) of patients exposed to SYMBYAX compared with none of the 342 placebo patients and 3.5% (23/665) of olanzapine-treated patients. The difference between SYMBYAX and placebo was statistically significant. Of the SYMBYAX patients who started normal at baseline and had increases in ALT ≥5 times the upper limit of normal range, none experienced jaundice and four had transient elevations >200 IU/L. ~~In the preexisting SYMBYAX controlled database, ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 6.3% (31/495) of patients exposed to SYMBYAX compared with 3.5% (8/384) of the placebo patients and 1.5% (25/560) of olanzapine-treated patients (see Adverse Reactions (6.1)).~~

In olanzapine placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared with 0% (0/115) of the placebo patients. None of these patients experienced jaundice. In 2 of these patients, liver enzymes decreased toward normal despite continued treatment, and in 2 others, enzymes decreased upon discontinuation of olanzapine. In the remaining 2 patients, 1, seropositive for hepatitis C, had persistent enzyme elevations for 4 months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger olanzapine premarketing database of about 2400 patients with baseline SGPT ≤90 IU/L, the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued. Among all 2500 patients in olanzapine clinical studies, approximately 1% (23/2500) discontinued treatment due to transaminase increases.

MAR 2 8 2007

G. Brophy

10

Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period.

Caution should be exercised in patients who signs and symptoms of hepatic impairment, in patients with predisposing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant hepatic disease *[see Warnings and Precautions (5.24)]*.

5.15 Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding *[see Drug Interactions (7.22, 7.24)]*. Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of SYMBYAX with NSAIDs, aspirin, or other drugs that affect coagulation.

5.16 Hyponatremia

Hyponatremia has been observed in SYMBYAX premarketing clinical studies. In controlled trials, no SYMBYAX-treated patients had a treatment-emergent serum sodium below 129 mmol/L; however, a lowering of serum sodium below the reference range occurred at an incidence of 1.6% (11/693) of SYMBYAX-treated patients compared with 0.3% (2/380) of placebo patients. This difference was not statistically significant. In open label studies, 0.0% (1/2376) of these SYMBYAX-treated patients had a treatment-emergent serum sodium below 129 mmol/L.

Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported with fluoxetine. The hyponatremia appeared to be reversible when fluoxetine was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In two 6-week controlled studies in patients ≥60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

5.17 Cognitive and Motor Impairment

Sedation-related adverse events were commonly reported with SYMBYAX treatment occurring at an incidence of 26.6% in SYMBYAX-treated patients compared with 10.9% in placebo-treated patients. Sedation-related adverse events (sedation, somnolence, hypersomnia, and lethargy) led to discontinuation in 2% (15/771) of patients in the controlled clinical studies. As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them adversely.

5.18 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic drugs. Appropriate care is advised when prescribing SYMBYAX for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

5.19 Use in Patients with Concomitant Illness

Clinical experience with SYMBYAX in patients with concomitant systemic illnesses is limited *[see Clinical Pharmacology (12.4)]*. The following precautions for the individual components may be applicable to SYMBYAX.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical studies, SYMBYAX was associated with constipation, dry mouth, and tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events were not often the basis for study discontinuations; SYMBYAX should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, a history of paralytic ileus, or related conditions.

In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse events were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse events was significantly greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

MAR 2 8 2007

G. Brophy

11

If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised *[see Box Warning and Warnings and Precautions (5.1)]*.

As with other CNS-active drugs, SYMBYAX should be used with caution in elderly patients with dementia. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised *[see Box Warning and Warnings and Precautions(5.1)]*.

SYMBYAX has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the premarket testing.

Caution is advised when using SYMBYAX in cardiac patients and in patients with diseases or conditions that could affect hemodynamic responses *[see Warnings and Precautions (5.10)]*.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower dose of the fluoxetine-component of SYMBYAX should be used in patients with cirrhosis. Caution is advised when using SYMBYAX in patients with diseases or conditions that could affect its metabolism *[see Clinical Pharmacology (12.4) and Dosage and Administration (2.3)]*.

Olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not routinely required *[see Clinical Pharmacology (12.4)]*.

5.20 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, SYMBYAX elevates prolactin levels, and a modest elevation persists during administration; however, possibly associated clinical manifestations (e.g., galactorrhea and breast enlargement) were infrequently observed.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds that increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. However, neither clinical studies nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

5.21 Concomitant Use of Olanzapine and Fluoxetine Products

SYMBYAX contains the same active ingredients that are in Zyprexa and Zyprexa Zydis (olanzapine) and in Prozac, Prozac Weekly, and Sarafem (fluoxetine HCl). Caution should be exercised when prescribing these medications concomitantly with SYMBYAX *[see Overdosage (10)]*.

5.22 Long Half-Life of Fluoxetine

Because of the long elimination half-lives of fluoxetine and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment *[see Clinical Pharmacology (12.3)]*.

5.23 Discontinuation of Treatment with SYMBYAX

During marketing of fluoxetine, a component of SYMBYAX, and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with fluoxetine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy, which may minimize the risk of discontinuation symptoms with this drug *[see Dosage and Administration (2.4)]*.

5.24 Laboratory Tests

Periodic assessment of transaminases is recommended in patients with significant hepatic disease *[see Warnings and Precautions, 5.14)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

MAR 2 8 2007

G. Brophy

12

The information below is derived from a clinical study database for SYMBYAX consisting of 2347 patients with treatment resistant depression, bipolar depression, major depressive disorder with psychosis, or sexual dysfunction with approximately 1085 patient-years of exposure. The conditions and duration of treatment with SYMBYAX varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or long-term exposure.

Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories.

In the tables and tabulations that follow, MedDRA or COSTART Dictionary terminology has been used to classify reported adverse events. The data in the tables represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is possible that events reported during therapy were not necessarily related to drug exposure.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing clinician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Incidence in Controlled Clinical Studies

The following findings are based on the short-term, controlled studies including bipolar depression and treatment resistant depression.

Adverse events associated with discontinuation of treatment — Overall, 11.3% of the 771 patients in the SYMBYAX group discontinued due to adverse events compared with 4.4% of the 477 patients for placebo. Adverse events leading to discontinuation associated with the use of SYMBYAX (incidence of at least 1% for SYMBYAX and greater than that for placebo) using MedDRA Dictionary coding were weight increased (2%) and sedation (1%) versus placebo patients which had 0% incidence of weight increased and sedation.

Commonly observed adverse events in controlled clinical studies — The most commonly observed adverse events associated with the use of SYMBYAX (incidence ≥5% and at least twice that for placebo in the SYMBYAX-controlled database) using MedDRA Dictionary coding were: disturbance in attention, dry mouth, fatigue, hypersomnia, increased appetite, peripheral edema, sedation, somnolence, tremor, vision blurred and weight increased. Adverse events reported in clinical trials of olanzapine/fluoxetine in combination are generally consistent with treatment-emergent adverse events during olanzapine or fluoxetine monotherapy.

Adverse events occurring at an incidence of 2% or more in short-term controlled clinical studies — Table 1 enumerates the treatment-emergent adverse events associated with the use of SYMBYAX (incidence of at least 2% for SYMBYAX and twice or more than for placebo). The SYMBYAX-controlled column includes patients with various diagnoses while the placebo column includes only patients with bipolar depression and major depression with psychotic features.

Table 1: Treatment-Emergent Adverse Events: Incidence in Controlled Clinical Studies

System Organ Class	Adverse Event	Percentage of Patients Reporting Event	
		SYMBYAX-Controlled (N=771)	Placebo (N=477)
Eye disorders	Vision blurred	5	2
Gastrointestinal disorders	Dry mouth	15	6
	Flatulence	3	1
	Abdominal distention	2	0
General disorders and administration site conditions	Fatigue	12	2
	Edema peripheral	9	0
	Edema	3	0
	Asthenia	3	1
	Pain	2	1

MAR 2 6 2007

G. Brophy

13

	Pyrexia	2	1
Infections and infestations	Sinusitis	2	1
Investigations	Weight increased	25	3
Metabolism and nutrition disorders	Increased appetite	20	4
Musculoskeletal and connective tissue disorders	Arthralgia	4	1
	Pain in extremity	3	1
	Musculoskeletal stiffness	2	1
Nervous system disorders	Somnolence	14	6
	Tremor	9	3
	Sedation	8	4
	Hypersomnia	5	1
	Disturbance in attention	5	1
	Lethargy	3	1
Psychiatric disorders	Restlessness	4	1
	Thinking abnormal	2	1
	Nervousness	2	1
Reproductive system and breast disorders	Erectile dysfunction	2	1

Additional Findings Observed in Clinical Studies

Effect on cardiac repolarization — The mean increase in QT, interval for SYMBYAX-treated patients (4.4 msec) in clinical studies was significantly greater than that for placebo-treated (-0.8 msec), olanzapine-treated (-0.3 msec) patients, and fluoxetine-treated (1.7 msec) patients. There were no significant differences between patients treated with SYMBYAX, placebo, olanzapine, or fluoxetine in the incidence of QT, outliers (>500 msec).

[As discussed above, we intend to move and group together data relevant to treatment-emergent hyperglycemia, hyperlipidemia, and weight gain to Warnings/Precautions. In addition, the information in these sections will need to be revised to include new information based on requested new data searches and analyses.]

Laboratory changes — In SYMBYAX clinical studies, (including treatment resistant depression, bipolar depression, major depressive disorder with psychosis, or sexual dysfunction) SYMBYAX was associated with statistically significantly greater frequencies for the following treatment-emergent findings in laboratory analytes (normal at baseline to abnormal at any time during the trial) compared to placebo: elevated random blood glucose levels of ≥200 mg/dL in patients with levels of <140 mg/dL at baseline (2.9% vs. 0.3%); elevated random cholesterol ≥240 mg/dL in patients with levels of <200 mg/dL at baseline (9.7% vs. 1.9%); elevated prolactin (27.6% vs. 4.8%); elevated urea nitrogen (2.8% vs. 0.8%); elevated uric acid (2.9% vs. 0.5%); low albumin (2.7% vs. 0.3%); low bicarbonate (14.1% vs. 8.8%); low hemoglobin (2.6% vs. 0%); low inorganic phosphorus (1.9% vs. 0.3%); low lymphocytes (1.9% vs. 0%); and low total bilirubin (13.3% vs. 3.9%).

In olanzapine clinical studies among olanzapine-treated patients with random triglyceride levels of <150 mg/dL at baseline (N=659), 0.5% of patients experienced triglyceride levels of ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=1185) had a mean increase of 20 mg/dL in triglycerides from a mean baseline value of 175 mg/dL.

Sexual dysfunction — In the pool of controlled SYMBYAX studies in patients with bipolar depression, there were higher rates of the treatment-emergent adverse events decreased libido, anorgasmia, impotence and abnormal ejaculation in the SYMBYAX group than in the placebo group. One case of decreased libido led to discontinuation in the SYMBYAX group. In the controlled studies that contained a fluoxetine arm, the rates of decreased libido and abnormal ejaculation in the SYMBYAX group were less than the rates in the fluoxetine group. None of the differences were statistically significant.

Sexual dysfunction, including priapism, has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Vital signs — Tachycardia, bradycardia, and orthostatic hypotension have occurred in SYMBYAX-treated patients *[see Warnings and Precautions (5.10)]*. The mean standing pulse rate of SYMBYAX-treated patients was reduced by 0.7 beats/min.

MAR 26 2007

G. Brophy

14

Other Events Observed in Clinical Studies

Following is a list of treatment-emergent adverse events reported by patients treated with SYMBYAX in clinical trials. This listing is not intended to include events (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo.

Events are classified by body system using the following definitions: frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; and rare events are those occurring in fewer than 1/1000 patients.

[Provide your justification for modifying the listings of events below from currently approved labeling.]

Body as a Whole — *Frequent:* chills, neck rigidity, photosensitivity reaction.

Cardiovascular System — *Frequent:* vasodilation; *Infrequent:* QT-interval prolonged.

Digestive System — *Frequent:* diarrhea; *Infrequent:* gastritis, gastroenteritis, nausea and vomiting, peptic ulcer; *Rare:* gastrointestinal hemorrhage, intestinal obstruction, liver fatty deposit, pancreatitis.

Hemic and Lymphatic System — *Frequent:* ecchymosis; *Infrequent:* anemia; *Rare:* leukopenia, purpura.

Metabolic and Nutritional — *Frequent:* generalized edema, weight loss; *Infrequent:* glycosuria, obesity; *Rare:* bilirubinemia, creatinine increased, gout.

Musculoskeletal System — *Rare:* osteoporosis.

Nervous System — *Frequent:* amnesia; *Infrequent:* ataxia, buccoglossal syndrome, cogwheel rigidity, dysarthria, emotional lability, euphoria, extrapyramidal syndrome, hypokinesia, movement disorder, myoclonus; *Rare:* dystonia, hyperkinesia, libido increased, withdrawal syndrome.

Respiratory System — *Infrequent:* epistaxis, yawn; *Rare:* laryngismus.

Skin and Appendages — *Infrequent:* alopecia, dry skin, pruritis; *Rare:* exfoliative dermatitis.

Special Senses — *Frequent:* taste perversion; *Infrequent:* abnormality of accommodation, dry eyes.

Urogenital System — *Frequent:* breast pain, menorrhagia[1], urinary frequency, urinary incontinence; *Infrequent:* amenorrhea[1], female lactation[1], hypomenorrhea[1], metrorrhagia[1], urinary retention, urinary urgency, urination impaired; *Rare:* breast engorgement[1].

[1] Adjusted for gender.

Other Events Observed with Olanzapine or Fluoxetine Monotherapy

The following adverse events were not observed in SYMBYAX-treated patients during premarketing clinical studies but have been reported with olanzapine or fluoxetine monotherapy: aplastic anemia, cholestatic jaundice, diabetic coma, dyskinesia, eosinophilic pneumonia, erythema multiforme, jaundice, rhabdomyolysis, serotonin syndrome, vasculitis, venous thromboembolic events (including pulmonary embolism and deep venous thrombosis), violent behaviors. Random triglyceride levels of ≥1000 mg/dL have been rarely reported.

7 DRUG INTERACTIONS

The risks of using SYMBYAX in combination with other drugs have not been extensively evaluated in systematic studies. The drug-drug interactions of the individual components are applicable to SYMBYAX. As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility. Caution is advised if the concomitant administration of SYMBYAX and other CNS-active drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status *(see Clinical Pharmacology (12.3))*.

7.1 Antihypertensive agents

Because of the potential for olanzapine to induce hypotension, SYMBYAX may enhance the effects of certain antihypertensive agents *[see Warnings and Precautions (5.10)]*.

7.2 Anti-Parkinsonians

The olanzapine component of SYMBYAX may antagonize the effects of levodopa and dopamine agonists.

7.3 Benzodiazepines

Multiple doses of olanzapine did not influence the pharmacokinetics of diazepam and its active metabolite N-desmethyldiazepam. However, the coadministration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine.

MAR 2 6 2007

G. Brophy

15

When concurrently administered with fluoxetine, the half-life of diazepam may be prolonged in some patients *[see Clinical Pharmacology (7.29, 12.3)]*. Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

7.4 **Biperiden**

Multiple doses of olanzapine did not influence the pharmacokinetics of biperiden.

7.5 **Carbamazepine**

Carbamazepine therapy (200 mg BID) causes an approximate 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Patients on stable doses of carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

7.6 **Clozapine**

Elevation of blood levels of clozapine has been observed in patients receiving concomitant fluoxetine.

7.7 **CNS Acting Drugs**

Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs.

7.8 **Electroconvulsive therapy (ECT)**

There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment *[see Warnings and Precautions (5.12)]*.

7.9 **Ethanol**

Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The coadministration of ethanol with SYMBYAX may potentiate sedation and orthostatic hypotension.

7.10 **Fluvoxamine**

Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine C_{max} following fluvoxamine administration of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of the olanzapine component of SYMBYAX should be considered in patients receiving concomitant treatment with fluvoxamine.

7.11 **Haloperidol**

Elevation of blood levels of haloperidol has been observed in patients receiving concomitant fluoxetine.

7.12 **Lithium**

Multiple doses of olanzapine did not influence the pharmacokinetics of lithium.

There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored in patients taking SYMBYAX concomitantly with lithium.

7.13 **Monoamine oxidase inhibitors**

SYMBYAX should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. There have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with an MAOI, and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses *[see Clinical Pharmacology (12.3)]* should be allowed after stopping SYMBYAX before starting an MAOI. *[See Contraindications (4)]*.

7.14 **Phenytoin**

Patients on stable doses of phenytoin have developed elevated plasma levels of phenytoin with clinical phenytoin toxicity following initiation of concomitant fluoxetine.

7.15 **Pimozide**

Concomitant use of fluoxetine and pimozide is contraindicated. Clinical studies of pimozide with other antidepressants demonstrate an increase in drug interaction or QT_c prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QT_c prolongation warrants restricting the concurrent use of pimozide and fluoxetine. *[See Contraindications (4)]*.

MAR 2 8 2007

G. Brophy

7.16 Serotonergic Drugs

Based on the mechanism of action of SYMBYAX and the potential for serotonin syndrome, caution is advised when SYMBYAX is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort *[see Warnings and Precautions (5.6)]*. The concomitant use of SYMBYAX with other SSRIs, SNRIs or tryptophan is not recommended *[see Drug Interactions (7.21)]*.

7.17 Theophylline

Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

7.18 Thioridazine

Thioridazine should not be administered with SYMBYAX or administered within a minimum of 5 weeks after discontinuation of SYMBYAX.

In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs that inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine *[see Contraindications (4)]*.

Thioridazine administration produces a dose-related prolongation of the QT, interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism *[see Contraindications (4)]*.

7.19 Tricyclic antidepressants (TCAs)

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

In two fluoxetine studies, previously stable plasma levels of imipramine and desipramine have increased >2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when SYMBYAX is coadministered or has been recently discontinued *[see Drug Interactions (7.15) and Clinical Pharmacology (12.3)]*.

7.20 Triptans

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of SYMBYAX with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Warnings and Precautions (5.6)]*.

7.21 Tryptophan

Five patients receiving fluoxetine in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress. Concomitant use with tryptophan is not recommended.

7.22 Valproate

In vitro studies using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. Thus, a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

7.23 Warfarin

Warfarin (20-mg single dose) did not affect olanzapine pharmacokinetics. Single doses of olanzapine did not affect the pharmacokinetics of warfarin.

Altered anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin *[see Warnings and Precautions (5.13)]*. Patients receiving warfarin therapy should receive careful coagulation monitoring when SYMBYAX is initiated or stopped.

7.24 Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding *[see Warnings and Precautions (5.13)]*. Thus, patients should be cautioned about the use of such drugs concurrently with SYMBYAX.

7.25 Drugs metabolized by CYP2D6

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP2D6. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by this enzyme.

MAR 2 6 2007

G. Brophy

17

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6. Such individuals have been referred to as poor metabolizers of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most antidepressants, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite, the sum of the plasma concentrations of the 4 enantiomers is comparable between poor and extensive metabolizers *[see Clinical Pharmacology (12.3)]*.

Fluoxetine, like other agents that are metabolized by CYP2D6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble poor metabolizers. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous five weeks. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for a decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (including but not limited to, flecainide, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated thioridazine plasma levels, thioridazine should not be administered with fluoxetine or within a minimum of five weeks after fluoxetine has been discontinued *[see Contraindications (4) and Drug Interactions (7.18)]*.

7.26 Drugs metabolized by CYP3A

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

In an in vivo interaction study involving the coadministration of fluoxetine with single doses of terfenadine (a CYP3A substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A activity is not likely to be of clinical significance.

7.27 Effect of olanzapine on drugs metabolized by other CYP enzymes

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, and CYP2C19. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

7.28 The effect of other drugs on olanzapine

Fluoxetine, an inhibitor of CYP2D6, decreases olanzapine clearance a small amount *[see Clinical Pharmacology (12.3)]*. Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Fluvoxamine, an inhibitor of CYP1A2, decreases olanzapine clearance *[see Drug Interactions (7.10)]*. The effect of CYP1A2 inhibitors, such as fluvoxamine and some fluoroquinolone antibiotics, on SYMBYAX has not been evaluated. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

7.29 Drugs highly bound to plasma protein

The in vitro binding of SYMBYAX to human plasma protein is similar to the individual components. The interaction between SYMBYAX and other highly protein-bound drugs has not been fully evaluated. Because fluoxetine is highly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is highly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects — Pregnancy Category C

[We have removed inaccurate and redundant information in the following section.]

SYMBYAX — ~~SYMBYAX has been shown to be teratogenic (at or have an embryocidal effect at other adverse effect) in rats when given in doses of olanzapine and fluoxetine in combination at 3 and 1 times the human dose respectively. There are no adequate and well-controlled studies in pregnant women. SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.~~ Embryo fetal development studies were conducted in rats and rabbits with olanzapine and fluoxetine in low-dose and high-dose combinations. In rats, the doses were: 2 and 6 mg/kg/day (low-dose) [1 and 0.5 times the MRHD on a mg/m^2 basis, respectively], and 4 and 8 mg/kg/day (high-dose) [2 and 1 times the MRHD on a mg/m^2 basis, respectively]. In rabbits, the doses were 4 and 4 mg/kg/day (low-dose) [4 and 1 times the MRHD on a mg/m^2 basis, respectively], and 8 and 8 mg/kg/day (high-dose) [9 and 2 times the MRHD on a mg/m^2 basis, respectively]. In these studies, olanzapine and fluoxetine were

MAR 3 6 2007

G. Brophy

18

also administered alone at the high-doses (4 and 8 mg/kg/day, respectively, in the rat; 8 and 8 mg/kg/day, respectively, in the rabbit). In the rabbit, there was no evidence of teratogenicity; however, the high-dose combination produced decreases in fetal weight and retarded skeletal ossification in conjunction with maternal toxicity. Similarly, in the rat there was no evidence of teratogenicity; however, a decrease in fetal weight was observed with the high-dose combination.

In a pre- and postnatal study conducted in rats, olanzapine and fluoxetine were administered during pregnancy and throughout lactation in combination (low-dose: 2 and 4 mg/kg/day [1 and 0.5 times the MRHD on a mg/m^2 basis], respectively, high-dose: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m^2 basis], respectively, and alone: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m^2 basis], respectively). Administration of the high-dose combination resulted in a marked elevation in offspring mortality and growth retardation in comparison to the same doses of olanzapine and fluoxetine administered alone. These effects were not observed with the low-dose combination; however, there were a few cases of testicular degeneration and atrophy, depletion of epididymal sperm and infertility in the male progeny. The effects of the high-dose combination on postnatal endpoints could not be assessed due to high progeny mortality.

There are no adequate and well-controlled studies with SYMBYAX in pregnant women.

SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Olanzapine — In reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the MRHD on a mg/m^2 basis, respectively), no evidence of teratogenicity was observed. In a rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD on a mg/m^2 basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the MRHD on a mg/m^2 basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled clinical studies with olanzapine in pregnant women. Seven pregnancies were observed during premarketing clinical studies with olanzapine, including two resulting in normal births, one resulting in neonatal death due to a cardiovascular defect, three therapeutic abortions, and one spontaneous abortion.

Fluoxetine — In embryo fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times the MRHD on a mg/m^2 basis, respectively) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis).

Treatment of Pregnant Women During the Third Trimester — Neonates exposed to fluoxetine, a component of ~~SYMBYAX~~SYMBYAX, and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Contraindications (4) and Drug Interactions (7.16)]*. When treating pregnant women with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering fluoxetine in the third trimester.

8.2 Labor and Delivery

SYMBYAX — The effect of SYMBYAX on labor and delivery in humans is unknown. Parturition in rats was not affected by SYMBYAX. SYMBYAX should be used during labor and delivery only if the potential benefit justifies the potential risk.

Olanzapine — The effect of olanzapine on labor and delivery in humans is unknown. Parturition in rats was not affected by olanzapine.

Fluoxetine — The effect of fluoxetine on labor and delivery in humans is unknown. Fluoxetine crosses the placenta; therefore, there is a possibility that fluoxetine may have adverse effects on the newborn.

8.3 Nursing Mothers

SYMBYAX — There are no adequate and well-controlled studies with SYMBYAX in nursing mothers or infants. Studies evaluating the individual components of SYMBYAX (olanzapine and fluoxetine) in nursing mothers are described below. It is not known whether SYMBYAX is excreted in human milk and because of the potential for serious adverse reactions in nursing infants

MAR 2 0 2007

G. Brophy

TOTAL P.23

19

from SYMBYAX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is recommended that women not breast-feed when receiving SYMBYAX.

Olanzapine — In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving olanzapine should not breast-feed.

Fluoxetine — Fluoxetine is excreted in human breast milk. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on fluoxetine developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the 2nd day of feeding.

8.4 Pediatric Use

SYMBYAX — Safety and effectiveness in the pediatric population have not been established *[see Box Warning and Warnings and Precautions (5.1)]*. Anyone considering the use of SYMBYAX in a child or adolescent must balance the potential risks with the clinical need.

Fluoxetine — Significant toxicity, including myotoxicity, long-term neurobehavioral and reproductive toxicity, and impaired bone development, has been observed following exposure of juvenile animals to fluoxetine. Some of these effects occurred at clinically relevant exposures.

In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from weaning (Postnatal Day 21) through adulthood (Day 90), male and female sexual development was delayed at all doses, and growth (body weight gain, femur length) was decreased during the dosing period in animals receiving the highest dose. At the end of the treatment period, serum levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and hypospermia) was observed at the high dose. When animals were evaluated after a recovery period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased reactivity at all doses and learning deficit at the high dose) and reproductive functional impairment (decreased mating at all doses and impaired fertility at the high dose) were seen; in addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were found in the high dose group, indicating that the reproductive organ effects seen at the end of treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dose in this study were approximately 0.1-0.2, 1-2, and 5-10 times, respectively, the average exposure in pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat exposures to the major metabolite, norfluoxetine, were approximately 0.3-0.8, 1-8, and 3-20 times, respectively, pediatric exposure at the MRD.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg, intraperitoneal) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These doses did not affect overall growth (body weight gain or femoral length). The doses administered to juvenile mice in this study are approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area (mg/m^2) basis.

In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric MRD on a mg/m^2 basis. Because of the early dosing period in this study, the significance of these findings to the approved pediatric use in humans is uncertain.

8.5 Geriatric Use

SYMBYAX — Clinical studies of SYMBYAX did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Dosage and Administration (2.1)]*.

Olanzapine — Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263 patients) were ≥65 years of age. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared with younger patients. Studies in patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared with younger patients with schizophrenia. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the

MAR 2 6 2007

G. Brophy

20

treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised [see Box Warning, Warnings and Precautions (5.19) and Dosage and Administration (2.3)].

As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient.

Fluoxetine — US fluoxetine clinical studies (10,782 patients) included 687 patients ≥65 years of age and 93 patients ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients.

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

SYMBYAX, as with fluoxetine and olanzapine, has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical studies did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of SYMBYAX (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

In studies in rats and rhesus monkeys designed to assess abuse and dependence potential, olanzapine alone was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence at oral doses up to 15 (rat) and 8 (monkey) times the MRHD (20 mg) on a mg/m^2 basis.

10 OVERDOSAGE

SYMBYAX — During premarketing clinical studies of the olanzapine/fluoxetine combination, overdose of both fluoxetine and olanzapine were reported in five study subjects. Four of the five subjects experienced loss of consciousness (3) or coma (1). No fatalities occurred.

Adverse events involving overdose of fluoxetine and olanzapine in combination, and SYMBYAX, have been reported spontaneously to Eli Lilly and Company. An overdose of combination therapy is defined as confirmed or suspected ingestion of a dose of >20 mg olanzapine in combination with a dose of >60 mg fluoxetine. Adverse events associated with these reports included somnolence (sedation), impaired consciousness (coma), impaired neurologic function (ataxia, confusion, convulsions, dysarthria), arrhythmias, lethargy, essential tremor, agitation, acute psychosis, hypotension, hypertension, and aggression. Fatalities have been confounded by exposure to additional substances including alcohol, thioridazine, oxycodone, and propoxyphene.

Olanzapine — In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia as well as a patient that experienced sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

Fluoxetine — Worldwide exposure to fluoxetine is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdose, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdose were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients

MAR 2 8 2007

G. Brophy

21

had an unknown outcome. One of the 6 fatalities was a 9-year-old boy who had a history of OCD, Tourette's Syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams, which was non-lethal.

Other important adverse events reported with fluoxetine overdose (single or multiple drugs) included coma, delirium, ECG abnormalities (such as QT-interval prolongation and ventricular tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like events, pyrexia, stupor, and syncope.

10.2 Management of Overdose

In managing overdose, the possibility of multiple drug involvement should be considered. In case of acute overdose, establish and maintain an airway and ensure adequate ventilation, which may include intubation. Induction of emesis is not recommended as the possibility of obtundation, seizures, or dystonic reactions of the head and neck following overdose may create a risk for aspiration. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

A specific precaution involves patients who are taking or have recently taken SYMBYAX and may have ingested excessive quantities of a TCA (tricyclic antidepressant). In such cases, accumulation of the parent TCA and/or an active metabolite may increase the possibility of serious sequelae and extend the time needed for close medical observation.

Due to the large volume of distribution of olanzapine and fluoxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidote for either fluoxetine or olanzapine overdose is known. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Do not use epinephrine, dopamine, or other sympathomimetics with β-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.

The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*.

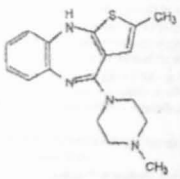
11 DESCRIPTION

SYMBYAX® (olanzapine and fluoxetine HCl capsules) combines 2 psychotropic agents, olanzapine (the active ingredient in Zyprexa®, and Zyprexa Zydis®) and fluoxetine hydrochloride (the active ingredient in Prozac®, Prozac Weekly™, and Sarafem®).

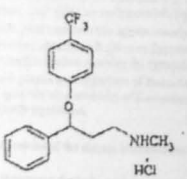
Olanzapine belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44.

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI). The chemical designation is (±)-N-methyl-γ-phenyl-3-[(α,α,α-trifluoro-p-tolyl)oxy]propylamine hydrochloride. The molecular formula is $C_{17}H_{18}F_3NO{\cdot}HCl$, which corresponds to a molecular weight of 345.79.

The chemical structures are:



Olanzapine



fluoxetine hydrochloride

Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

MAR 2 6 2007

G. Brophy

22

Each capsule also contains pregelatinized starch, gelatin, dimethicone, titanium dioxide, sodium lauryl sulfate, edible black ink, red iron oxide, yellow iron oxide, and/or black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Although the exact mechanism of SYMBYAX is unknown, it has been proposed that the activation of 5 monoaminergic neural systems (serotonin, norepinephrine, and dopamine) is responsible for its enhanced antidepressant effect. This is supported by animal studies in which the olanzapine/fluoxetine combination has been shown to produce synergistic increases in norepinephrine and dopamine release in the prefrontal cortex compared with either component alone, as well as increases in serotonin.

12.2 Pharmacodynamics

Olanzapine is a psychotropic agent with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$ (K_i=4 and 11 nM, respectively), dopamine D_{1-4} (K_i=11 to 31 nM), muscarinic M_{1-5} (K_i=1.9 to 25 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors (K_i=19 nM). Olanzapine binds weakly to $GABA_A$, BZD, and β-adrenergic receptors (K_i>10 μM). Fluoxetine is an inhibitor of the serotonin transporter and is a weak inhibitor of the norepinephrine and dopamine transporters.

Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its antiholinergic effects. The antagonism of histamine H_1 receptors by olanzapine may explain the somnolence observed with this drug. The antagonism of α_1-adrenergic receptors by olanzapine may explain the orthostatic hypotension observed with this drug. Fluoxetine has relatively low affinity for muscarinic, α_1-adrenergic, and histamine H_1 receptors.

12.3 Pharmacokinetics

SYMBYAX — Fluoxetine (administered as a 60-mg single dose or 60 mg daily for 8 days) caused a small increase in the mean maximum concentration of olanzapine (16%) following a 5-mg dose, an increase in the mean area under the curve (17%) and a small decrease in mean apparent clearance of olanzapine (16%). In another study, a similar decrease in apparent clearance of olanzapine of 14% was observed following olanzapine doses of 6 or 12 mg with concomitant fluoxetine doses of 25 mg or more. The decrease in clearance reflects an increase in bioavailability. The terminal half-life is not affected, and therefore the time to reach steady state should not be altered. The overall steady-state plasma concentrations of olanzapine and fluoxetine when given as the combination in the therapeutic dose ranges were comparable with those typically attained with each of the monotherapies. The small change in olanzapine clearance, observed in both studies, likely reflects the inhibition of a minor metabolic pathway for olanzapine via CYP2D6 by fluoxetine, a potent CYP2D6 inhibitor, and was not deemed clinically significant. Therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination.

Absorption and Bioavailability

SYMBYAX — Following a single oral 12-mg/50-mg dose of SYMBYAX, peak plasma concentrations of olanzapine and fluoxetine occur at approximately 6 and 8 hours, respectively. The effect of food on the absorption and bioavailability of SYMBYAX has not been evaluated. The bioavailability of olanzapine given as Zyprexa, and the bioavailability of fluoxetine given as Prozac were not affected by food. It is unlikely that there would be a significant food effect on the bioavailability of SYMBYAX.

Olanzapine — Olanzapine is well absorbed and reaches peak concentration approximately 6 hours following an oral dose. Food does not affect the rate or extent of olanzapine absorption when olanzapine is given as Zyprexa. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation.

Fluoxetine — Following a single oral 40-mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine given as Prozac, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant.

Distribution

SYMBYAX — The in vitro binding to human plasma proteins of the olanzapine/fluoxetine combination is similar to the binding of the individual components.

Olanzapine — Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1-acid glycoprotein.

Fluoxetine — Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated *[see Drug Interactions (7.2)]*.

MAR 2 8 2007

G. Brophy

23

Metabolism and Elimination

SYMBYAX — SYMBYAX therapy yielded steady-state concentrations of norfluoxetine similar to those seen with fluoxetine in the therapeutic dose range.

Olanzapine — Olanzapine displays linear pharmacokinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr). Administration of olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.4)]*.

Following a single oral dose of ^{14}C-labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and CYP450-mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYP1A2, CYP2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6-mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Fluoxetine — Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Fluoxetine is extensively metabolized in the liver to its only identified active metabolite, norfluoxetine, via the CYP2D6 pathway. A number of unidentified metabolites exist.

In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical Issues Related to Metabolism and Elimination

The complexity of the metabolism of fluoxetine has several consequences that may potentially affect the clinical use of SYMBYAX.

Variability in metabolism — A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme CYP2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants (TCAs). In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative nonsaturable pathways (non-CYP2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because the metabolism of fluoxetine, like that of a number of other compounds including TCAs and other selective serotonin antidepressants, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions *[see Drug Interactions (7.19 and 7.35)]*.

Accumulation and slow elimination — The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because the metabolism of fluoxetine is not proportional to dose. However, norfluoxetine appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine.

MAR 2 8 2007

G. Brophy

24

12.4 Special Populations

Geriatric — Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in geriatric patients. Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity.

In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly subjects (≥65 years of age) than in non-elderly subjects (≤65 years of age).

The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in these elderly patients.

Renal Impairment — The pharmacokinetics of SYMBYAX has not been studied in patients with renal impairment. However, olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not routinely required.

Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on olanzapine metabolite elimination has not been studied.

In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.

Hepatic Impairment — Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in patients with hepatic impairment. The lowest starting dose should be considered for patients with hepatic impairment *[see Warnings and Precautions (5.19) and Dosage and Administration (2.3)]*.

Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (N=6) with clinically significant cirrhosis (Childs-Pugh Classification A and B) revealed little effect on the pharmacokinetics of olanzapine.

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects.

Gender — Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status — Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely required.

Race — No SYMBYAX pharmacokinetic study was conducted to investigate the effects of race. Results from an olanzapine cross-study comparison between data obtained in Japan and data obtained in the US suggest that exposure to olanzapine may be about 2-fold greater in the Japanese when equivalent doses are administered. Olanzapine clinical study safety and efficacy data, however, did not suggest clinically significant differences among Caucasian patients, patients of African descent, and a 3rd pooled category including Asian and Hispanic patients. Dosage modifications for race, therefore, are not routinely required.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance of olanzapine in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. SYMBYAX dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of the olanzapine component *[see Dosage and Administration (2.3)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity, or fertility studies were conducted with SYMBYAX. The following data are based on findings in studies performed with the individual components.

MAR 2 6 2007

G. Brophy

Carcinogenesis

Olanzapine — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, and 30/20 mg/kg/day [equivalent to 0.8 to 5 times the maximum recommended human daily dose (MRHD) on a mg/m^2 basis] and 0.25, 2, and 8 mg/kg/day (equivalent to 0.06 to 2 times the MRHD on a mg/m^2 basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, and 4 mg/kg/day (males) and 0.25, 1, 4, and 8 mg/kg/day (females) (equivalent to 0.1 to 2 and 0.1 to 4 times the MRHD on a mg/m^2 basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in females dosed at 8 mg/kg/day (2 times the MRHD on a mg/m^2 basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2 to 5 times the MRHD on a mg/m^2 basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the MRHD on a mg/m^2 basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the finding of prolactin-mediated endocrine tumors in rodents is unknown *[see Warning and Precautions (5.20)]*.

Fluoxetine — The dietary administration of fluoxetine to rats and mice for two years at doses of up to 10 and 12 mg/kg/day, respectively (approximately 1.2 and 0.7 times, respectively, the MRHD on a mg/m^2 basis), produced no evidence of carcinogenicity.

Mutagenesis

Olanzapine — No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Fluoxetine — Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of Fertility

SYMBYAX — Fertility studies were not conducted with SYMBYAX. However, in a repeat-dose rat toxicology study of three months duration, ovary weight was decreased in females treated with the low-dose [2 and 4 mg/kg/day (1 and 0.5 times the MRHD on a mg/m^2 basis), respectively] and high-dose [4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m^2 basis), respectively] combinations of olanzapine and fluoxetine. Decreased ovary weight, and corpora lutea depletion and uterine atrophy were observed to a greater extent in the females receiving the high-dose combination than in females receiving either olanzapine or fluoxetine alone. In a 3-month repeat-dose dog toxicology study, reduced epididymal sperm and reduced testicular and prostate weights were observed with the high-dose combination of olanzapine and fluoxetine (5 and 5 mg/kg/day (9 and 2 times the MRHD on a mg/m^2 basis), respectively] and with olanzapine alone (5 mg/kg/day or 9 times the MRHD on a mg/m^2 basis).

Olanzapine — In a fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the MRHD on a mg/m^2 basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male-mating performance. In female rats, the prestrual period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the MRHD on a mg/m^2 basis). Diestrous was prolonged and estrous was delayed at 1.1 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis); therefore, olanzapine may produce a delay in ovulation.

Fluoxetine — Two fertility studies conducted in adult rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m^2 basis) indicated that fluoxetine had no adverse effects on fertility *[see Use in Specific Populations (8.4)]*.

14 CLINICAL STUDIES

14.1 Bipolar Depression

The efficacy of SYMBYAX for the treatment of depressive episodes associated with bipolar disorder was established in 2 identically designed, 8-week, randomized, double-blind, controlled studies of patients who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for Bipolar I Disorder, Depressed utilizing flexible dosing of SYMBYAX (6/25, 6/50, or 12/50 mg/day), olanzapine (5 to 20 mg/day), and placebo. These studies included patients (≥18 years of age (n=735)) with or without psychotic symptoms and with or without a rapid cycling course.

MAR 2 8 2007

G. Brophy

26

The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 to 60. The primary outcome measure of these studies was the change from baseline to endpoint in the MADRS total score. In both studies, SYMBYAX was statistically significantly superior to both olanzapine monotherapy and placebo in reduction of the MADRS total score. The results of the studies are summarized below (Table 3).

Table 3: MADRS Total Score
Mean Change from Baseline to Endpoint

	Treatment Group	Baseline Mean	Change to Endpoint Mean[1]
Study 1	SYMBYAX (N=62)	30	-16*
	Olanzapine (N=162)	32	-12
	Placebo (N=184)	31	-10
Study 2	SYMBYAX (N=62)	32	-15*
	Olanzapine (N=165)	33	-14
	Placebo (N=174)	31	-9

[1] Negative number denotes improvement from baseline.
* Statistically significant compared to both olanzapine and placebo

14.2 Treatment Resistant Depression

[We have revised the following section to more accurately reflect the data used to assess efficacy.]

The efficacy of SYMBYAX in treatment resistant depression was demonstrated with data from 5 3 clinical studies (n=579) (Table 3). Doses evaluated in these studies ranged from 6/5 - 12 - 20 mg for olanzapine and 25/25 - 50 - 50 - 60 mg for fluoxetine.

Two identically designed An 8-week randomized, double-blind controlled studies (Study 1 and 5) in where conducted to evaluate the efficacy of SYMBYAX in patients (n = 300) who met DSM-IV criteria for major depressive disorder and did not respond to 2 antidepressants of adequate dose and duration in their current episode (N=601). Patients who were not responding to an antidepressant in their current episode entered an 8-week open-label fluoxetine lead-in; non-responders were randomized (1:1:1) to receive SYMBYAX, olanzapine, or fluoxetine, and were treated for 8 weeks. SYMBYAX was flexibly dosed between 6/50 mg, 12/50 mg, and 18/50 mg. Results from one (Study 1) of these 2 studies this study yielded statistically significant greater reduction (p=0.001) in mean total MADRS scores from baseline to endpoint for SYMBYAX (-14.6) versus fluoxetine (-9.0) and olanzapine (-9.7). A second study with the same treatment-resistant patient population (n=278), when analyzed with change in MADRS as the primary outcome measure, demonstrated statistically significantly greater reduction in MADRS scores for SYMBYAX versus fluoxetine and olanzapine. Additionally A third study (-3, similarly designed studies (Study 2, 3, and 5) of 6-12 weeks duration (n=86, 251, 260, respectively) demonstrated statistically significantly greater reduction in total MADRS scores for SYMBYAX versus fluoxetine (p=0.012, 0.024, 0.106) and or olanzapine. Also (p=0.035, 0.003, 0.007) respectively, when analyzed for the same(full subpopulation of depressed patients (n=231) who met the definition of treatment resistance (patients who were had not responding responded to 2 antidepressants of adequate dose and duration, both during in the current episode).

An integrated analysis of the 5 studies yielded statistically significant greater reduction in mean total MADRS scores from baseline to endpoint in the defined population (p=0.015, p=0.007 versus fluoxetine and olanzapine, respectively) for SYMBYAX (-12.2) versus fluoxetine (-8.5) and olanzapine (-8.7).

Table 3: MADRS Total Score
Mean Change from Baseline to Endpoint in
Treatment Resistant Depression

MAR 2 6 2007
G. Brophy

27

	Treatment Group	Baseline Mean	Change to Endpoint Value[1]
Study 1	SYMBYAX (N=93)	30.6	-14.6
	Fluoxetine (N=101)	30.1	-9.0[a]
	Olanzapine (N=103)	30.7	-7.5[a]
Study 2	SYMBYAX (N=110)	29.4	-13.6
	Fluoxetine (N=40)	32.8	-1.2[a]
	Olanzapine (N=42)	35.0	-2.8[a]
Study 3	SYMBYAX (N=163)	30.3	-13.2
	Fluoxetine (N=43)	31.1	-10.0[a]
	Olanzapine (N=43)	31.5	-8.8[a]
Study 4	SYMBYAX (N=91)	29.4	-9.0
	Fluoxetine (N=88)	28.9	-7.0[a,b]
	Olanzapine (N=90)	28.4	-5.1[a]
Study 5	SYMBYAX (N=181)	28.5	-10.8
	Fluoxetine (N=100)	28.9	-8.4[a,b]
	Olanzapine (N=85)	29.7	-10.1[a,b]
Integrated analysis of 5 studies	SYMBYAX (N=653)	29.9	-12.2
	Fluoxetine (N=542)	29.6	-8.5[a]
	Olanzapine (N=443)	29.6	-7.7[a]

[1] Negative sign for denotes improvement from baseline.
[a] SYMBYAX statistically significant ($p<0.05$) compared to fluoxetine and olanzapine.
[b] SYMBYAX demonstrated a greater reduction in total MADRS score, however did not reach statistical significance ($p<0.05$)

16 HOW SUPPLIED/STORAGE AND HANDLING

SYMBYAX capsules are supplied in 3/25-, 6/25-, 6/50-, 12/25-, and 12/50-mg (mg equivalent olanzapine/mg equivalent fluoxetine*) strengths.

SYMBYAX	CAPSULE STRENGTH				
	3 mg/25 mg	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
Color	Peach & Light Yellow	Mustard Yellow & Light Yellow	Mustard Yellow & Light Grey	Red & Light Yellow	Red & Light Grey
Capsule No.	PU3230	PU3231	PU3233	PU3232	PU3234
Identification	Lilly 3230 3/25	Lilly 3231 6/25	Lilly 3233 6/50	Lilly 3232 12/25	Lilly 3234 12/50
NDC Codes					
Bottles 30	0002-3230-30	0002-3231-30	0002-3233-30	0002-3232-30	0002-3234-30
Bottles 100		0002-3231-02	0002-3233-02	0002-3232-02	0002-3234-02
Bottles 1000		0002-3231-04	0002-3233-04	0002-3232-04	0002-3234-04
Blisters ID* 100		0002-3231-33	0002-3233-33	0002-3232-33	0002-3234-33

* Fluoxetine base equivalent.
* IDENTI-DOSE®, Unit Dose Medication, Lilly.

MAR 2 C 2007

G. Brophy

28

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Keep tightly closed and protect from moisture.

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SYMBYAX and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for SYMBYAX. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SYMBYAX.

Patients should be cautioned about the concomitant use of SYMBYAX and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding *[see Warnings and Precautions (5.15)]*.

Patients should be advised to avoid alcohol while taking SYMBYAX.

As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them adversely.

Patients should be advised to inform their physician if they are taking Prozac®, Prozac Weekly™, Sarafem®, fluoxetine, Zyprexa®, or Zyprexa Zydis®. Patients should be advised to inform their physicians if they are taking or plan to take any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions. Patients should also be advised to inform their physicians if they plan to discontinue any medications they are taking while taking SYMBYAX, as stopping a medication may also impact the overall blood level of SYMBYAX.

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Patients, if taking SYMBYAX, should be advised not to breast-feed.

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol *[see Warnings and Precautions (5.16) and Drug Interactions (7)]*.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during SYMBYAX therapy.

Patients should be advised to notify their physician if they develop a rash or hives while taking SYMBYAX.

Patients should be advised to take SYMBYAX exactly as prescribed, and to continue taking SYMBYAX as prescribed even after their mood symptoms improve. Patients should be advised that they should not alter their dosing regimen, or stop taking SYMBYAX, without consulting their physician.

Patient information is printed at the end of this insert. Physicians should discuss this information with their patients and instruct them to read the Medication Guide before starting therapy with SYMBYAX and each time their prescription is refilled.

17.2 Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

17.3 Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of SYMBYAX and triptans, tramadol or other serotonergic agents.

17.4 FDA-Approved Medication Guide

MAR 2 6 2007

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About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called suicidality or *being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. *No one committed suicide in these studies*, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your health care provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her health care provider

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your health care provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's health care provider between visits if needed.

3. You Should Watch for Certain Signs if Your Child is Taking an Antidepressant

Contact your child's health care provider *right away* if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

MAR 2 3 2007

G. Brophy

30

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her health care provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your health care provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine, and clomipramine (Anafranil®).

Your health care provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your health care provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your health care provider or pharmacist where to find more information.

Prozac® is a registered trademark of Eli Lilly and Company.
Zoloft® is a registered trademark of Pfizer Pharmaceuticals.
Anafranil® is a registered trademark of Mallinckrodt Inc.

This Medication Guide has been approved by the US Food and Drug Administration for all antidepressants.

Rx only

Literature revised September 8, 2006

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03-11

October 5, 2007

Re: Safety data on Zyprexa® (olanzapine) and Symbyax® (olanzapine and fluoxetine HCl capsules) – Hyperglycemia, Weight Gain, and Hyperlipidemia

Dear Health Care Professional,

Eli Lilly and Company would like to inform you of important information being added to the Zyprexa® (olanzapine) and Symbyax® (olanzapine and fluoxetine HCl) labels. These labeling updates include new WARNINGS for Weight Gain and Hyperlipidemia and updated information in the WARNING for Hyperglycemia. These changes reflect results of recently completed pooled analyses of clinical trials in adults and adolescents as well as information from two published large studies of atypical antipsychotics, CATIE[1] and CAFE[2].

The new labeling language is detailed below. Monitoring of glucose, weight, and lipids is recommended during olanzapine and olanzapine/fluoxetine combination treatment. Guidelines published by the American Diabetes Association (ADA) following the consensus development conference[3] provide recommendations for the monitoring of blood glucose, weight, and lipid levels in those treated with atypical antipsychotics. Other highlights of the updated labeling include:

- Abnormal or borderline glucose levels at baseline are an important risk factor for further glucose increase.
- While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.
- Significantly greater mean increases in total cholesterol, LDL cholesterol, and triglycerides were observed in Zyprexa-treated patients compared with placebo-treated patients both with and without evidence of dyslipidemia at baseline.
- Labeling provides information on magnitude and distribution of weight gain over a two year period in Zyprexa-treated patients.
- Labeling also provides information on glucose, weight gain, and lipids from studies of Zyprexa for adolescent patients. Please note that Zyprexa and Symbyax are not approved currently for use in children and adolescents aged less than 18 years old.

Exhibit H
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
Page 1 of 27

Zyprexa Plaintiff's Exhibit 10095

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Eli Lilly and Company remains committed to providing you with the most current product information available for the management of your patients and we will continue our ongoing research and analyses in these areas.

Please refer to the full prescribing information for Zyprexa and Symbyax included with this letter.

Should you have any questions or would like additional information regarding this important safety information, please contact the Lilly medical department at 1-800-Lilly-Rx or your Eli Lilly and Company sales representative.

The Medical Community can further our understanding of adverse events by reporting all cases to the Agency via the MedWatch program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, via the MedWatch website at www.fda.gov/medwatch or by mail:

MEDWATCH
Food and Drug Administration
5515 Security Lane
Suite 5100, HFD-001
Rockville, MD 20852

Sincerely,

Tim Garnett, M.D.
Vice President,
Global Patient Safety
Eli Lilly and Company

The following are the updated Hyperglycemia WARNINGS and the new Hyperlipidemia and Weight WARNINGS included in the Zyprexa label.

WARNINGS:

Zyprexa:

The following is updated language in the WARNINGS section of the Zyprexa package insert, and will be reflected in other materials.

Hyperglycemia — Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase I of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the two highest serum concentrations was 15.0 mg/dl.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse events, patients treated with antidiabetic agents, patients with a baseline random glucose level ≥200 mg/dL, and/or a baseline fasting glucose level ≥126 mg/dL). These patients had a statistically significantly greater mean increase in HbA_{1c} compared to placebo. In patients with baseline normal fasting glucose levels (<100 mg/dL), 2.2% (N= 543) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 3.4% (N= 293) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 17.4% (N=178) of those treated with

olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 11.5% (N=96) of those treated with placebo.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a statistically significantly greater mean change in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). In patients with baseline normal fasting glucose levels (<100 mg/dL), zero out of 124 (0%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 2 out of 14 (14.3%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus zero out of 13 (0%) of those treated with placebo.

Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus or having borderline increased blood glucose level (fasting 100–126 mg/dL, non-fasting 140–200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Hyperlipidemia — Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised.

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had statistically significant increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL,

4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse events, patients treated with lipid lowering agents, or patients with high baseline lipid levels. Table 1 shows categorical changes in fasting lipid values.

Table 1. Changes in Fasting Lipids Values from Adult Placebo-Controlled Olanzapine Monotherapy Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	745	39.6%*
		Placebo	402	26.1%
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Olanzapine	457	9.2%*
		Placebo	251	4.4%
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	135	39.3%*
		Placebo	65	20.0%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.6%*
		Placebo	402	9.5%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	392	2.8%
		Placebo	207	2.4%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Olanzapine	222	23.0%*
		Placebo	112	12.5%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	536	23.7%*
		Placebo	304	14.1%
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	154	0%
		Placebo	82	1.2%
	Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Olanzapine	302	10.6%
		Placebo	173	8.1%

* Statistically significant compared to placebo.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the mean increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), for fasting HDL cholesterol, no statistically significant

differences were observed between olanzapine-treated patients and placebo-treated patients. Table 2 shows categorical changes in fasting lipid values in adolescent patients.

Table 2. Changes in Fasting Lipids Values from Adolescent Placebo-Controlled Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	138	37.0%*
		Placebo	66	15.2%
	Normal to High (<90 mg/dL to >130 mg/dL)	Olanzapine	67	26.9%
		Placebo	28	10.7%
	Borderline to High (≥90 mg/dL and ≥130 mg/dL to >130 mg/dL)	Olanzapine	37	59.5%
		Placebo	17	35.3%
Fasting Total Cholesterol	Increase by >40 mg/dL	Olanzapine	138	14.5%*
		Placebo	66	4.5%
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%
		Placebo	43	2.3%
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	36	38.9%*
		Placebo	13	7.7%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%
		Placebo	63	11.1%
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%
		Placebo	44	4.5%
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%*
		Placebo	9	0%

* Statistically significant compared to placebo.

Weight Gain — Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight.

Olanzapine Monotherapy in Adults — In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg, which was statistically significantly different compared to an average 0.3 kg weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, which was statistically significantly different compared to 3% of placebo-treated patients, with a median exposure of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, which was statistically significantly different compared to 0.3% of placebo-treated patients, with a median exposure of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass

Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in zero placebo-treated patients.

During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

Table 3 includes data on weight gain with olanzapine pooled from 68 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 3. Weight Gain with Olanzapine Use

Amount Gained kg (lb)	6 Weeks (N=2976) (%)	6 Months (N=1536) (%)	12 Months (N=778) (%)	24 Months (N=422) (%)
≤0	27	21	20	22
0-5 (0-11 lb)	57	34	25	22
5-10 (11-22 lb)	15	26	25	22
10-15 (22-33 lb)	2	12	16	18
>15 (>33 lb)	0	6	14	16

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescent patients (ages 13 to 17 years), including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine-treated patients gained an average of 4.6 kg, which was statistically significantly different compared to an average of 0.3 kg in placebo-treated patients, with a median exposure of 3 weeks; 40.6% of olanzapine-treated patients gained at least 7% of their baseline body weight, which was statistically significantly different compared to 9.8% of placebo-treated patients, with a median exposure of 4 weeks; 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 2.7% of placebo-treated patients, with a median exposure of 19 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories, but mean changes in weight were greater in adolescents with BMI categories above normal at baseline. Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to zero placebo-treated patients.

During long-term continuation therapy with olanzapine, 65% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.4 kg.

Information for Patients:

Hyperglycemia — Patients should be advised of the potential risk of hyperglycemia-related adverse events. Patients should be monitored regularly for worsening of glucose control.

Weight Gain — Patients should be counseled that olanzapine is associated with weight gain. Patients should have their weight monitored regularly.

The following are the updated Hyperglycemia WARNINGS and the new Hyperlipidemia and Weight WARNINGS included in the Symbyax label.

WARNINGS:

Symbyax:
The following is updated language in the WARNINGS section of the Symbyax package insert, and will be reflected in other materials.

Hyperglycemia — Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase I of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the two highest serum concentrations was 15.0 mg/dL.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, SYMBYAX was associated with a statistically significantly greater mean change in random glucose compared to placebo (8.65 mg/dL versus -3.86 mg/dL). In patients with baseline normal random glucose levels (<140 mg/dL), 2.3% of those treated with SYMBYAX were found to have high glucose levels (≥200 mg/dl) during SYMBYAX treatment and were statistically significantly different compared to 0.3% of those treated with placebo. In patients with baseline borderline random glucose levels (≥140 mg/dL and <200 mg/dL), 34.1% of those treated with SYMBYAX were found to have high glucose levels (≥200 mg/dL) during SYMBYAX treatment and were statistically significantly different compared to 3.6% of those treated with placebo. The difference in mean changes between SYMBYAX and placebo was greater in patients with evidence of glucose dysregulation at baseline (including those patients diagnosed with diabetes mellitus or related adverse events, patients treated with anti-diabetic agents,

patients with a baseline random glucose level ≥200 mg/dL, or a baseline fasting glucose level ≥126 mg/dL). These patients had a greater mean increase in HbA_{1c}.

Controlled fasting glucose data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL vs 0.17 mg/dL).

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a statistically significantly greater mean change in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). In patients with baseline normal fasting glucose levels (<100 mg/dL), zero out of 124 (0%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 2 out of 14 (14.3%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus zero out of 13 (0%) of those treated with placebo.

Physicians should consider the risks and benefits when prescribing SYMBYAX to patients with an established diagnosis of diabetes mellitus or having borderline increased blood glucose level (fasting 100–126 mg/dL, nonfasting 140–200 mg/dL). Patients taking SYMBYAX should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Hyperlipidemia — Undesirable alterations in lipids have been observed with SYMBYAX use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using SYMBYAX, is advised.

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with SYMBYAX use. Significant increases in total cholesterol have also been seen with SYMBYAX use.

Controlled fasting lipid data is limited for SYMBYAX.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, SYMBYAX-treated patients had an increase from baseline in mean random total cholesterol of 12.1 mg/dL compared to a statistically significantly different increase from baseline in mean random total cholesterol of 4.8 mg/dL for olanzapine-treated patients and a decrease in mean random total cholesterol of 5.5 mg/dL for placebo-treated patients. Table 3 shows categorical changes in nonfasting lipid values.

Table 3. Changes in Nonfasting Lipids Values from Controlled Clinical Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients (%)
Nonfasting Triglycerides	Increase by 250 mg/dL	OFC	174	67.8%
		Olanzapine	172	72.7%
	Normal to High (<150 mg/dL to ≥500 mg/dL)	OFC	57	0%
		Olanzapine	58	0%
	Borderline to High (≥150 mg/dL and <500 mg/dL to ≥500 mg/dL)	OFC	106	15.1%
		Olanzapine	103	8.7%
Nonfasting Total Cholesterol	Increase by 240 mg/dL	OFC	685	35%[a,b]
		Olanzapine	749	22.7%
		Placebo	390	9%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	OFC	256	8.2%[a,b]
		Olanzapine	279	2.9%
		Placebo	175	1.7%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	OFC	213	36.2%[a,b]
		Olanzapine	261	27.6%
		Placebo	111	9.9%

[a] Statistically significant compared to olanzapine.
[b] Statistically significant compared to placebo.

Controlled fasting lipid data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had statistically significant increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in

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patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse events, patients treated with lipid lowering agents, patients with high baseline lipid levels. Table 4 shows categorical changes in fasting lipid values.

Table 4. Changes in Fasting Lipids Values from Adult Placebo-Controlled Olanzapine Monotherapy Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	745	39.6%*
		Placebo	402	26.1%
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Olanzapine	457	9.2%*
		Placebo	251	4.4%
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	135	39.3%*
		Placebo	65	20.0%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.6%*
		Placebo	402	9.5%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	392	2.8%
		Placebo	207	2.4%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Olanzapine	222	23.0%*
		Placebo	112	12.5%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	536	23.7%*
		Placebo	304	14.1%
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	154	0%
		Placebo	82	1.2%
	Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Olanzapine	302	10.6%
		Placebo	173	8.1%

* Statistically significant compared to placebo.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the median increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), for fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Table 5 shows categorical changes in fasting lipid values in adolescent patients.

Table 5. Changes in Fasting Lipids Values from Adolescent Placebo-Controlled Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by >50 mg/dL	Olanzapine	138	37.0%*
		Placebo	66	15.2%
	Normal to High (<90 mg/dL to ≥130 mg/dL)	Olanzapine	67	26.9%
		Placebo	28	10.7%
	Borderline to High (≥90 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	37	59.5%
		Placebo	17	35.3%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%*
		Placebo	66	4.5%
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%
		Placebo	43	2.3%
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	36	38.9%*
		Placebo	13	7.7%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%
		Placebo	63	11.1%
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%
		Placebo	44	4.5%
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%*
		Placebo	9	0%

* Statistically significant compared to placebo.

Weight Gain — Potential consequences of weight gain should be considered prior to starting SYMBYAX. Patients receiving SYMBYAX should receive regular monitoring of weight.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, the mean weight increase for SYMBYAX-treated patients was statistically significantly greater than placebo-treated (4 kg vs -0.3 kg). Twenty-two percent of SYMBYAX-treated patients gained at least 7% of their baseline weight, with a median exposure of 6 weeks. This was statistically significantly greater than in placebo-treated patients (1.8%). Approximately 3% of SYMBYAX-treated patients gained at least 15% of their baseline weight, with a median exposure of 8 weeks. This was statistically significantly greater than in placebo-treated patients (0%). Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 2.5% of SYMBYAX-treated patients and zero placebo-treated patients.

Table 6 includes data on weight gain with olanzapine pooled from 68 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 6. Weight Gain with Olanzapine Use

Amount Gained kg (lb)	6 Weeks (N=2976) (%)	6 Months (N=1536) (%)	12 Months (N=778) (%)	24 Months (N=422) (%)
≤0	27	21	20	22
0-5 (0-11 lb)	57	34	25	22
5-10 (11-22 lb)	15	26	25	22
10-15 (22-33 lb)	2	12	16	18
>15 (>33 lb)	0	6	14	16

During long-term continuation therapy with olanzapine monotherapy (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescent patients (ages 13 to 17 years), including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine-treated patients gained an average of 4.6 kg, which was statistically significantly different compared to an average of 0.3 kg in placebo-treated patients, with a median exposure of 3 weeks; 40.6% of olanzapine-treated patients gained at least 7% of their baseline body weight, which was statistically significantly different compared to 9.8% of placebo-treated patients, with a median exposure of 4 weeks; 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 2.7% of placebo-treated patients, with a median exposure of 19 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories, but mean changes in weight were greater in adolescents with BMI categories above normal at baseline. Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to zero placebo-treated patients.

During long-term continuation therapy with olanzapine, 65% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.4 kg.

Information for Patients:

Hyperglycemia — Patients should be advised of the potential risk of hyperglycemia-related adverse events. Patients should be monitored regularly for worsening of glucose control.

Weight Gain — Patients should be counseled that SYMBYAX is associated with weight gain. Patients should have their weight monitored regularly.

References:

1. Lieberman, JA, Stroup, TS, McEvoy, JP, S. Swartz, MS, Rosenheck, RA, Perkins, DO, Keefe, RSE, Davis, SM, Davis, CE, Lebowitz, BD, Severe, J, Hsiao, JK. 2005. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. New Engl J Med 353(12): 1209-1223.

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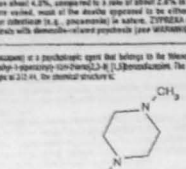
Zyprexa® (olanzapine) is indicated for the short-term and maintenance treatment of schizophrenia. Zyprexa is also indicated as monotherapy or in combination with lithium or valproate for the short-term treatment of acute mixed or manic episodes associated with Bipolar I Disorder and as maintenance treatment in bipolar disorder. Symbyax® (olanzapine and fluoxetine HCl capsules) is indicated for treatment of depressive episodes associated with bipolar disorder.

ZYPREXA® Olanzapine Tablets
ZYPREXA® ZYDIS® Olanzapine Orally Disintegrating Tablets
ZYPREXA® IntraMuscular Olanzapine for Injection

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis (see WARNINGS).

DESCRIPTION: ZYPREXA (olanzapine) is a psychotropic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. The chemical structure is:



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (5 μmol), 5 mg (16 μmol), 7.5 mg (24 μmol), 10 mg (32 μmol), 15 mg (48 μmol), or 20 mg (64 μmol), inactive ingredients are: carnauba wax, croscarmellose, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating systems: Opadry® Blue (all strengths), YS-1-7040, Blue No. 2 Aluminum Lake (10 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5, 7.5, and 15 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 μmol), 10 mg (32 μmol), 15 mg (48 μmol) or 20 mg (64 μmol), 5 targins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben and sodium propyl paraben.

ZYPREXA IntraMuscular (olanzapine for injection) is intended for intramuscular use only.

Each vial contains the equivalent of 10 mg (32 μmol) olanzapine with inactive ingredients 30 mg lactose monohydrate and 2.0 mg sorbitol base. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

CLINICAL PHARMACOLOGY: Pharmacodynamics—Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_3$, $5HT_6$ (K$_i$=4, 11, and 5 nM, respectively), dopamine D_{1-4} (K$_i$=11-31 nM), histamine H_1 (K$_i$= 7 nM), and adrenergic α_1 receptors (K$_i$=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ (K$_i$=57 nM) and muscarinic M_{1-5} (K$_i$=73, 96, 132, 32, and 45 nM, respectively). Olanzapine binds weakly to GABA$_A$, BZD, and β-adrenergic receptors (K$_i$>10 μM).

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT$_2$) antagonism. The mechanism of action of olanzapine in the treatment of acute manic episodes associated with Bipolar I Disorder is unknown.

Antagonism at receptors other than dopamine and $5HT_2$ may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic side effects. Olanzapine's antagonism of histamine H_1 receptors may explain its sedation observed with this drug. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics—Oral Administration—Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays three kinetic over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hours), and systemic plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about one week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of such demographic factors, gender, and age (see Special Populations).

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1130 ng/mL, binding primarily to albumin and α$_1$-acid glycoprotein.

Metabolism and Elimination—Following a single oral dose of ^{14}C-labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites were pharmacological activity at the concentrations observed.

In vitro studies with human liver microsomes ("HLM") identified oxidation and the primary metabolic pathways for olanzapine. *In vitro* studies suggest that CYP1A2 and 2D6, and the Flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 metabolizer status appears to be a minor metabolic pathway *in vivo*, because the clearance of olanzapine is not reduced in subjects who are deficient in CYP2D6.

Intramuscular Administration—ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Dose under the curve obtained after an intramuscular dose is similar to that obtained after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

Special Populations—Renal Impairment—Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that severe undetected kidney injury the degree of renal impairment is not important. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment—Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function (5 nonsmokers) with mild clinically significant (Child-Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Age—In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater (a slightly half-life) than in non-elderly subjects (see DOSAGE AND ADMINISTRATION). Elderly subjects exhibited somewhat greater sensitivity to the pharmacodynamic effects of olanzapine.

Gender—Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be routine.

Smoking Status—Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race—In vitro studies have shown that experience are similar among Japanese, Chinese and Caucasians, suggesting other considerations for race except differences. Dosage modifications for race are, therefore, not recommended.

Combined Effects—The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine (see DOSAGE AND ADMINISTRATION).

For specific information about the pharmacology of lithium or valproate, refer to the CLINICAL PHARMACOLOGY section of the package inserts for these other products.

CLINICAL EFFICACY DATA: Schizophrenia—The efficacy of oral olanzapine in the treatment of schizophrenia was established in 2 short-term (6-week) controlled trials of inpatients who met DSM-III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in one of the two trials, but this trial did not compare these two drugs on the full range of clinically relevant doses for both.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenics. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second multidimensional instrument, the Clinical Global Impression (CGI), utilizes the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two newly developed measures were employed: these included the 30-item Positive and Negative Symptom Scale (PANSS), in which are embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total, BPRS psychosis cluster, PANSS negative subscale or SANS, and CGI Severity. The results for the trials follow:

(1) In the 6-week, placebo-controlled trial (n=149) involving fixed dosage regimens (5 and 10 mg/day) and flexible dosage regimens (5-20 mg/day), olanzapine, at 10 mg/day (but not at 5 mg/day), was superior to placebo on the PANSS total score (also on the extended BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In the 6-week, placebo-controlled trial (n=235) involving 3 fixed dose ranges of olanzapine (5 ± 2.5 mg/day, 10 ± 2.5 mg/day, and 15 ± 2.5 mg/day) on a once daily schedule, the two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI Severity scores. The highest olanzapine dose group was also superior to placebo on the SANS. There was no clear advantage for the high dose group over the medium dose group.

(Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings).

In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open label treatment for at least 8 weeks were randomized in continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in PANSS positive symptoms or hospitalization, was planned for 12 months; however, patients were rerandomized to placebo due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 9 months.

Bipolar Disorder—Monotherapy—The efficacy of oral olanzapine in the treatment of acute manic or mixed episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in patients who met the DSM-IV criteria for bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician rated scale traditionally used to assess the degree of manic psychopathology (irritability, disinhibition/aggression behavior, elevy, elevated mood, speech, increased activity, sexual interest, sleep, disruptive/aggressive behavior, appearance, and insight) to a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In the 3-week, placebo-controlled trial (n=431) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar disorder who had responded during an initial open-label treatment phase for about two weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 99 and 56% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to ≤12 and HAM-D 21 to ≤8. Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to ≥16, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Combination Therapy—The efficacy of oral olanzapine with concomitant lithium or valproate in the treatment of acute manic episodes was established in two randomized trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

(1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in the therapeutic range of 0.8 mEq/L to 1.2 mEq/L or 75 μg/mL to 125 μg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.8 mEq/L to 1.2 mEq/L or 75 μg/mL to 125 μg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

Agitation Associated with Schizophrenia and Bipolar I Mania—The efficacy of intramuscular olanzapine for injection for the treatment of agitation was established in 2 short-term (24 hours of IM treatment) placebo-controlled trials in agitated inpatients from two diagnostic groups: schizophrenics and Bipolar I Disorder (manic or mixed episodes). Both of these trials included a single active comparator treatment arm of either haloperidol injection (haloperidol lactate) or lorazepam injection (lorazepam clinical study). Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation/aggression sufficient to require rapid control. The primary measure used to assess the effects of olanzapine, haloperidol, and lorazepam in these trials was the Excited Component of the 5-factor model of the Positive and Negative Syndrome Scale (PANSS) (Excited Component [i.e., poor cooperation, excitement, tension, uncooperativeness and excitement items] with at least one withdrawal item score of ≥4 using a 1-7 severity system (1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderately severe, 6=severe, 7=extreme). The mean baseline PANSS Excited Component score was 14.4, with scores ranging from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measures used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to three injections during the 24 hour treatment period; however, patients could and rarely received the second injection soon after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

(1) In a double-blind trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270), four fixed intramuscular olanzapine for injection doses (2.5 mg, 5 mg, 7.5 mg and 10 mg) were evaluated. All doses were statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the three highest doses. There were no significant additive differences for the 7.5 and 10 mg doses over the 5 mg dose.

(2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=311), one fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

(3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for Bipolar I Disorder (and exclusively displaying an acute manic or mixed episode with or without psychotic features) (n=201), one fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

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Exhibit H
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

006021

Table 1. Changes in Fasting Lipids Values from Adult Placebo-Controlled Olanzapine Monotherapy Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	745	39.2%*
		Placebo	488	20.1%
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Olanzapine	457	9.2%*
		Placebo	261	4.1%
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	138	30.3%*
		Placebo	83	20.0%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.2%*
		Placebo	488	10.1%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	392	2.8%
		Placebo	207	2.4%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Olanzapine	222	23.3%*
		Placebo	112	12.5%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	538	23.7%*
		Placebo	304	14.1%
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	174	0%
		Placebo	82	1.2%
	Borderline to High (≥100 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	202	10.8%
		Placebo	173	8.1%

* Statistically significant compared to placebo.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL, in phase 1 of CATIE, the mean increase in total cholesterol was 5.4 mg/dL.

Olanzapine Monotherapy in Adolescents—The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (mania or mixed episodes) (3 weeks), the fasting lipid, cholesterol, or statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Table 2 shows categorical changes in fasting lipid values in adolescent patients.

Table 2. Changes in Fasting Lipids Values from Adolescent Placebo-Controlled Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	138	37.0%*
		Placebo	86	15.2%
	Normal to High (<90 mg/dL to ≥130 mg/dL)	Olanzapine	67	26.9%
		Placebo	34	12.7%
	Borderline to High (≥90 mg/dL and ≤130 mg/dL to >130 mg/dL)	Olanzapine	37	54.5%
		Placebo	17	35.3%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%*
		Placebo	86	4.5%
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	67	6.0%
		Placebo	42	2.3%
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥240 mg/dL)	Olanzapine	36	38.9%*
		Placebo	13	7.7%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%*
		Placebo	60	3.3%
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%
		Placebo	44	4.5%
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%*
		Placebo	8	0%

* Statistically significant compared to placebo.

Weight Gain—Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should monitor regular monitoring of weight.

Olanzapine Monotherapy in Adults—In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.8 kg, which was statistically significantly different compared to an average 0.3 kg weight loss in placebo-treated patients with a median exposure of 8 weeks; 22.5% of olanzapine-treated patients gained at least 7% of their baseline weight, which was statistically significantly different compared to 3% of placebo-treated patients, with a median exposure of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, which was statistically significantly different compared to 0.7% of placebo-treated patients, with a median exposure of 12 weeks. Clinically significant weight gain was observed across all baseline body mass index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in zero placebo-treated patients.

Fasting long-term combination therapy with olanzapine (208 studies days of exposure), 16% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

Table 3 includes data on weight gain with olanzapine pooled from 68 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 3. Weight Gain with Olanzapine Use

Parameter, Discharge wt (kg)	6 Weeks (N=4378) (%)	8 Months (N=1934) (%)	12 Months (N=778) (%)	24 Months (N=422) (%)
≥7	37	71	80	93
0-6 (0-11 lb)	57	34	25	22
7-15 (11-22 lb)	18	26	33	22
15-15 (22-33 lb)	7	12	16	18
>15 (>33 lb)	2	8	16	18

Hyperglycemia and Diabetes Mellitus—The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. In an analysis of 4 placebo-controlled olanzapine monotherapy studies in adolescent patients (ages 13 to 17 years), fasting blood glucose measurements (4 weeks) or glucose challenge (3 weeks), olanzapine-treated patients gained an average of 4.4 kg, which was statistically significantly different compared to an average of 0.2 kg in placebo-treated patients, with a median exposure of 3 weeks; 40.6% of olanzapine-treated patients gained at least 7% of their baseline body weight, which was statistically significantly different compared to 3.8% of placebo-treated patients, with a median exposure of 4 weeks; 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 2.7% of placebo-treated patients, with a median exposure of 6 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories, but mean changes in weight were greater in adolescents with BMI categories above normal at baseline. Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to zero placebo-treated patients.

Fasting long-term combination therapy with olanzapine, 69% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.4 kg.

Hyperlipidemia, Hypercholesterolemia, and Hypertriglyceridemia—A potentially fatal syndrome complex sometimes referred to as Hyperlipidemic Hyperosmolar Syndrome (HHS) has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of HHS are hyperglycemia, muscle rigidity, altered mental status and evidence of atherosclerotic vascular changes such as blood pressure, hyperlipidemia, hypertension and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

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Exhibit H
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
Page 17 of 27
006022

Exhibit H
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
Page 18 of 27

Monitoring Parameters: In a study in bundling, inactive warmer, olanzapine was associated to [illegible] with. Mean blood doses of steady state were estimated to be 1.8% of the dose given. Also, it is recommended that women receiving olanzapine should not become [illegible]

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

Geriatric Use—Of the 2500 patients in premarketing clinical studies who received olanzapine, 11% (263) were 65 years of age or older. In patients with schizophrenia, there was no evidence of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient (see BOX WARNING, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: The information below is derived from a clinical trial database for olanzapine consisting of 8021 patients with schizophrenia, 4185 patients-years of exposure in oral olanzapine, and 722 patients with exposure to intramuscular olanzapine for injection. This database includes: (1) 2500 patients who participated in multiple dose oral olanzapine premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1232 patient-years of exposure as of February 14, 1996; (2) 187 patients who participated in one dose intramuscular premarketing bipolar mania trials representing approximately 66 patient-years of exposure; (3) 181 patients who participated in an oral olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5765 patients from 88 additional oral olanzapine clinical trials as of December 31, 1996; and (5) 722 patients who participated in intramuscular olanzapine for injection premarketing trials in patients (schizophrenia, bipolar, Tourette's disease or mental retardation), as shown in the table. Information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 274 patients who participated in bipolar mania trials with approximately 22 patient-years of exposure, is included below.

The conditions and duration of treatment with olanzapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatient and outpatient, fixed-dose and dose-titration studies, and short-term or long-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmoscopic examinations.

Certain portions of the discussion below relating to objective or research safety parameters, namely, dose-dependency adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar mania or manic/mixed. However, this information is also generally applicable to bipolar mania and agitation.

Adverse events during exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used initially to classify reported adverse events.

The stated frequencies of adverse events represent the proportions of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported events do not include those events that were not judged as likely to be drug-induced (see discussion below relating to "nonspecific events"). Events during olanzapine treatment that were subsequent to discontinuation are not generally included. Events listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the events occurred during treatment with olanzapine, they were not necessarily caused by it. The entire table should be read to gain a complete understanding of the safety profile of olanzapine.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contributions of drug and nondrug factors to the adverse event incidence in the population studied.

Incidence of Adverse Events in Short-Term, Placebo-Controlled and Combination Trials—The following findings are based on premarketing trials in (1) oral olanzapine for schizophrenia, bipolar mania, a substantial trial of patients having various psychiatric symptoms in association with Alzheimer's disease (see premarketing combination trials), and (2) intramuscular olanzapine for injection in agitated patients with schizophrenia or bipolar mania.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials—Schizophrenia—Overall, there was no difference in the likelihood of discontinuation due to adverse events (5% for oral olanzapine vs 4% for placebo). However, discontinuations due to increases in ASAT were considered to be drug related (2% for oral olanzapine vs 0% for placebo) (see PRECAUTIONS).

Bipolar Mania Monotherapy—Overall, there was no difference in the incidence of discontinuation due to adverse events (2% for oral olanzapine vs 2% for placebo).

Agitation—Overall, there was no difference in the incidence of discontinuation due to adverse events (0.4% for intramuscular olanzapine for injection vs 0% for placebo).

Adverse Events Associated with Discontinuation of Treatment in Short-Term Combination Trials—Bipolar Mania Combination Therapy—In a study in patients who were already receiving either lithium or valproate monotherapy, discontinuations due to adverse events were 11% for the combination of oral olanzapine with lithium or valproate compared to 3% for patients who received lithium or valproate monotherapies. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient were: nonadherence (2%), weight gain (1%), and extrapyramidal sickness (1%).

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials—The most commonly observed adverse events associated with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Oral Olanzapine in 6-Week Trials—SCHIZOPHRENIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=240)	Placebo (N=118)
Postural hypotension	5	2
Constipation	9	3
Weight gain	6	1
Dizziness	11	4
Personality disorder[1]	7	4
Akathisia	5	1

[1] Personality disorder is the COSTART term for inadequate, non-aggressive objectionable behavior.

Common Treatment-Emergent Adverse Events Associated with the Use of Oral Olanzapine in 3-Week and 4-Week Trials—BIPOLAR MANIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=125)	Placebo (N=129)
Asthenia	15	8
Dry mouth	12	5
Constipation	11	5
Dyspepsia	11	5
Increased appetite	6	3
Somnolence	35	13
Dizziness	18	6
Tremor	5	3

There was also adverse event (somnolence) observed at an incidence of 5% or greater among intramuscular olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24-hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar mania was 8% for intramuscular olanzapine for injection and 3% on placebo.

Adverse Events Occurring at an Incidence of 2% or More Among Oral Olanzapine-Treated Patients in Short-Term, Placebo-Controlled Trials—Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 2% or more of patients treated with oral olanzapine (those not 2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

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Table 4. Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Clinical Trials* with Oral Olanzapine

Body System/Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=532)	Placebo (N=294)
Body as a Whole		
Accidental injury	12	8
Asthenia	10	9
Fever	6	2
Back pain	5	3
Chest pain	3	1
Cardiovascular System		
Postural hypotension	3	1
Tachycardia	3	1
Hypertension	2	1
Digestive System		
Dry mouth	8	3
Constipation	8	4
Dyspepsia	7	5
Vomiting	4	3
Increased appetite	3	2
Hemic and Lymphatic System		
Ecchymosis	3	3
Metabolic and Nutritional		
Edema	3	1
Peripheral edema	3	1

Body System/Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=532)	Placebo (N=294)
Musculoskeletal System		
Extremity pain		
(other than joint)	5	3
Joint pain	3	1
Nervous System		
Somnolence	25	13
Insomnia	12	11
Dizziness	11	4
Abnormal gait	6	1
Tremor	4	3
Akathisia	3	2
Hypertonia	3	2
Articulation impairment	2	1
Respiratory System		
Rhinitis	7	6
Cough increased	5	3
Pharyngitis	3	2
Special Senses		
Amblyopia	2	2
Urogenital System		
Urinary incontinence	2	1
Urinary tract infection	2	1

*Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion, depression, diarrhea, extrapyramidal symptoms, hypertonia, nervousness, paresthesia, rash, sinusitis, speech disorder, twitching, vasodilation, vertigo, yawning, hyperkinesia, amnesia, nausea, nervousness, personality disorder, abnormal thinking, abnormal vision, and urinary frequency. Personality disorder (COSTART term for disagreeable, non-aggressive objectionable behavior), rash, thinking abnormal, weight loss.

Commonly Observed Adverse Events in Short-Term Combination Trials—In the bipolar mania combination placebo-controlled trial, the most commonly observed adverse events associated with the combination of olanzapine and lithium or valproate (incidence of 5% and at least twice placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Oral Olanzapine in 6-Week Trials—BIPOLAR MANIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine with lithium or valproate (N=225)	Placebo with lithium or valproate (N=115)
Dry mouth	26	7
Weight gain	26	7
Increased appetite	24	7
Dizziness	14	7
Back pain	8	4
Constipation	8	4
Speech disorder	7	1
Increased salivation	6	2
Amnesia	5	2
Pyrexia	5	2

Adverse Events Occurring at an Incidence of 2% or More Among Oral Olanzapine-Treated Patients in Short-Term Combination Trials—Table 5 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 2% or more of patients treated with the combination of olanzapine (doses up together) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

Table 5. Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Combination Clinical Trials* with Oral Olanzapine

Body System/Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine with lithium or valproate (N=225)	Placebo with lithium or valproate (N=115)
Body as a Whole		
Asthenia	18	15
Back pain	6	4
Accidental injury	4	2
Chest pain	3	2
Cardiovascular System		
Hypertension	2	1
Digestive System		
Dry mouth	32	9
Increased appetite	24	8
Thirst	10	5
Constipation	8	4
Increased salivation	6	2
Metabolic and Nutritional Disorders		
Weight gain	26	7
Peripheral edema	6	4
Edema	2	1
Nervous System		
Somnolence	50	27
Tremor	23	13
Depression	18	17
Dizziness	14	7

Body System/Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine with lithium or valproate (N=225)	Placebo with lithium or valproate (N=115)
Nervous System (cont.)		
Speech disorder	7	1
Amnesia	5	2
Ataxia	4	2
Confusion	4	1
Euphoria	3	2
Hypokinesia	3	0
Respiratory System		
Pharyngitis	4	1
Rhinitis	3	1
Skin and Appendages		
Sweating	3	1
Acne	2	0
Dry skin	2	0
Special Senses		
Amblyopia	9	5
Abnormal vision	2	1
Urogenital System		
Dysmenorrhea	2	0
Vaginitis	2	0

*Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, abnormal dreams, accidental injury, agitation, anorexia, anxiety, asthenia, cough increased, diarrhea, dyspepsia, extrapyramidal symptoms, hypertonia, hypotension, libido decreased, nervousness, pain, paresthesia, pharyngitis, rash, rhinitis, speech disorder, sweating, twitching, vasodilation, vertigo, yawning, abnormal thinking, abnormal vision, and urinary frequency. Personality disorder (COSTART term for disagreeable, non-aggressive objectionable behavior), rash, thinking abnormal, weight loss.

†Common treatment-emergent adverse events associated with the combination of olanzapine and lithium or valproate (incidence of 5% and at least twice placebo) were: dry mouth, weight gain, increased appetite, somnolence, dizziness, tremor, asthenia, back pain, accidental injury, chest pain, confusion, euphoria, hypokinesia, speech disorder, amnesia, ataxia, abnormal vision, dry skin, and vaginitis.

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Exhibit H
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
Page 19 of 27

006024

For specific information about the adverse reactions observed with Ziprasidone, refer to the ADVERSE REACTIONS section of the package inserts for these other products.

Adverse Events Occurring at an Incidence of 1% or More Among Intramuscular Ziprasidone for Injection-Treated Patients in Short-Term, Placebo-Controlled Trials—Table 6 enumerates the treatment-emergent adverse events that occurred at 1% or more of patients treated with intramuscular ziprasidone for injection (dose range of 5.0-10 mg/injection) and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania.

Table 6. Treatment-Emergent Adverse Events: Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trials with Intramuscular Ziprasidone for Injection in Agitated Patients with Schizophrenia or Bipolar Mania*†

Body System/Adverse Event	Percentage of Patients Reporting Event	
	Ziprasidone (N=115)	Placebo (N=104)
Body as a Whole		
Asthenia	2	1
Cardiovascular System		
Hypertension	2	0
Postural hypotension	1	0
Nervous System		
Somnolence	6	3
Dizziness	4	2
Tremor	3	1

* Events reported by at least 1% of patients treated with ziprasidone for injection, except the following events which had an incidence equal to or less than placebo: agitation, anxiety, dry mouth, headache, hypertension, insomnia, nervousness.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials—Extrapyramidal Symptoms—The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analysis of factors rating akathisia during acute therapy in the same controlled clinical trial comparing three dosages of 5 fixed doses with placebo in the treatment of schizophrenia.

Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales: Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Ziprasidone in Schizophrenia—Acute Phase*

	Percentage of Patients Reporting Event			
	Placebo	Ziprasidone 5 ± 2.5 mg/day (N=68)	Ziprasidone 10 ± 2.5 mg/day (N=64)	Ziprasidone 15 ± 2.5 mg/day (N=60)
Parkinsonism†	15	14	12	14
Akathisia‡	23	18	19	27

* No statistically significant differences.
† Percentage of patients with a Simpson-Angus Scale total score ≥3.
‡ Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorically reported adverse events during acute therapy in the same controlled clinical trial comparing dosages of 5 fixed doses with placebo in the treatment of schizophrenia.

Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Events: Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Ziprasidone in Schizophrenia—Acute Phase

	Percentage of Patients Reporting Event			
	Placebo (N=68)	Ziprasidone 5 ± 2.5 mg/day (N=68)	Ziprasidone 10 ± 2.5 mg/day (N=64)	Ziprasidone 15 ± 2.5 mg/day (N=60)
Dystonic events†	1	3	1	3
Parkinsonism events‡	10	7	14	20
Akathisia events§	3	5	11*	10*
Dyskinetic events¶	4	0	2	1
Restless events#	1	0	5	3
Any extrapyramidal event	12	15	29	32*

* Statistically significantly different from placebo.
† Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.
‡ Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
§ Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
¶ Patients with the following COSTART terms were counted in this category: buccolingual syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
# Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analysis of factors rating acute dystonia during controlled clinical trials comparing fixed doses of intramuscular ziprasidone for injection with placebo in agitation. Patients in each dose group could receive up to three injections during the trials (see CLINICAL EFFICACY DATA). Patient assessments were conducted during the 24 hours following the initial dose of intramuscular ziprasidone for injection. There were no statistically significant differences from placebo.

Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales: Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Ziprasidone for Injection in Agitated Patients with Schizophrenia*

	Percentage of Patients Reporting Event			
	Placebo	Ziprasidone IM 2.5 mg	Ziprasidone IM 5 mg	Ziprasidone IM 7.5 mg	Ziprasidone IM 10 mg
Parkinsonism†	0	0	0	0	0
Akathisia‡	0	0	0	0	3

* No statistically significant differences.
† Percentage of patients with a Simpson-Angus total score ≥3.
‡ Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse events in the same controlled clinical trial comparing fixed doses of intramuscular ziprasidone for injection with placebo in agitated patients with schizophrenia. There were no statistically significant differences from placebo.

Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Events: Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Ziprasidone for Injection in Agitated Patients with Schizophrenia*

	Percentage of Patients Reporting Event			
	Placebo (N=61)	Ziprasidone IM 2.5 mg (N=62)	Ziprasidone IM 5 mg (N=61)	Ziprasidone IM 7.5 mg (N=62)	Ziprasidone IM 10 mg (N=61)
Dystonia events†	0	0	0	0	0
Parkinsonism events‡	0	0	0	0	0
Akathisia events§	0	0	0	0	0
Dyskinetic events¶	0	0	0	0	0
Restless events#	0	0	0	0	0
Any extrapyramidal event	0	4	0	0	0

* No statistically significant differences.
† Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.
‡ Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
§ Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
¶ Patients with the following COSTART terms were counted in this category: buccolingual syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
# Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

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Other Adverse Events—The following table addresses those adverse events that were not already listed in a schizophrenia trial involving fixed dosage ranges of oral olanzapine. It enumerates the percentage of patients with treatment-emergent adverse events in the three fixed-dose olanzapine groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse events for which there was a statistically significant trend.

Adverse Event	Percentage of Patients Reporting Event			
	Placebo (N=568)	Olanzapine 5 ± 2.5 mg/day (N=465)	Olanzapine 10 ± 2.5 mg/day (N=464)	Olanzapine 15 ± 2.5 mg/day (N=459)
Asthenia	15	17	19	20
Dry mouth	2	3	5	13
Rhinitis	6	6	8	9
Somnolence	19	20	30	30
Tremor	3	6	8	9

Additional Findings—In a single 6-week randomized, double-blind, fixed-dose study comparing 10 (N=299), 20 (N=295) and 40 (N=290) mg/day of olanzapine to patients with schizophrenia or schizophreniform disorder, statistically significant differences among 3 dose groups were observed for the following safety outcomes: weight gain, prolactin elevation, fatigue and dizziness. Mean baseline to endpoint increase in weight (10 mg/day: 1.8 kg; 20 mg/day: 2.3 kg; 40 mg/day: 3 kg) was observed with significant differences between 10 vs 40 mg/day, (incidence of treatment-emergent prolactin elevation >24.2 ng/mL (female) or >18.77 ng/mL (male) at any time during the trial (10 mg/day: 31.2%, 20 mg/day: 42.7%, 40 mg/day: 51.1%) with significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day; fatigue (10 mg/day: 1.3%; 20 mg/day: 2.1%; 40 mg/day: 4.6%) with significant difference between 10 vs 40 and 20 vs 40 mg/day; and dizziness (10 mg/day: 2.5%; 20 mg/day: 1.8%; 40 mg/day: 5.8%) with significant difference between 20 vs 40 mg, was observed.

Additional Findings Observed in Clinical Trials—The following findings are based on clinical trials.

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (see PRECAUTIONS).

Laboratory Changes—An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in SGPT, SGOT, and GGT (see PRECAUTIONS). Olanzapine administration was also associated with increases in serum prolactin (see PRECAUTIONS), with an asymptomatic elevation of the estimated cause in 0.37% of patients, and with an isolated PCV.

Given the common clinical relationship between antipsychotic compounds and the finding of asymptomatic associated with the administration of olanzapine in several animal models (see ANIMAL TOXICOLOGY), careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

ECG Changes—Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant discrepancies in the incidence or in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was not associated with a dose increase in heart rate of 2.4 beats per minute compared to no change among placebo patients. This slight tendency to tachycardia may be related to olanzapine's potential for inducing orthostatic changes (see PRECAUTIONS).

Other Adverse Events Observed During the Clinical Trial Evaluation of Ziprasidone—Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with oral ziprasidone (at multiple doses of ≥ mg/day) in clinical trials (5551 patients), 4 NDA patient-years of exposure). The listing may not include those events already listed in previous tables or elsewhere in labeling. Those events for which a drug cause was remote, those events too general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole—*Frequent*: dental pain and its syndromes; *infrequent*: abdomen enlarged, chills, face edema, intentional injury, malaise, maldaise, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, and sudden death; *rare*: ascites and fever, neoplasm aggravated, and tolerance death.

Cardiovascular System—*Frequent*: hypertension; *infrequent*: atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, thrombophlebitis, and ventricular extrasystoles; *rare*: arrhythmia, heart failure, and thrombosis/embolism.

Digestive System—*Frequent*: flatulence, increased salivation, and thirst; *infrequent*: dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, stomach ulceration, stomatitis, and tenesmus; *rare*: abnormal stools, bloody diarrhea, cholestatic jaundice, colitis, duodenal ulcer perforation, esophageal hemorrhage, eructation, esophageal spasm, esophageal stricture, gastric hemorrhage, gastrointestinal anemia, gastrointestinal hemorrhage, gastrointestinal obstruction, gastrointestinal perforation, gastrointestinal ulcer perforation, gastrointestinal ulceration, gastrointestinal ulcer with hemorrhage, gastrointestinal ulcer with hemorrhage and perforation, gastrointestinal ulcer with obstruction, gastrointestinal ulcer with obstruction and perforation, gastrointestinal ulcer with pain, gastrointestinal ulcer with pain and hemorrhage, gastrointestinal ulcer with pain and obstruction, gastrointestinal ulcer with pain, hemorrhage and perforation, gastrointestinal ulcer with pain, obstruction and perforation, gastrointestinal ulcer with perforation, gastrointestinal ulcer with perforation and hemorrhage, gastrointestinal ulcer with perforation and obstruction, gastrointestinal ulcer with perforation, hemorrhage and obstruction, gastrointestinal ulcer with perforation, hemorrhage and pain, gastrointestinal ulcer with perforation, obstruction and pain, gastrointestinal ulcer with perforation, pain and hemorrhage, gastrointestinal ulcer with pain, gastrointestinal ulcer with pain and hemorrhage, gastrointestinal ulcer with pain and obstruction, gastrointestinal ulcer with pain, obstruction and perforation, gastrointestinal ulcer with pain, perforation and hemorrhage, gastrointestinal ulcer with perforation, gastrointestinal ulcer with perforation and hemorrhage

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class——Olanzapine is not a controlled substance.

Preclinical and Psychological Dependence—In studies' prospectively designed to assess abuse and dependence potential, olanzapine was shown to cause acute dependence (DD) effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 10 times the maximum recommended human daily oral dose (30 mg) and rhesus monkeys administered oral doses up to 5 times the maximum recommended human daily oral dose on a mg/m² basis.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trial did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE: Human Experience—In preapproving trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there was no abnormalities indicating an adverse change in laboratory analytes or ECGs. Vital signs were usually within normal limits following overdosage.

In postmarketing reports of overdose with oral olanzapine alone, symptoms have been reported in the majority of cases, in symptomatic patients, symptoms with a 90% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious events, aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and slow patient experiencing stress prone with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/distress, convulsion, hypotension, and hypertension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In one case of death, the amount of orally ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

Overdosage Management—The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of intoxication, voluntary, or dystonic reactions of the head and neck following exposure may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION: Schizophrenia—*Usual Dose*—Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg/day are recommended.

Efficacy for schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than 10 mg/day and, the increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical reassessment. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Caution in Special Populations—The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine (see CLINICAL PHARMACOLOGY; also see Use in Patients with Concomitant Illness and Drug Interactions under PRECAUTIONS). When indicated, dose escalation should be performed with caution in these patients.

Maintenance Treatment—While there is no body of evidence available to answer the question of how long the patient treated with olanzapine should remain on it, the effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on OLANZAPINE for approximately 6 months has been followed for a period of up to 2 years (see CLINICAL EFFICACY DATA). Patients should be periodically reassessed to determine the need for maintenance treatment with olanzapine.

Bipolar Disorder—Usual Monotherapy Dose—Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the presentation of the patient-to-patient trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Maintenance Monotherapy—The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a response (taken for an average duration of 4 to 6 weeks), was demonstrated in a controlled trial (see CLINICAL EFFICACY DATA). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Bipolar Mania—Usual Dose in Combination with Lithium or Valproate—When administered in combination with lithium or valproate, oral olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals.

Short-term (3 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Switching From Conventional Antipsychotics—*Use Caution to Avoid Concomitant Use*

Administration of ZYPREXA (Olanzapine orally disintegrating tablet)—After opening package, peel back foil to expose. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place intact ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquids.

Switching From Conventional Antipsychotics to Bipolar Mania—*Usual Dose for Adjunct Patients with Schizophrenia or Bipolar Mania*—The efficacy of intramuscular olanzapine for reduction in psychotic agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant (see CLINICAL EFFICACY DATA). If additional intramuscular olanzapine doses prove to be necessary the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for duration in excess of 24 hours has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximum dosing of intramuscular olanzapine (e.g., three doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension (see PRECAUTIONS, Hematological Effects). Thus, it is recommended that patients receiving subsequent intramuscular injections be monitored for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended.

If long-term olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate (see *Schizophrenia or Bipolar Disorder* under DOSAGE AND ADMINISTRATION).

Intramuscular Dosing in Special Populations—A dose of 5 mg per injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg per injection should be considered for patients who otherwise might be predisposed to hypotensive reactions, or in more pharmacodynamically sensitive to olanzapine (see CLINICAL PHARMACOLOGY; also see Use in Patients with Concomitant Illness and Drug Interactions under PRECAUTIONS).

Administration of ZYPREXA Intramuscular—ZYPREXA Intramuscular is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for preparation of ZYPREXA Intramuscular with Sterile Water for Injection—Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. ZYPREXA Intramuscular reconstituted with Sterile Water for Injection should be used immediately before it time; after reconstitution, discard any unused portion.

The following table provides volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

Dose and Olanzapine	Volume of Injection, mL Withdraw total contents of vial
10	2
7.5	1.5
5	1
2.5	0.5

Physical Incompatibility Information—ZYPREXA Intramuscular should be reconstituted only with Sterile Water for Injection. ZYPREXA Intramuscular should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed. Lorazepam injection should not be used to sedate patients receiving ZYPREXA Intramuscular as this combination results in a delayed reconstitution time. ZYPREXA Intramuscular should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

HOW SUPPLIED: The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 12 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. The tablets are available as follows:

	TABLET STRENGTH				
	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	20 mg
Tablet No. Identification	4112 LILLY 4112	4115 LILLY 4115	4116 LILLY 4116	4117 LILLY 4117	4418 LILLY 4418	4420 LILLY 4420
NDC Codes:						
Bottles 30	NDC 0002- 4112-30	NDC 0002- 4115-30	NDC 0002- 4116 30	NDC 0002- 4117-30	NDC 0002- 4418-30	NDC 0002- 4420-30
Blister-Rx* 100	NDC 0002- 4112-32	NDC 0002- 4115 32	NDC 0002- 4116-23	NDC 0002- 4117-32	NDC 0002- 4418-32	NDC 0002- 4420-32
Bottles 1000	NDC 0002- 4112-03	NDC 0002- 4115-04	NDC 0002- 4116-04	NDC 0002- 4117-04	NDC 0002- 4418-04	NDC 0002- 4420-04

* Unit-Dose® bank dose medication, Lilly).

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:

ZYPREXA ZYDIS Tablets	TABLET STRENGTH			
	5 mg	10 mg	15 mg	20 mg
Tablet No.	4453	4454	4455	4456
Debossed	5	10	15	20
NDC Codes:				
Dose Pack 28 (Child-Resistant)	NDC 0002-4453-03	NDC 0002-4454-28	NDC 0002-4455-03	NDC 0002-4456-03

ZYPREXA is a registered trademark of Eli Lilly and Company.
ZYDIS is a registered trademark of Catalent Pharma Solutions.
ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Catalent Pharma Solutions, United Kingdom, (SHS BNL).

ZYPREXA Intramuscular is available in:
NDC 0002-7597-01 (Rx, VL7597) - 10 mg vial (1s)

Store ZYPREXA tablets, ZYPREXA ZYDIS, and ZYPREXA Intramuscular vials (before reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP]. Reconstituted ZYPREXA Intramuscular may be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP] for up to 1 hour if necessary. Discard any unused portion of reconstituted ZYPREXA Intramuscular. The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect ZYPREXA tablets and ZYPREXA ZYDIS from light and moisture. Protect ZYPREXA Intramuscular from light, do not freeze.

ANIMAL TOXICOLOGY: In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 12 mg/kg (17 times the maximum recommended human daily oral dose on a mg/m² basis), dose-related increases in lymphocytes and neutrophils in mice, and lymphocytosis in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a mg/m² basis) in studies of 3 months' duration. Nonspecific lymphopenia, correlated with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily oral dose on a mg/m² basis) for 3 months or 15 mg/kg (3 times the maximum recommended human daily oral dose on a mg/m² basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrow was normocellular or hypercellular, indicating that the reductions in circulating blood cells was probably due to peripheral (non-marrow) factors.

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PV 5199 AMP

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www.ZYPREXA.com

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ZYPREXA® (Olanzapine Tablets)
ZYPREXA® ZYDIS® (Olanzapine Orally Disintegrating Tablets)
ZYPREXA® Intramuscular (Olanzapine for Injection)

PV 5199 AMP

Exhibit H
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
Page 21 of 27

006026

SYMBYAX® (olanzapine and fluoxetine HCl capsules)

WARNING

Suicidality and Antidepressant Drugs—Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SYMBYAX or an antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SYMBYAX is not approved for use in pediatric patients. [See WARNINGS, Clinical Worsening and Suicide Risk, PRECAUTIONS, Information for Patients, and PRECAUTIONS, Pediatric Use.]

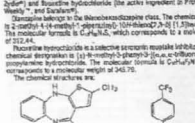
Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. In analyses of 17 placebo-controlled trials (mostly duration of 10 weeks) in these patients received a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. SYMBYAX (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with dementia-related psychosis [see WARNINGS].

DESCRIPTION: SYMBYAX® (olanzapine and fluoxetine HCl capsules) combines 2 psychotropic agents, olanzapine (the active ingredient in Zyprexa®, and Zyprexa Zydis®) and fluoxetine hydrochloride (the active ingredient in Prozac®, Prozac Weekly™, and Sarafem®).

Olanzapine belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine. Its molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44.

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI). The chemical designation is (±)-*N*-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy] propylamine hydrochloride. The molecular formula is $C_{17}H_{18}F_3NO \cdot HCl$, which corresponds to a molecular weight of 345.79.

The chemical structures are:



Olanzapine Fluoxetine hydrochloride

Olanzapine is a yellow crystalline solid, which is practically insoluble in water. Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

SYMBYAX capsules are available for oral administration in the following strength combinations:

	3 mg/ 25 mg	6 mg/ 25 mg	6 mg/ 50 mg	12 mg/ 25 mg	12 mg/ 50 mg
Olanzapine equivalent	3	6	6	12	12
Fluoxetine base equivalent	25	25	50	25	50

Each capsule also contains pregelatinized starch, gelatin, dimethicone, titanium dioxide, sodium lauryl sulfate, edible black ink, shellac base, and potassium hydroxide. Each capsule also contains pregelatinized starch, gelatin, dimethicone, titanium dioxide, sodium lauryl sulfate, edible black ink, shellac base, and ammonium hydroxide.

CLINICAL PHARMACOLOGY: Pharmacodynamics—Although the exact mechanism of SYMBYAX is unknown, it has been proposed that the activities of monoaminergic neural systems (serotonin, norepinephrine, and dopamine) is responsible for its enhanced antidepressant effect. This is supported by animal studies in which the olanzapine/fluoxetine combination has been shown to produce synergistic increases in norepinephrine and dopamine release in the prefrontal cortex compared with either component alone, as well as increases in serotonin.

Olanzapine is a psychotropic agent with high affinity binding to the following receptors: serotonin 5HT$_{2A/2C}$, 5HT$_3$, (K$_d$=4, 11, and 5 nM, respectively), dopamine D$_{1-4}$ (K$_d$=11 to 31 nM), histamine H$_1$ (K$_d$=7 nM), and adrenergic α$_1$ receptors (K$_d$=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT$_2$ (K$_d$=57 nM) and muscarinic M$_{1-5}$ (K$_d$=73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds weakly to GABA$_A$, BZD, and β-adrenergic receptors (K$_d$>10 μM). Fluoxetine is an inhibitor of the serotonin transporter and is a weak inhibitor of the norepinephrine and dopamine transporters.

Antagonism at receptors other than dopamine and 5HT$_2$ may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M$_{1-5}$ receptors may explain its anticholinergic-like effects. The antagonism of histamine H$_1$ receptors by olanzapine may explain the somnolence observed with this drug. The antagonism of α$_1$-adrenergic receptors by olanzapine may explain the orthostatic hypotension observed with this drug. Fluoxetine has relatively low affinity for muscarinic-, α$_1$-adrenergic, and histamine H$_1$ receptors.

Pharmacoelectrocardiography—Fluoxetine (administered as a 60 mg single dose or 60 mg daily for 8 days) caused a small increase in QTc mean maximum change from placebo. Olanzapine (5 mg) following a 5-mg dose, an increase in the mean area under the curve (12%) and a small decrease in mean apparent clearance of olanzapine (14%). In another study, a similar decrease in apparent clearance of olanzapine of 16% was observed following olanzapine dose of 5 or 10 mg with concomitant fluoxetine dose of 25 mg or more. This decrease in clearance reflects an increase in bioavailability. The terminal half-life is not affected, and therefore the time to reach steady state should not be altered. The overall steady-state plasma concentrations of olanzapine and fluoxetine when given as the combination in the therapeutic dose ranges were comparable with those typically attained with each of the monotherapies. The small change in olanzapine clearance, observed in both studies, likely reflects the inhibition of a minor metabolic pathway for olanzapine via CYP2D6 by fluoxetine, a potent CYP2D6 inhibitor, and was not deemed clinically significant. Therefore, the pharmacokinetics of the individual components is expected to adequately characterize the overall pharmacokinetics of the combination.

Absorption and Bioavailability—SYMBYAX—Following a single oral 12 mg/50 mg dose of SYMBYAX, peak plasma concentrations of olanzapine and fluoxetine occur at approximately 4 and 6 hours, respectively. The effect of food on the absorption and bioavailability of SYMBYAX has not been evaluated. The bioavailability of olanzapine given as Zyprexa, and the bioavailability of fluoxetine given as Prozac or olanzapine given as Zyprexa, and the bioavailability of fluoxetine given as Prozac were not significantly altered by food. It is unlikely that there would be a significant food effect on the bioavailability of SYMBYAX.

Olanzapine—Olanzapine is well absorbed and reaches peak concentrations approximately 6 hours following an oral dose. Food does not affect the rate or extent of olanzapine absorption when olanzapine is given as Zyprexa. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation.

Fluoxetine—Following a single oral 40-mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine given as Prozac, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant.

Distribution—SYMBYAX—The in vitro binding to human plasma proteins of the olanzapine/fluoxetine combination is similar to the binding of the individual components.

Olanzapine—Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1130 ng/mL, binding primarily to albumin and α$_1$-acid glycoprotein.

Fluoxetine—Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α$_1$-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated [see PRECAUTIONS, SYMBYAX is highly bound to plasma proteins].

Metabolism and Elimination—SYMBYAX—SYMBYAX therapy yielded steady-state concentrations of norfluoxetine similar to those seen with fluoxetine in the therapeutic dose ranges.

Olanzapine—Olanzapine displays linear pharmacokinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (95% confidence interval of 30 to), and plasma clearance ranges from 12 to 47 L/hr (2h to 82h percentile; mean of 25 L/hr). Administration of olanzapine once daily leads to steady-state concentrations in the second week of dosing. Olanzapine makes the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine vary between individuals on the basis of such factors as smoking status, gender, and age [see Special Populations].

Following a single oral dose of ^{14}C-labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and CYP450-mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYP1A2, CYP2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6-mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Fluoxetine—Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and to the predominant enantiomer present in plasma at steady state.

Fluoxetine is extensively metabolized in the liver to its only identified active metabolite, norfluoxetine, via the CYP450 pathway responsible for fluoxetine metabolism.

In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical Issues Related to Metabolism and Elimination—The complexity of the metabolism of fluoxetine has several consequences that may potentially affect the clinical use of SYMBYAX.

Variability in metabolism—Subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme CYP2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, sparteine/phenytoin, and the tricyclic antidepressants (TCAs). In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and had evidence higher plasma clearance of *R*-fluoxetine. Consequently, concentrations of *R*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine to these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same.

Alternate drug metabolism pathway (non-CYP2D6) when competing with the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration over a time-increasing without limit.

Because the metabolism of fluoxetine, like that of a number of other compounds including TCAs and other selective serotonin reuptake inhibitors, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions [see PRECAUTIONS, Drug Interactions].

Nonlinearity and dose elimination—The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species to chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Steady-state concentrations of fluoxetine were higher than those predicted by single-dose experiments, because the metabolism of fluoxetine is not proportional to dose. However, norfluoxetine appears to have linear pharmacokinetics. By mass balance and steady-state studies, the dose-normalized data and other studies, the steady-state levels after prolonging dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even following abrupt discontinuation, drug withdrawal will persist for the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation occurs or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine.

Special Populations—*Geriatric*—Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in geriatric patients. Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity.

In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly subjects (>65 years of age) than in non-elderly subjects (≤65 years of age).

SYMBYAX® (olanzapine and fluoxetine HCl capsules) PV 5418 AMP

The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant illnesses. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (65 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in these elderly patients.

Renal impairment—The pharmacokinetics of SYMBYAX has not been studied in patients with renal impairment. However, olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not routinely required.

Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on olanzapine metabolite elimination has not been studied.

In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renal impairment.

Hepatic impairment—Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in patients with hepatic impairment. The lowest starting dose should be considered for patients with hepatic impairment [see PRECAUTIONS, Use in Patients with Concomitant Illness and DOSAGE AND ADMINISTRATION, Special Populations].

Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function (Child-Pugh [Child-Turcotte-Pugh] Classification A and B) revealed little effect on the pharmacokinetics of olanzapine.

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in healthy subjects without liver disease. Norfluoxetine elimination was also changed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects.

Gender—Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender alone will not be needed.

Smoking Status—Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely required.

Race—No SYMBYAX pharmacokinetic study was conducted to investigate the effects of race. In vitro studies have shown that exposures to olanzapine are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race, therefore, are not routinely required.

Combined Effects—The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in olanzapine. The clearance of olanzapine in young smoking male women is 3 times higher than in elderly nonsmoking females. SYMBYAX dosage modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of the olanzapine component [see DOSAGE AND ADMINISTRATION, Special Populations].

CLINICAL STUDIES: The efficacy of SYMBYAX for the treatment of depressive episodes associated with bipolar disorder was established in 2 identically designed, 8-week, randomized, double-blind, controlled studies of patients who met Diagnostic and Statistical Manual-4th edition (DSM-IV) criteria for Bipolar I Disorder, Depressed (dosing flexible dosing of SYMBYAX (6/25, 6/50, or 12/50 mg/day), olanzapine (5 to 20 mg/day), and placebo. These studies included patients (≥18 years of age) with or without psychotic symptoms and with or without a rapid cycling course.

The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 to 60. The primary outcome measure of these studies was the change from baseline to endpoint in the MADRS total score. In both studies, SYMBYAX was statistically significantly superior to both olanzapine monotherapy and placebo in reduction of the MADRS total score. The results of the studies are summarized below (Table 1):

Table 1: MADRS Total Score
Mean Change from Baseline to Endpoint

	Treatment Group	Baseline Mean	Change in Endpoint Mean*
Study 1	SYMBYAX (N=69)	30	-18
	Olanzapine (N=150)	32	-12
	Placebo (N=151)	31	-10
Study 2	SYMBYAX (N=62)	32	-19
	Olanzapine (N=169)	33	-14
	Placebo (N=174)	31	-9

* Negative number denotes improvement from baseline.
† Statistically significant difference between olanzapine and placebo.

INDICATIONS AND USAGE: SYMBYAX is indicated for the treatment of depressive episodes associated with bipolar disorder. The efficacy of SYMBYAX was established in 2 identically designed, 8-week, randomized, double-blind clinical studies.

Unlike with unipolar depression, there are no established guidelines for the length of time patients with bipolar disorder exercising a major depressive episode should be treated with agents containing antidepressant drugs.

The effectiveness of SYMBYAX for maintaining antidepressant response to this patient population beyond 8 weeks has not been established in controlled clinical studies. Physicians who elect to use SYMBYAX for extended periods should periodically reevaluate the benefits of SYMBYAX for the individual patient.

CONTRAINDICATIONS: *Hypersensitivity*—SYMBYAX is contraindicated in patients with a known hypersensitivity to the product or any component of the product.

Monoamine Oxidase Inhibitors (MAOI)—There have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with an MAOI, and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore,

Exhibit H
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
Page 22 of 27

006027

SYMBYAX should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks (perhaps longer, particularly if fluoxetine has been used chronically and/or at higher doses [see CLINICAL PHARMACOLOGY, Accumulation and Slow Elimination]) should pass between discontinuation of SYMBYAX before starting an MAOI.

Pimozide—Concomitant use in patients taking pimozide is contraindicated [see PRECAUTIONS].

Thioridazine—Thioridazine should not be administered with SYMBYAX or administered within a minimum of 5 weeks after discontinuation of SYMBYAX [see WARNINGS, Thioridazine].

WARNINGS: *Clinical Worsening and Suicidal Risk*—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials in 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk-difference (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 2.

Table 2

Age Range	Drug-Placebo Differences in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuation of Treatment with SYMBYAX, for a description of the risks of discontinuation of SYMBYAX).

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need for close observation for emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for SYMBYAX should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

It should be noted that SYMBYAX is not approved for use in treating any indications in the pediatric population.

Screening Patients for Bipolar Disorder—A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represents such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SYMBYAX is approved for use in treating bipolar depression.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SYMBYAX (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with dementia-related psychosis (see BOX WARNING).

In olanzapine placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

Cerebrovascular Adverse Events (CVAE), Including Stroke, in Elderly Patients with Dementia-Related Psychosis—Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials

of olanzapine in elderly patients with dementia-related psychosis, in placebo-controlled trials. There was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia—Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in study 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the two highest serum concentrations was 15.9 mg/dL.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, hyperglycemia was associated with a statistically significantly greater mean change in random glucose compared to placebo (6.6 mg/dL versus -3.86 mg/dL). In patients with baseline normal random glucose levels (<140 mg/dl), 2.3% of those treated with SYMBYAX were found to have high glucose levels (≥200 mg/dL) during SYMBYAX treatment and were statistically significantly different compared to 0.2% of those treated with placebo. In patients with baseline borderline random glucose levels (≥140 mg/dL and <200 mg/dL), 24.1% of those treated with SYMBYAX were found to have high glucose levels (≥200 mg/dL) during SYMBYAX treatment and were statistically significantly different compared to 2.8% of those treated with placebo. The difference in mean changes between SYMBYAX and placebo was greater in patients with evidence of glucose dysregulation at baseline (including those patients diagnosed with diabetes mellitus or related adverse events, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥200 mg/dL, or a baseline fasting glucose level ≥126 mg/dL). These patients had a greater mean increase in HbA$_{1c}$.

Controlled fasting glucose data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL vs 0.17 mg/dL).

Glucosuria Attributed to Adolescents—The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks), or bipolar disorder (mania or mixed episodes) (3 weeks), olanzapine was associated with a statistically significantly greater mean change in fasting glucose levels compared to placebo (3.5 mg/dL versus -2.59 mg/dL). In patients with baseline normal fasting glucose levels (<100 mg/dL), 3 out of 124 (2%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus zero out of 79 (0%) of those treated with placebo.

Physicians should consider the risks and benefits when prescribing SYMBYAX to patients with an established diagnosis of diabetes mellitus, those having borderline increased blood glucose level (fasting 100-126 mg/dL, nonfasting 140-200 mg/dL). Patients taking SYMBYAX should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug. Hyperlipidemia—Undesirable alterations in lipids have been observed with SYMBYAX use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using SYMBYAX, is advised.

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with SYMBYAX use. Significant increases in total cholesterol have also been seen with SYMBYAX use.

Controlled fasting lipid data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had statistically significantly increased mean baseline-to-mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 32.6 mg/dL, respectively, compared to increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 0.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with hyperlipidemia or related adverse events, patients treated with lipid-lowering agents, or patients with high baseline lipid levels. Table 4 shows categorical changes in fasting lipid values.

Table 4: Changes in Fasting Lipids Values from Adult Placebo-Controlled Olanzapine Monotherapy Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	745	29.8%*
		Placebo	492	26.1%
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Olanzapine	457	3.2%*
		Placebo	251	4.4%
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	135	36.3%*
		Placebo	65	20.0%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	743	21.6%*
		Placebo	492	9.8%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	282	2.8%
		Placebo	207	2.4%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Olanzapine	232	23.0%*
		Placebo	112	12.5%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	536	23.7%*
		Placebo	304	14.1%
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	194	2.6%
		Placebo	82	1.2%
	Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Olanzapine	302	10.6%*
		Placebo	173	6.1%

*Statistically significant compared to placebo

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 49.5 mg/dL. In phase 1 of CATIE, the median increase in total cholesterol was 8.4 mg/dL.

Glucosuria Monotherapy in Adolescents—The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (mania or mixed episodes) (3 weeks), for fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Table 5 shows categorical changes in fasting lipid values in adolescent patients.

Table 5: Changes in Fasting Lipids Values from Adolescent Placebo-Controlled Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	138	57.0%*
		Placebo	66	15.2%
	Normal to High (<80 mg/dL to ≥130 mg/dL)	Olanzapine	67	23.9%*
		Placebo	28	10.7%
	Borderline to High (≥80 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	37	59.5%*
		Placebo	17	35.3%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%*
		Placebo	66	4.5%
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	97	6.9%
		Placebo	43	2.3%
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	36	30.9%*
		Placebo	13	7.7%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	127	17.9%
		Placebo	63	11.1%
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	69	5.1%
		Placebo	44	2.3%
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%*
		Placebo	9	0%

*Statistically significant compared to placebo

Weight Gain—Significant weight gain should be considered when prescribing SYMBYAX. Patients receiving SYMBYAX should undergo regular monitoring of weight.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, the mean weight increase for SYMBYAX-treated patients was statistically significantly greater than placebo-treated patients (4 kg vs -0.3 kg). Twenty-two percent of SYMBYAX-treated patients gained at least 7% of their baseline weight, with a median exposure of 9 weeks. This was statistically significantly greater than in placebo-treated patients (1.5%). Approximately 3% of SYMBYAX-treated patients gained at least 15% of their baseline weight, with a median exposure of 9 weeks. This was statistically significantly greater than in placebo-treated patients (0%). Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 2.5% of SYMBYAX-treated patients and zero placebo-treated patients.

Table 6 includes data on weight gain with olanzapine pooled from 65 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Exhibit H
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
Page 23 of 27
006028

Table 8: Weight Data with Olanzapine Use

Adolescent Subjects' Age (yr)	6 Weeks (No.=376) (%)	12 Months (No.=308) (%)	24 Months (No.=220) (%)
13	27	31	32
0-5 (0-11 lb)	10	24	23
5-10 (11-22 lb)	16	20	23
10-15 (23-33 lb)	2	12	18
>15 (>33 lb)	0	3	8

During long-term continuation therapy with olanzapine monotherapy (238 median days of exposure), 86% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight, whereas 22% met the criterion during long-term therapy was 3.4 kg.

Discussion Monotherapy in Adolescents—The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescents (studies ages 13 to 17 years), including those with schizophrenia (3 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine-treated patients gained an average of 4.8 kg, which was statistically significantly different compared to an average of 0.3 kg in placebo-treated patients, with a median exposure of 3 weeks; 40.8% of olanzapine-treated patients gained at least 7% of their baseline body weight, which was statistically significant compared to 9.9% of placebo-treated patients, with a median exposure of 4 weeks. 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 2.7% of placebo-treated patients, with a median exposure of 19 weeks. Clinically significant weight gain was observed across all baseline body mass index (BMI) categories. The mean change in weight was greater in adolescents with BMI categories above normal at baseline. Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to zero placebo-treated patients.

During long-term continuation therapy with olanzapine, 89% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight, Average weight gain during long-term therapy was 7.4 kg.

Orthostatic Hypotension—SYMBYAX may reduce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period.

In the bipolar depression studies, statistically significantly more orthostatic changes occurred with the SYMBYAX group compared to placebo and olanzapine groups. Orthostatic systolic blood pressure decreases of at least 20 mm Hg occurred in 7.2% (9/62), 1.4% (1/344), and 1.4% (3/222) in the SYMBYAX, olanzapine and placebo groups, respectively. Among the group of controlled clinical studies with SYMBYAX, an orthostatic systolic blood pressure decrease of ≥30 mm Hg occurred in 4% (21/512) of SYMBYAX-treated patients, 5% (10/204) of fluoxetine-treated patients, 3% (10/344) of olanzapine-treated patients, and 2% (8/443) of placebo-treated patients. In this group of studies, the incidence of syncope in SYMBYAX-treated patients was 0.4% (2/521) compared to placebo 0.2% (1/477).

In a clinical pharmacology study of SYMBYAX, three healthy subjects were discontinued from the trial after experiencing severe, but self-limited, hypotension and bradycardia that occurred 2 to 4 hours following a single 12 mg/50 mg dose of SYMBYAX. Reactions consisting of this combination of hypotension and bradycardia (and also severe hypotension and severe pause) have been observed in at least three other healthy subjects treated with various formulations of olanzapine (oral, two intramuscular). In randomized clinical studies, the incidence in patients with a ≥20 bpm decrease in orthostatic pulse concomitantly with a ≥20 mm Hg decrease in orthostatic systolic blood pressure was 0.4% (2/549) in the SYMBYAX group, 0.2% (1/456) in the placebo group, 0.9% (5/559) in the olanzapine group, and 0% (0/241) in the fluoxetine group.

SYMBYAX should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure or conduction abnormalities), cerebrovascular disease, or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Allergic Events and Rashes—In SYMBYAX premarketing clinical double-blind studies, the overall incidence of rash or allergic events in SYMBYAX-treated patients (4.9% (26/527)) was similar to that of placebo (5.2% (25/477)). The majority of the cases of rash and/or allergic events were mild; however, three patients discontinued (one due to rash, which was moderate in severity, and two due to allergic events, one of which included face edema).

In fluoxetine US clinical studies, 7% of 10,782 fluoxetine-treated patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical studies, almost a third were associated with a concomitant illness or the rash and/or urticaria appeared to be associated with the drug. Clinical findings reported in association with rash include fever, leukocytosis, arthralgia, edema, laryngeal spasm, dyspnea, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adequate treatment with antihistaminics or steroids, and all patients experiencing these events were reported to recover completely.

In fluoxetine premarketing clinical studies, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient could a definite unequivocal diagnosis be made, but it was considered to have a toxic/epidermal necrolysis, and the other, a severe desquamating illness that was considered to possibly be a vasculitis or erythema multiforme. Other patients have had systemic symptomatic syndromes suggestive of serum sickness.

Since the introduction of fluoxetine, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria have occurred in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only presenting symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenetic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Given the appearance of rash or of other possible allergic phenomena for which an alternative etiology cannot be identified, SYMBYAX should be discontinued.

Serotonin Syndrome—The development of a potentially life-threatening serotonin syndrome may occur with SSRIs and SNRIs, including SYMBYAX, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of SYMBYAX with MAOIs intended to treat depression is contraindicated (see CONTRAINDICATIONS). Monoamine Oxidase Inhibitors (MAOI) and PRECAUTIONS, Drug Interactions).

If concomitant treatment of SYMBYAX with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see PRECAUTIONS, Drug Interactions).

The concomitant use of SYMBYAX with serotonin precursors (such as tryptophan) is not recommended (see PRECAUTIONS, Drug Interactions).

SYMBYAX® (olanzapine and fluoxetine HCl capsules) PV 5416 AMP

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of olanzapine and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If after recovering from NMS, a patient requires treatment with an antipsychotic, the patient should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia—A syndrome of potentially irreversible, involuntary dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. SYMBYAX should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on SYMBYAX, drug discontinuation should be considered. However, some patients may require treatment with SYMBYAX despite the presence of the syndrome. The need for continued treatment should be reassessed periodically.

Seizures—In a study of 19 healthy male subjects, which included 8 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of bupropion produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for bupropion in the slow hydroxylators compared with the rapid hydroxylators. The rate of bupropion hydroxylation is felt to be mediated by the CYP2D6 isozyme activity. Thus, this study suggests that drugs that inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of bupropion (see PRECAUTIONS).

Fluoxetine administration produces a dose-related prolongation of the QT interval, which has been associated in nonfatal overdose, with torsades de pointes-type arrhythmias and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of biochemically metabolized (see CONTRAINDICATIONS, Thioridazine).

PRECAUTIONS: General—*Potential for Interaction of Olanzapine and Fluoxetine Products*—SYMBYAX contains the same active ingredients that are in Zyprexa and Sarafem Cycle (olanzapine and fluoxetine HCl) Weekly, and Sarafem (fluoxetine HCl). Caution should be exercised when prescribing these medications concomitantly with SYMBYAX.

Abnormal Bleeding—Published case reports have documented the occurrences of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent to these reports, epidemiological studies, both of case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of SYMBYAX and NSAIDs, aspirin, or other drugs that affect coagulation.

Hyponatremia—In the two controlled bipolar depression studies there was no statistically significant difference in the incidence of events (manic reaction or manic aggravation requiring hospitalization) between SYMBYAX- and placebo-treated patients. In one of the studies, the incidence of manic events was (7% [34/503]) in SYMBYAX-treated patients compared to (3% [13/443]) in placebo-treated patients. In the other study, the incidence of manic events was 2% (7/430) in SYMBYAX-treated patients compared to 3% (10/391) in placebo-treated patients. This limited controlled trial experience of SYMBYAX in the treatment of bipolar depression does not allow for informed these findings until additional data is obtained. Because of this and the cyclical nature of bipolar disorder, patients should be monitored closely for the development of symptoms of manic/hypomanic activity (see PRECAUTIONS).

Body Temperature Regulation—Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SYMBYAX for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., exercising, strenuous exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

Cognitive and Motor Impairment—Somnolence was a commonly reported adverse event associated with SYMBYAX treatment, occurring at a incidence of 22% in SYMBYAX patients compared with 11% in placebo patients. Somnolence should be monitored closely for the development of symptoms of manic/hypomanic activity (see PRECAUTIONS).

Discontinuation of Treatment with SYMBYAX—Events reported by withdrawal, emotional lability, hostility, agitation, disturbances in concentration, anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with fluoxetine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy, which may minimize the risk of discontinuation symptoms with this drug (see DOSAGE AND ADMINISTRATION).

Dysphagia—Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Rash—Because of the long elimination half-lives of fluoxetine and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal (see CLINICAL PHARMACOLOGY, Accumulation and slow elimination).

Hyperprolactinemia—As with other drugs that antagonize dopamine D2 receptors, SYMBYAX elevates prolactin levels, and a modest elevation persists during administration; however, possibly associated clinical manifestations (e.g., galactorrhea and breast enlargement) were infrequently observed.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro; a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer of this type. Although clinical studies such as case-control, prevalence, or cohort studies, and prevalence have been reported with prolactin-elevating compounds, the clinical significance of such findings is not known. To date, no consistent pattern of tumorigenesis has been observed in humans; however, neither clinical studies nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

Hyponatremia—Hyponatremia has been rarely reported in SYMBYAX premarketing clinical studies. In controlled trials, no SYMBYAX-treated patients had a sodium concentration below the lower limit of normal; however, a lowering of serum sodium below the reference range occurred at an incidence of 2% (10/506) of SYMBYAX patients compared with 0.2% (2/360) of placebo patients in open trials, 0.3% (5/1880) of these SYMBYAX-treated patients had a treatment-emergent sodium below the reference range.

Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported with fluoxetine. The hyponatremia appeared to be reversible when fluoxetine was discontinued. Although these cases were reported with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In two fluoxetine controlled studies in patients ≥65 years of age, 10 of 323 fluoxetine patients and 0 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed incidences were not clinically significant.

Seizures—Seizures occurred in 0.2% (4/2560) of SYMBYAX-treated patients during open-label premarketing clinical studies. No seizures occurred in the placebo-controlled SYMBYAX premarketing studies. Seizures have also been reported with olanzapine and fluoxetine monotherapy. Therefore, SYMBYAX should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of ≥65 years of age.

Transaminase Elevations—As with olanzapine, asymptomatic elevations of hepatic transaminases (ALT (SGPT), AST (SGOT)) and alkaline phosphatase have been observed with SYMBYAX. In the SYMBYAX-controlled clinical trials database, transaminase elevations (to values greater than 3 times the upper limit of the normal range) were observed in 8.3% (31/496) of patients exposed to SYMBYAX compared with 0.3% (2/594) of the placebo patients and 4.3% (15/566) of olanzapine-treated patients. The difference between SYMBYAX and placebo was statistically significant. None of these 31 SYMBYAX-treated patients experienced jaundice and three had transient elevations >200 IU/L.

In olanzapine placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (5/543) of olanzapine-treated patients compared to 0% (2/313) of the placebo patients. None of these patients experienced jaundice. In 2 of these patients, liver enzymes decreased toward normal despite continued treatment, and in 2 others, enzymes decreased upon discontinuation of olanzapine. In the remaining 3 patients, 1, unprovoked, had enzymes normalized and one elevations for 4 months after discontinuation, and the other had insufficient follow-up to determine if enzymes decreased.

Within the larger olanzapine premarketing database of about 1400 patients with baseline SGPT and SGOT, the prevalence of SGPT elevation to >200 IU/L was 2% (30/2381). Again, none of these patients experienced jaundice and other symptoms attributable to liver impairment and most had transient changes that tended to resolve with continued olanzapine treatment even without any dose adjustment. In olanzapine clinical studies, approximately 1% (23/2540) discontinued treatment due to transaminase increases.

Rare post-marketing reports of hepatitis have been received. Very rare cases of jaundice or abnormal liver function tests have been reported in the post-marketing period.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant hepatic disease (see Laboratory Tests).

Use in Patients with Concomitant Illness—Clinical experience with SYMBYAX in patients with concomitant systemic illnesses is limited (see CLINICAL PHARMACOLOGY, Renal impairment and Hepatic impairment). The following precautions for the individual components may be applicable to SYMBYAX.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical studies, SYMBYAX was associated with constipation, dry mouth, and somnolence, a process possibly related to cholinergic antagonism. Such adverse events were not often the basis for study discontinuations. SYMBYAX should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, a history of paralytic ileus, or related conditions.

In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse events were reported in olanzapine-treated patients at an incidence of at least 2% and twice the rate of placebo: somnolence (including sedation), gait abnormal, asthenia, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse events was significantly greater with olanzapine than placebo (13% vs. 8%). In a study of patients with dementia-related psychosis treated with olanzapine and an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised (see BOX WARNING and WARNINGS).

Use in Patients with Concomitant Illness—Clinical experience with SYMBYAX has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the premarket testing.

SYMBYAX® (olanzapine and fluoxetine HCl capsules) PV 5416 AMP

Exhibit H
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
Page 24 of 27
006029

Caution is advised when using SYMBYAX in cardiac patients and in patients with diseases or conditions that could affect hemodynamic responses (see WARNINGS, Orthostatic Hypotension).

In patients with diseases of the liver, the pharmacokinetics of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower dose of the fluoxetine component of SYMBYAX should be used in patients with cirrhosis. Caution is advised when using SYMBYAX in patients with diseases or conditions that could affect its metabolism (see CLINICAL PHARMACOLOGY, Hepatic Impairment and DOSING AND ADMINISTRATION, Special Populations).

Olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. SYMBYAX dosing adjustment in patients with renal impairment is not routinely required. (see CLINICAL PHARMACOLOGY, Renal Impairment).

Information for Patients—Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SYMBYAX and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions" is available for SYMBYAX. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SYMBYAX.

Clinical Worsening and Suicide Risk—Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possible changes in the medication.

Hypotension—Patients should be advised of the potential risk of hypotension and adverse events. Patients should be cautioned regularly for worsening in glucose control.

Weight Gain—Patients should be counseled that SYMBYAX may cause weight gain. Patients should have their weight monitored regularly.

Serotonin Syndrome—Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of SYMBYAX and triptans, tramadol or other serotonergic agents.

Abnormal Bleeding—Patients should be cautioned about the concomitant use of SYMBYAX and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding (see PRECAUTIONS, Abnormal Bleeding).

Alcohol—Patients should be advised to avoid alcohol while taking SYMBYAX.

Cognitive and Motor Impairment—As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them adversely.

Concomitant Medication—Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions.

Pregnancy—Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during SYMBYAX therapy.

Nursing—Patients should be advised to notify their physician if they are breast-feeding an infant.

Pharmacy Administration—Patients should be advised to take SYMBYAX exactly as prescribed, and not to discontinue taking SYMBYAX or change the dose without consulting their physician. Patients should be advised that they should not allow their supply to run out completely before obtaining their prescription.

Patients should be informed of the risk of the interaction between SYMBYAX and MAOIs, and of a minimum of 14 days between discontinuation of MAOI therapy and initiation of SYMBYAX therapy, and at least five weeks between discontinuing fluoxetine and initiating MAOI therapy (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors (MAOIs) and WARNINGS, Thioridazine).

Drug Interactions—Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions.

Concomitant Medication—Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions.

Alcohol—Patients should be advised to avoid alcohol while taking SYMBYAX

were a low index of testicular degeneration and atrophy, cessation of epididymal sperm and infertility in the male progeny. The effects of fluoxetine on parturition and on postnatal endpoints could not be assessed due to high progeny mortality.

There are no adequate and well-controlled studies with SYMBYAX in pregnant women.

SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Olanzapine—In reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (5 and 30 times the human dose on a mg/m² basis, respectively), no evidence of teratogenicity was observed. In a rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (3 times the MRHD on a mg/m² basis). Olanzapine was prolonged at 10 mg/kg/day (2 times the MRHD on a mg/m² basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (10 times the MRHD on a mg/m² basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled clinical studies with olanzapine in pregnant women. Seven pregnancies were observed during premarketing clinical studies with olanzapine, including two resulting in normal newborns, one resulting in neonatal death due to a cardiovascular defect, three therapeutic abortions, and one spontaneous abortion.

Fluoxetine—In embryo fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times the MRHD on a mg/m² basis, respectively) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in live pups, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m² basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m² basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m² basis).

Nonteratogenic Effects—Neonates exposed to fluoxetine and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no consistent evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar risks of PPHN.

When treating a pregnant woman with fluoxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION, Dosage Adjustments During Pregnancy). A prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Labor and Delivery—*SYMBYAX*—The effect of SYMBYAX on labor and delivery in humans is unknown. Parturition in rats was not affected by olanzapine. This effect of olanzapine on labor and delivery in humans is unknown.

Olanzapine—Parturition in rats was not affected by olanzapine. This effect of olanzapine on labor and delivery in humans is unknown.

Fluoxetine—The effect of fluoxetine on labor and delivery in humans is unknown. Fluoxetine crosses the placental barriers, there is the possibility that fluoxetine may have adverse effects on the newborn.

Nursing Mothers—*SYMBYAX*—There are no adequate and well-controlled studies with SYMBYAX in nursing mothers or infants. No studies have been conducted to examine the excretion of olanzapine or fluoxetine in breast milk following SYMBYAX treatment. It is recommended that women not breast-feed when receiving SYMBYAX.

Olanzapine—In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose.

Fluoxetine—Fluoxetine is excreted in human breast milk. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on fluoxetine developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the 2nd day of therapy.

Pediatric Use—Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of SYMBYAX in a child or adolescent must balance the potential risks with the clinical need.

Fluoxetine—Significant toxicity, including myotoxicity, long-term neurobehavioral and reproductive toxicity, and impaired bone development, has been observed following exposure of juvenile animals to fluoxetine. Some of these effects occurred at clinically relevant exposures.

In a study in which fluoxetine (5, 10, or 20 mg/kg) was orally administered to young rats from weanling (Postnatal Day 21) through adulthood (Day 90), male and female sexual characteristics were delayed at all doses, and growth (body weight gain, tibial length) was decreased during the dosing period in animals receiving the highest dose. At the end of the treatment period, serum levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolization and hypospermia) was observed at the high dose. When animals were evaluated after a recovery period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased reactivity at all doses and learning deficit at the high dose) and reproductive toxicities (impairment [decreased mating at all doses and impaired fertility at the high dose] were seen). In addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were noted in the high dose group, indicating that the reproductive organ effects seen at the end of treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma fluoxetine (AUC) in fluoxetine-treated juvenile rats receiving the low, intermediate, and high dose in this study were approximately 0.1–0.2 ×, 1–2 ×, and 5–10 times, respectively, the AUC exposures in pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat exposures to the males' metabolite, norfluoxetine, were approximately 0.3–0.8, 1–4, and 2–20 times, respectively, pediatric exposure at the MRD.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 10 mg/kg, subcutaneous) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and bone density. These doses did not affect overall growth (body weight gain) or skeletal length. The doses administered to juvenile mice in this study are approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area (mg/m²) basis. In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneally) during early postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric MRD on a mg/m² basis. Because of the early dosing period in this study, the significance of these findings to the approved pediatric use in humans is uncertain.

Geriatric Use—*SYMBYAX*—Clinical studies of SYMBYAX did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION).

Olanzapine—Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263 patients) were 65 years of age. In patients with schizophrenia, there was no difference on the basis of age in the frequency of discontinuation from the studies compared with younger patients. Studies in patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared with younger patients with schizophrenia. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to placebo-treated patients. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised (see BOX WARNING, WARNINGS, PRECAUTIONS, Use in Patients with Concomitant Illness and DOSAGE AND ADMINISTRATION, Special Populations).

As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient.

Fluoxetine—Of fluoxetine clinical studies (10,782 patients) included 687 patients 65 years or age and 93 patients ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients.

ADVERSE REACTIONS: The information below is derived from a premarketing clinical study database for SYMBYAX consisting of 2906 patients with various diagnoses with approximately 1561 patient-years of exposure. The conditions and duration of treatment with SYMBYAX varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and flexible-dose treatments, and short-term and long-term exposures.

Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number (i.e., reduced) number of standardized event categories.

In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The data in the tables and tabulations represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is possible that events reported during therapy were not necessarily related to drug exposure.

The procedure should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The adverse figures, however, do provide the prescribing clinician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Incidence in Controlled Clinical Studies—The following findings are based on the short-term, controlled premarketing studies in various dosages including bipolar depression.

Adverse events associated with discontinuation of treatment—Overall, 10% of the patients in the SYMBYAX group discontinued due to adverse events compared with 4.6% for placebo. Table 6 enumerates the adverse events leading to discontinuation associated with the use of SYMBYAX (incidence of at least 1% for SYMBYAX and greater than that for placebo). The bipolar depression clinical trials showed the incidence of adverse events within SYMBYAX in the bipolar depression studies and the "SYMBYAX-Controlled" column shows the incidence in the controlled SYMBYAX studies; the placebo column shows the incidence in the pooled controlled studies that included a placebo arm.

Table 7: Adverse Events Associated with Discontinuation*

Adverse Event	Percentage of Patients Reporting Event		
	SYMBYAX		Placebo
	Bipolar Depression (N=86)	SYMBYAX-Controlled (N=571)	(N=477)
Asthenia	0	1	0
Somnolence	0	2	0
Weight gain	0	2	0
Dizziness	0	1	0
Dizziness	0	1	0

*Table includes events associated with discontinuation of at least 1% and greater than placebo

Concomitant observed adverse events in controlled clinical studies—The most commonly observed adverse events associated with the use of SYMBYAX (incidence of 5% and at least twice that for placebo in the SYMBYAX-controlled database) were: asthenia, edema, increased appetite, peripheral edema, pharyngitis, somnolence, thinking abnormal, tremor, and weight gain.

Adverse events associated with an incidence of 2% or more in controlled clinical studies: Table 8 enumerates the treatment-emergent adverse events associated with the use of SYMBYAX (incidence of at least 2% for SYMBYAX and twice or more that for placebo).

Table 8: Treatment-Emergent Adverse Events: Incidence in Controlled Clinical Studies

Body System/ Adverse Event†	Percentage of Patients Reporting Event		
	SYMBYAX		Placebo
	Bipolar Depression (N=86)	SYMBYAX-Controlled (N=571)	(N=477)
Body as a Whole			
Asthenia	13	19	3
Accidental Injury	5	3	2
Fever	1	2	0
Cardiovascular System			
Hypertension	2	2	1
Tachycardia	2	2	0
Digestive System			
Diarrhea	19	11	8
Dry mouth	16	11	8
Increased appetite	13	15	4
Tooth disorder	1	2	0
Metabolic and Nutritional Disorders			
Weight gain	17	21	3
Peripheral edema	0	2	0
Edema	0	2	0
Musculoskeletal System			
Joint disorder	1	2	0
Twitching	6	3	1
Arthralgia	0	2	0
Nervous System			
Somnolence	21	22	11
Tremor	9	9	3
Thinking abnormal	6	5	2
Libido decreased	2	2	0
Hyperkinesia	2	2	1
Personality disorder	2	2	1
Libido disorder	1	2	0
Amnesia	1	2	0
Respiratory System			
Pharyngitis	4	3	2
Dyspnea	1	2	1
Special Senses			
Amblyopia	5	2	1
Ear pain	2	2	1
Otitis media	2	0	0
Speech disorder	1	2	0
Urogenital System			
Abnormal ejaculation†	7	2	1
Impotence†	2	2	1
Anorgasmia	3	2	0

†Listed are events reported by at least 2% of patients taking SYMBYAX except the following, which had an incidence on placebo at SYMBYAX: accidental pain, abnormal dreams, agitation, akathisia, anorexia, anxiety, apathy, back pain, chest pain, constipation, cough increased, depression, dizziness, dysmenorrhea (reported for gender), dyspepsia, flatulence, lib syndrome, headache, hypertonia, impotence, manic reaction, myalgia, nausea, nervousness, pain, palpitation, paresthesia, rash, rhinitis, sinusitis, sweating, vomiting.

*Adjusted for gender.

Additional Findings Observed in Clinical Studies—The following findings are based on clinical studies.

Effect on cardiac repolarization—The mean increase in QT$_c$ interval for SYMBYAX-treated patients (4.9 msec) in clinical studies was significantly greater than that for placebo-treated (-2.9 msec) and olanzapine-treated (5.6 msec) patients, but was not significantly different from fluoxetine-treated (2.7 msec) patients. There were no differences between patients treated with SYMBYAX, placebo, olanzapine, or fluoxetine in the incidence of QT$_c$ outliers (>500 msec).

Laboratory changes—In SYMBYAX clinical studies, SYMBYAX was associated with asymptomatic mean increases in alkaline phosphatase, cholesterol, GGT, and uric acid compared with placebo (see PRECAUTIONS, Laboratory Changes).

SYMBYAX was associated with a slight decrease in hemoglobin that was statistically significantly greater than that seen with placebo, olanzapine, and fluoxetine.

An exception in serum prolactin was observed with SYMBYAX. This elevation was not statistically different than that seen with olanzapine (see PRECAUTIONS, Hyperprolactinemia).

Sexual dysfunction—In the pool of combined SYMBYAX studies, there were higher rates of the treatment-emergent adverse events decreased libido, anorgasmia, impotence and abnormal ejaculation in the SYMBYAX group than in the pooled group. One case of decreased libido led to discontinuation in the SYMBYAX group. In the controlled studies that contained a fluoxetine arm, the rates of decreased libido and abnormal ejaculation in the SYMBYAX group were less than the rates in the fluoxetine group. None of the differences were statistically significant.

Sexual dysfunction, including priapism, has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, ophthalmic should routinely inquire about sexual side effects.

Vital signs—Tachycardia, bradycardia, and orthostatic hypotension have occurred in SYMBYAX-treated patients (see WARNINGS, Orthostatic Hypotension). The mean pulse of SYMBYAX-treated patients was not increased by 1.6 beats/min.

Additional findings—In a single 8-week randomized, double-blind, fixed-dose, study comparing 12 (N=186), 20 (N=204) and 40 (N=200) mg/day of olanzapine in patients with schizophrenia or schizoaffective disorder, statistically significant differences among 3 dose groups were observed for the following safety outcomes: weight gain, prolactin elevation, QTc prolongation. Mean baseline to endpoint increase in weight (10 mg/day: 1.9 kg; 20 mg/day: 2.5 kg; 40 mg/day: 3 kg) was observed with significant differences between 10 vs 40 mg/day. Incidence of treatment emergent prolactin elevation >24.2 ng/mL (female) or

Exhibit H
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

006031

≥ 10-17 mg/mL (mostly at any time during the trial (16 mg/mL: 21.2%, 20 mg/day: 20 vs. 40 mg/day: 41.7%) with significant differences between 10 vs 40 mg/day and 20 vs. 40 mg/day; fatigue (16 mg/day: 1.2%, 20 mg/day: 2.1%, 40 mg/day: 6.6%) with significant differences between 10 vs 40 and 20 vs 40 mg/day, and dizziness (10 mg/day: 2.6%, 20 mg/day: 1.8%, 40 mg/day: 6.6%) with significant differences between 20 vs 40 mg, was observed.

Other Events Observed in Clinical Studies—Following is a list of all treatment-emergent adverse events reported as anytime by individuals taking SYMBYAX in clinical studies except: (1) those listed in the body or footnotes in Table 7 and 8 above or elsewhere in labeling, (2) those for which the COSTART terms were ambiguous or misleading, (3) those events for which a causal relationship to SYMBYAX was not considered remote, and (4) events occurring in only 1 patient treated with SYMBYAX and which did not have a substantial probability of being acutely life-threatening.

Events are classified within body system categories using the following definitions: frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients, infrequent adverse events are those occurring on 1/100 to 1/1000 patients, and rare events are those occurring on <1/1000 patients.

Body as a Whole—Frequent: chills, infection, neck pain, neck rigidity, photosensitivity reaction; *Infrequent:* cellulitis, cyst, hernia, intestinal injury, intentional overdose, malaise, moniliasis, overdose, pelvic pain, suicide attempt; *Rare:* death, tolerance decreased.

Cardiovascular System—Frequent: migraine, vasodilatation; *Infrequent:* arrhythmia, bradycardia, cerebral ischemia, electrocardiogram abnormal, hypertension, [Withheld pursuant] flush, angina pectoris, stroke, syncope, acute myocardial infarction, bundle branch block, congestive heart failure, myocardial infarct, peripheral vascular disorder, T-wave inverted.

Digestive System—Frequent: increased salivation, thirst; *Infrequent:* cheilitis, colitis, eructation, esophagitis, gastritis, gastroenteritis, gingivitis, hepatomegaly, nausea and vomiting, pelvic pain, periodontal abscess, stomatitis, tooth disorder, bare epithelial disorder, fecal incontinence, gastrointestinal hemorrhage, peptic hemorrhage, intestinal obstruction, liver fatty deposit, pancreatitis.

Endocrine System—Infrequent: hypothyroidism.

Hemic and Lymphatic System—Frequent: ecchymosis; *Infrequent:* anemia, leukocytosis, lymphadenopathy; *Rare:* coagulation disorder, leukopenia, purpura, thrombocythemia.

Metabolic and Nutritional—Frequent: generalized edema, weight loss; *Infrequent:* alcohol intolerance, dehydration, glycosuria, hyperthermia, hypoglycemia, hypokalemia, obesity; *Rare:* acidosis, bilirubinemia, creatinine increased, gout, hyperkalemia, hypoglycemic reaction.

Musculoskeletal System—Infrequent: arthritis, bone disorder, generalized spasm, leg cramps, tendinous contracture, tenosynovitis; *Rare:* arthrosis, bursitis, myasthenia, myopathy, osteoporosis, rheumatoid arthritis.

Nervous System—Infrequent: abnormal gait, ataxia, buccoglossal syndrome, cerebellar ataxia, coma, confusion, depersonalization, dysarthria, emotional lability, euphoria, extrapyramidal syndrome, hostility, hypesthesia, hypokinesia, incoordination, movement disorder, myoclonus, neuralgia, neurosis, vertigo; *Rare:* acute brain syndrome, aphasia, dysphonia, libido increased, subarachnoid hemorrhage, withdrawal syndrome.

Respiratory System—Frequent: bronchitis, lung disorder; *Infrequent:* apnea, asthma, epistaxis, hiccup, hyperventilation, laryngitis, pneumonia, voice alteration, yawn; *Rare:* atelectasis, hemoptysis, laryngismus.

Skin and Appendages—Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, pruritis, psoriasis, skin discoloration, vesiculobullous rash; *Rare:* exfoliative dermatitis, maculopapular rash, seborrhea, skin ulcer.

Special Senses—Frequent: abnormal vision, taste perversion, tinnitus; *Infrequent:* abnormality of accommodation, conjunctivitis, deafness, diplopia, dry eyes, eye pain, mitosis; *Rare:* eye hemorrhage.

Urogenital System—Frequent: breast pain, menorrhagia*, urinary frequency, urinary incontinence, urinary tract infection; *Infrequent:* amenorrhea, breast enlargement, breast neoplasm, cystitis, dysuria, female lactation*, fibrocystic breast*, hematuria, hypomenorrhea*, leukorrhea*, menopause*, metrorrhagia*, oliguria, ovarian disorder*, polyuria, urinary retention, urinary urgency, urination impaired, vaginal hemorrhage*, vaginal moniliasis*, vaginitis*; *Rare:* breast carcinoma, breast engorgement, endometrial disorder*, gynecomastia*, kidney calculus, uterine fibroids enlarged*.

*Adjusted for gender.

Other Events Observed with Olanzapine or Fluoxetine Monotherapy—The following adverse events were not observed in SYMBYAX-treated patients during premarketing clinical studies but have been reported with olanzapine or fluoxetine monotherapy: aplastic anemia, cholestatic jaundice, diabetic coma, disorientation, hemolytic anemia, pancreatitis, erythema multiforme, hepatocellular necrosis, jaundice, neutropenia, priapism, pulmonary embolism, thrombocytopenia, convulsion, tardive dyskinesia, rare dizziness-like reaction, sudden unexplained death, suicidal ideation, vasculitis, venous thromboembolic events (including pulmonary embolism and deep venous thrombosis), altered thinking, transient cholesterol levels of ≥240 mg/dL, and random triglycerides levels of ≥1000 mg/dL have been reported.

DRUG ABUSE AND DEPENDENCE: *Controlled Substance Class*—SYMBYAX is not a controlled substance.

Physical and Psychological Dependence—SYMBYAX, as with fluoxetine and olanzapine, has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical studies did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and closely watch patients closely, observing them for signs of misuse or abuse of SYMBYAX (e.g., development of tolerance, increase/escalation of dose, drug-seeking behavior).

No studies in rats and rhesus monkeys designed to assess abuse and dependence potential, olanzapine administered alone was shown to cause depressive CNS effects, little or no potential of abuse or physical dependence at oral doses up to 10 (rat) and 8 (monkey) times the MRHD (20 mg) on a mg/m² basis.

OVERDOSAGE: SYMBYAX—During premarketing clinical studies of the olanzapine/fluoxetine combination, overdoses of both fluoxetine and olanzapine were reported in few study subjects. Four of the five subjects experienced loss of consciousness (3) or coma (1). No fatalities occurred.

Since the marked introduction of olanzapine in October 1996, adverse event cases involving combination use of fluoxetine and olanzapine have been reported to Eli Lilly and Company. An overdose of combination therapy is defined as confirmed or suspected ingestion of a dose of olanzapine 20 mg or greater in combination with a dose of fluoxetine 60 mg or greater. As of 1 February 2002, 13 cases of combination therapy overdose were reported, most of which involved additional substances. Adverse events associated with these reports included

somnolence, impaired consciousness (coma, lethargy), impaired neurologic function (ataxia, confusion, convulsion, dysarthria), arrhythmias, and fatality. Fatalities have been associated by exposure to additional substances including alcohol, barbiturates, amphetamine, and propoxyphene.

Olanzapine—As postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia as well as a patient that experienced short paroxysmal episodes of ventricular tachycardia), fever, delirium, seizure, possible rhabdomyolysis, multiple organ system failure, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1,500 mg.

Fluoxetine—Worldwide exposure to fluoxetine is estimated to be over 38 million patients (circa 1999). Of the 1,578 cases of overdose involving fluoxetine alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine alone, 24 resulted in a fatal outcome, 378 completely recovered, and 75 patients experienced sequelae after overdose, including abnormal accommodation, abnormal gait, confusion, nonspecific central nervous system depression, dyskinesia, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdose were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine in adult patients was 8 grams; a patient who took approximately 4 grams alone or in combination survived and recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

Among pediatric patients (ages 3 months to 17 years), there were 105 cases of overdose (primarily involving fluoxetine, SSRIs, or fluoxetine with other drugs). Six patients died, 72 patients completely recovered, 1 patient experienced renal failure, and 26 patients had an unknown outcome. One of the 6 fatalities was a 9-year-old boy who had a history of OCD, Tourette's Syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 8 months in addition to clonidine, methylphenidate, and pimozide/tics. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 2 grams, which was not lethal.

Other important adverse events reported with fluoxetine overdose (single or multiple drugs) included coma, delirium, ECG conduction disturbances (such as QT-interval prolongation and ventricular tachycardia, including torsades de pointes-type arrhythmias), hypomania, mania, neuroleptic malignant syndrome-like events, psychosis, shock, and seizure.

Management of Overdose—In managing overdose, the possibility of multiple drug involvement should be considered. In case of acute overdose, establish and maintain an airway and ensure adequate ventilation, which may include intubation. Induction of emesis is not recommended as the possibility of convulsions, seizures, or dystonic reactions of the head and neck following overdose may create a risk for aspiration. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

A specific prevention involves patients who are taking or have recently taken SYMBYAX and may have ingested excessive quantities (see DOSAGE AND ADMINISTRATION). In such cases, accumulation of the parent TCA and/or an active metabolite may increase the possibility of serious sequelae and extend the time needed for close medical observation.

Due to the large volume of distribution of olanzapine and fluoxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidote for either fluoxetine or olanzapine overdose is known. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Do not use epinephrine, dopamine, or other sympathomimetics with β-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.

The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*.

DOSAGE AND ADMINISTRATION: SYMBYAX should be administered once daily in the evening, generally beginning with the 3-mg/25-mg capsule. While lipid has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of SYMBYAX has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with SYMBYAX in a dose range of olanzapine 5 to 12 mg and fluoxetine 25 to 50 mg/day (see CLINICAL STUDIES).

The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies.

Special Populations—The dose of SYMBYAX 3 mg/25 mg is rarely to be exceeded in those patients with a predisposition to hypotensive reactions, patients with liver impairment, or patients who exhibit a combination of factors that may slow the metabolism of SYMBYAX (female gender, geriatric age, nonsmoking status) or these patients who may be pharmacodynamically sensitive to olanzapine. When indicated, dose escalation should be performed with caution in these patients. SYMBYAX has not been systematically studied in patients over 65 years of age or in patients <18 years of age (see WARNINGS, Orthostatic Hypotension, PRECAUTIONS, Pediatric Use, and Geriatric Use, and CLINICAL PHARMACOLOGY, Pharmacokinetics).

Treatment of Pregnant Women During the Third Trimester—Neonates exposed to fluoxetine, a component of SYMBYAX, and other SSRIs or SNRIs, late in the third trimester of pregnancy have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering fluoxetine in the third trimester.

Discontinuation of Treatment with SYMBYAX—Symptoms associated with discontinuation of fluoxetine, a component of SYMBYAX, and other SSRIs and SNRIs, have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy which may minimize the risk of discontinuation symptoms with this drug.

HOW SUPPLIED: SYMBYAX capsules are supplied in 3/25, 6/25, 6/50, 12/25, and 12/50-mg (mg olanzapine/mg fluoxetine equivalent) fluoxetine†) strengths.

SYMBYAX	CAPSULE STRENGTH				
	3 mg/ 25 mg	6 mg/ 25 mg	6 mg/ 50 mg	12 mg/ 25 mg	12 mg/ 50 mg
Color	Peach & Light Yellow	Mustard Yellow & Light Yellow	Mustard Yellow & Yellow	Red & Light Yellow	Red & Light Yellow
Capsule No.	PD3258	PD3257	PD3253	PD3233	PD3234
Identification	Lilly 3258 3/25	Lilly 3257 6/25	Lilly 3253 6/50	Lilly 3233 12/25	Lilly 3234 12/50
NDC Codes					
Bottles 30	0002-3258-30	0002-3257-30	0002-3253-30	0002-3233-30	0002-3234-30
Bottles 100	0002-3258-03	0002-3257-03	0002-3253-03	0002-3233-03	0002-3234-03
Bottles 1000	0002-3258-74	0002-3257-74	0002-3253-74	0002-3233-74	0002-3234-74
Blisters 8×100	0002-3258-84	0002-3257-84	0002-3253-84	0002-3233-84	0002-3234-84

† Fluoxetine base equivalent.
‡ UNIT-DOSE®, Unit Dose Medication, Lilly.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Keep tightly closed and protect from moisture.

Literature revised October 1, 2007

PV 5418 AMP

PRINTED IN USA

Lilly

Eli Lilly and Company
Indianapolis, IN 46285

www.SYMBYAX.com

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Medication Guide

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. Talk to your, or your family member's, healthcare provider about:

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.**
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

Never stop an antidepressant medicine without first talking to a healthcare provider. Stopping an antidepressant medicine suddenly can cause other symptoms.

Antidepressants are medicines used to treat depression and other illnesses. It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

Antidepressant medicines have other side effects. Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.

Antidepressant medicines can interact with other medicines. Know all of the medicines that you or your family member take. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

Not all antidepressant medicines prescribed for children are FDA approved for use in children. Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the US Food and Drug Administration for all antidepressants.

PV 5586 AMP

Patient Information revised June 21, 2007

SYMBYAX® (olanzapine and fluoxetine HCl capsules) PV 5418 AMP

Exhibit H
SOA Request for Clarification of the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI
Page 27 of 27

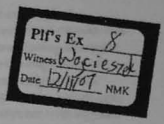
006032

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-520 – Symbyax (olanzapine/fluoxetine combination)
NDA 20-592 – Zyprexa (olanzapine) tablets
NDA 21-086 – Zyprexa Zydis (olanzapine) orally disintegrating tablets
NDA 21-253 – Zyprexa IntraMuscular (olanzapine for injection)



Eli Lilly and Company
Attention: Robin Wojcieszek, R.Ph.
Associate Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Wojcieszek:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbyax (olanzapine/fluoxetine combination), Zyprexa (olanzapine) tablets, Zyprexa Zydis (olanzapine) orally disintegrating tablets, and Zyprexa IntraMuscular (olanzapine for injection).

We also refer to your April 25, 2007 submission, containing a briefing document that summarizes results on weight gain, lipids, glucose dysregulation, and metabolic syndrome.

We have reviewed the data you have submitted thus far as well as the available literature, and we would like to request that you make the labeling changes listed below pertaining to the effect of olanzapine and Symbyax on body weight, lipids, and glucose. We anticipate that additional labeling changes will be necessary when we have reviewed the results of the additional analyses that we have requested. Given that your completing these analyses and our review of them will take some time, we believe that it is in the best interest of the public health to make interim labeling changes now based on the data that we already have available.

We request that the following language regarding hyperglycemia be implemented in the WARNINGS subsection in place of the present language in labeling regarding this risk. In addition, we request the following language regarding weight gain and hyperlipidemia be added as new WARNINGS subsections: (strike through font denotes deletions to our labeling and double underline font denotes additions).

WARNINGS

~~Hyperglycemia and Diabetes Mellitus — Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus~~

~~in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.~~

~~Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.~~

Hyperglycemia

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. The relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Olanzapine (and clozapine) treatments have been associated with a greater potential to induce hyperglycemia than other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase I of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The exposure adjusted mean increase from baseline to the average of the two highest serum concentrations of serum glucose was 13.7 mg/dl.

In another clinical trial database, where olanzapine and fluoxetine were administered individually and in combination in separate arms of the trial, a significantly higher number of patients who were normoglycemic (non-fasting blood glucose < 140 mg/dl) before treatment became hyperglycemic (non-fasting blood glucose ≥ 200 mg/dl) at some point during the 6-12 weeks of treatment (olanzapine vs. placebo: 2.4% vs. 0.3% and olanzapine/fluoxetine combination vs. placebo: 2.9% vs. 0.3% placebo). Approximately one-third of patients on olanzapine (33.3%, n=27) and one-half of patients on the olanzapine/fluoxetine combination (45.7%, n=27) who had borderline increased serum blood glucose (non-fasting, between 140 and 200 mg/dl) at the beginning of the study progressed to high blood glucose (≥ 200 mg/dl) at some time during the 6-12 weeks olanzapine treatment.

Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus or having borderline increased blood glucose level (fasting 100 – 140 mg/dl, non-fasting 140 – 200 mg/dl). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes

mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

WARNINGS

Weight Gain

In placebo-controlled, 6-week studies, olanzapine-treated patients gained an average of 2.8 kg (6.2 lb), compared to an average 0.4 kg (0.9 lb) weight loss in placebo-treated patients; 29% of olanzapine-treated patients gained greater than 7% of their baseline weight, compared to 3% of placebo-treated patients. During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg (11.9 lb).

Table 1 includes data on weight gain with olanzapine pooled from 68 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 1. Weight Gain with Olanzapine Use

Amount Gained Kg (lb)	6 weeks (N=2,976) (%)	6 months (N=1536) (%)	12 months (N=778) (%)	24 months (N=422) (%)
≤0	27	21	20	22
0-5 (0-11 lb)	57	34	25	22
5-10 (11-22 lb)	15	26	25	22
10-15 (22-33 lb)	2	12	16	18
>15 (>33 lb)	0	6	14	16

Adolescents — In pooled data from two placebo-controlled olanzapine monotherapy studies of adolescent patients with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), weight gain was reported as an adverse event in 29.6% of olanzapine-treated patients compared to 5.6% of placebo-treated patients. Olanzapine-treated patients gained an average of 2.9 kg, compared to an average of 0.2 kg in placebo-treated patients; 43.5% of olanzapine-treated patients gained greater than 7% of their baseline body weight, compared to 6.8% of placebo-treated patients. A categorization of patients by baseline on the basis of body mass index (BMI) revealed a similar mean increase in weight in the olanzapine-treated patients in each category. During long-term continuation therapy with olanzapine, 65% of olanzapine-treated patients met

the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.3 kg.

Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight.

WARNINGS

Hyperlipidemia

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. In clinical trials among olanzapine-treated patients with random triglyceride levels of <150 mg/dL at baseline (N=659), 0.5% of patients experienced triglyceride levels of ≥500 mg/dL some time during the trials. [Note to sponsor: Insert placebo data here.]. In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in fasting triglycerides in patients taking olanzapine was 40.5 mg/dL.

Modest mean increases in total cholesterol and decreases in HDL cholesterol have also been seen with olanzapine use. In phase 1 of CATIE, the median increase in fasting total cholesterol was 9.4 mg/dL.

Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised.

We request that you make these labeling changes within 30 days of this letter. In addition, we are requesting that you issue a "Dear Healthcare Practitioner" letter conveying this new prescribing information pertaining to the metabolic effects of olanzapine and Symbyax. Please submit this "Dear Health Care Practitioner" letter to us for review prior to distributing it.

We request that you include as the last paragraph of the "Dear Healthcare Practitioner" letter the following language:

> The Medical Community can further our understanding of adverse events by reporting all cases to the Agency via the MedWatch program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, via the MedWatch website at www.fda.gov/medwatch, or by mail:
>
> MEDWATCH
> Food and Drug Administration
> 5515 Security Lane
> Suite 5100, HFD-001
> Rockville, MD 20852

If you have any questions, call Sonny Saini, Pharm.D., Safety Regulatory Project Manager, at 301-796-0532.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
8/28/2007 12:36:53 PM

Charles M Beasley Jr
11/10/99 03:48 PM

To: Norma Kim Ascroft/AM/LLY@Lilly, Anna Thornton/AM/LLY@Lilly
cc: John A Krueger/AM/LLY@Lilly
Subject: Executive Steering Committee for Olanzapine-associated Weight Changes and Hyperglycemia

Anna:

Please forward my summary of the post-marketing hyperglycemia data to Norma, she may want to convert it to slide format.
Charles

---------- Forwarded by Charles M Beasley Jr/AM/LLY on 11/10/99 03:43 PM ----------

Norma Kim Ascroft
11/10/99 12:10 PM

To: Charles M Beasley Jr/AM/LLY@Lilly, Jamie Dananberg/AM/LLY@Lilly, Lawrence Gelbert/AM/LLY@Lilly, Mark L Heiman/AM/LLY@Lilly, J David Leander/AM/LLY@Lilly
cc: Norma Kim Ascroft/AM/LLY@Lilly
Subject: Executive Steering Committee for Olanzapine-associated Weight Changes and Hyperglycemia

In preparation of the Steering committee meeting on the 23rd, it would be greatly appreciated to forward electronically your 2-4 slides that will be utilized in the overviews to Barbara Whitaker, Sr Asst to Alan Breier (please cc; Norma Ascroft), by November 17, 1999. The acetates will be collated and ready for the presentation on the 23rd.
Thank you and we look forward to seeing you on the 23rd.

---------- Forwarded by Norma Kim Ascroft/AM/LLY on 11/10/99 12:04 PM ----------

Alan Breier
11/09/99 05:03 PM

To: Charles M Beasley Jr/AM/LLY@Lilly, Thomas F Bumol/AM/LLY@Lilly, Frank Bymaster/AM/LLY@Lilly, Jose F Caro/AM/LLY@Lilly, Jamie Dananberg/AM/LLY@Lilly, Richard D DiMarchi/AM/LLY@Lilly, H Christian Fibiger/AM/LLY@Lilly, Dong-Jing Fu/AM/LLY@Lilly, Lawrence Gelbert/AM/LLY@Lilly, Brian Grinnell/AM/LLY@Lilly, Mark L Heiman/AM/LLY@Lilly, Richard Deane Hockett/AM/LLY@Lilly, J David Leander/AM/LLY@Lilly, Karena Maehan/AM/LLY@Lilly, Edmundo Muniz/AM/LLY@Lilly, Steven M Paul/AM/LLY@Lilly, Gregory S Probst/AM/LLY@Lilly, Eric Ravussin/AM/LLY@Lilly, Paul R Rosteck Jr/AM/LLY@Lilly, Gary D Tollefson/AM/LLY@Lilly, Louis Vignati/AM/LLY@Lilly
cc: Norma Kim Ascroft/AM/LLY@Lilly, Alan Breier/AM/LLY@Lilly, John C Lechleiter/AM/LLY@Lilly, August M Watanabe/AM/LLY@Lilly
Subject: Executive Steering Committee for Olanzapine-associated Weight Changes and Hyperglycemia

Olanzapine-associated weight gain and possible hyperglycemia is a major threat to the long-term success of this critically important molecule. In addition, it could be argued that Eli Lilly, with its strengths in neuroscience, metabolism, endocrinology and diabetology is better positioned than any other institution to elucidate the mechanisms and developed treatments for this side effect. Thus,

ZY 1972 1720

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Zyprexa MDL Plaintiffs' Exhibit No.08262
8262-001 / 1
006039
8262-001

we have formed a cross-functional action team to meet these challenges. Success of this effort will contribute to securing the future of olanzapine and the financial health of our company, and likely spur the development of next generation antipsychotic drugs (i.e. olanzapine without the weight gain) and drugs for obesity.

A pivotal meeting of the Olanzapine-Associated Weight Changes and Hyperglycemia Cross-Functional Action Team has been placed on your calenders for **Tuesday, November 23, 1999, 3:00 PM to 5:00 PM.** The purpose of this meeting is for the Executive Steering Committee, comprised of Alan Breier, Jose Caro, Richard DiMarchi, Chris Fibiger, Steve Paul, Greg Probst and Gary Tollefson, to review the ongoing work, future study plans and resource needs and provide guidance for the scope and direction for future activities. The format of the meeting will be 1:15 minutes of presentations followed by a 45 minute closed meeting of the Steering Committee. The agenda is attached.

I want to thank you in advance for joining us to work on this important project and look forward to seeing you on the 23rd.

Alan agendaNov23Mtg.doc

ZY 1972 1721

Robert W Baker
10/10/2000 10:19 AM

To: Charles M Beasley Jr/AM/LLY@Lilly
cc:
Subject: Re: meeting with endocrinologic consultants

Dear Charles -

thanks. Agree regarding weight gain and we've been shifting in the direction of more acknowledgement and talking about potential interventions. At least within the mania group we're now testing a "sell sheet" with recommendations including that for some patients risk-benefit ratio may favor another drug with less effect on weight. Probably won't be popular internally, but we are exploring it.

From diabetes standpoint, I'm tweaking medical slides to be more cautious in tone, will forward soon for your comment.

Thanks,

R
Charles M Beasley Jr

Charles M Beasley Jr
10/10/2000 10:00 AM

To: Robert W Baker/AM/LLY@Lilly
cc: Paul Berg/AM/LLY@Lilly, Alan Breier/AM/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, W Scott Clark/AM/LLY@Lilly, John H Holcombe/AM/LLY@Lilly, Jack E Jordan/AM/LLY@Lilly, Roland Powell/AM/LLY@Lilly, Alvin H Rampey Jr/AM/LLY@Lilly, Roy N Tamura/AM/LLY@Lilly, Paula T Trzepacz/AM/LLY@Lilly

Subject: Re: meeting with endocrinologic consultants

Agree but believe that the emphasis on marketing approach is to acknowledge weight gain and not underplay it while for diabetes to becautious until we are sure.
Charles

Robert W Baker

Robert W Baker

10/10/2000 09:00 AM

To: Charles M Beasley Jr/AM/LLY@Lilly
cc: Paul Berg/AM/LLY@Lilly, Alan Breier/AM/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, W Scott Clark/AM/LLY@Lilly, John H Holcombe/AM/LLY@Lilly, Jack E Jordan/AM/LLY@Lilly, Roland Powell/AM/LLY@Lilly, Alvin H Rampey Jr/AM/LLY@Lilly, Roy N Tamura/AM/LLY@Lilly, Paula T Trzepacz/AM/LLY@Lilly

Subject: Re: meeting with endocrinologic consultants

Dear Charles:

ZY 2224 247

Actually I think that our "takes" are about the same on this - they were quite concerned about the weight issue and due to that or perhaps due to misunderstandings, they were looking for reasons to not believe our analysis. I agree that they would feel more comfortable with the analysis if we can secondarily address mean changes, or adverse effects on glycemia as you've phrased it. I would add that they are quite keen on seeing what happens to the subjects we've excluded (history of diabetes and/or baseline glucose>140). If there is anything I can do to be helpful, let me know.

Regarding the marketing side, I agree that we heard a sentiment (though not sure it is unanimous) that we should not aggressively defend ourselves; in fact I thought we were getting suggestions to more vocally tell clinicians that olanzapine may well have a diabetes problem, based again largely on weight issues. To me, this reinforces the need to take an appropriately cautious tone with our findings. On the other hand, data are data and I do not feel impelled to state the case more negatively than it appears to us; our competitors are handling that quite nicely. I do think that what to say pending more "proof" is a key area for medical and marketing discussion.

I appreciate your help with this and second your suggestion that any additional resources will be a small price to pay for the molecule.

Best,

Robert
Charles M Beasley Jr

Charles M Beasley Jr
10/10/2000 08:33 AM

To: Alan Breier/AM/LLY@Lilly
cc: Robert W Baker/AM/LLY@Lilly, Paul Berg/AM/LLY@Lilly, W Scott Clark/AM/LLY@Lilly, John H Holcombe/AM/LLY@Lilly, Roland Powell/AM/LLY@Lilly, Alvin H Rampey Jr/AM/LLY@Lilly, Roy N Tamura/AM/LLY@Lilly

Subject: Re: meeting with endocrinologic consultants

I have a somewhat different take and believe that a number of individuals in attendance did not understand what was being said. We should talk. There is the marketing approach and then the scientific analyses approach. There are 2 issues -- weight gain and hyperglycemia.

These guys were really concerned about the weight gain, not only because of a diabetes risk but all the other potential health risks. They initially thought it might simply be a response to improvement in schizophrenia with a few outliers (a rather naive view, but they ain't shrinks). When they understood that this is seen in non-psychotic "normals" and animals on fixed diets (less concern with animals) and that olanzapine is the worst offender, other than clozapine, they advocated a different marketing strategy than we are taking. They believe we should "aggressively face the issue" and work with physicians to address methods of reducing weight gain. Although we did not get into details, they seemed more interested in psychosocial and behavioral approaches than pharmacologic. There does not seem much to say about scientific analyses of weight gain, we know it's a weighty problem. When you translate 1-2% gain of 40+ kilos into the absolute number based on 5 million patients, the number is 50,000 to 100,000. 100,000 people putting on 90 pounds of weight is a lot.

On the diabetes side, the concern was about the use of categorical analyses. It was not that they necessarily did not believe our findings, but that such analyses can be very easily not believed (subtle difference), a la, Fellow Simeon Taylor and others. The issue is the arbitrary nature of any categorical analysis with respect to cut points defining a case. This is especially pertinent to our situation where diabetologists don't really like defining diabetes based on random glucoses (in spite of the info on the ADA web site). The meeting helped me appreciate the difference between 2 questions: 1) What is the rate of development of impaired glucose tollerance / diabetes associated with olanzapine relative to other agents (including placebo)? and 2) Does olanzapine adversely affect glycemia relative to other agents? We've been attempting to address the first question. It is probably the more clinically relevant question. I believe we have been doing a good job at addressing it with our methodology. The problem is the arbitrary nature of the cut points and the potential for big shifts depending on those cut points and the fact that we chose the cut points (not really, they came from ADA web site). They specifically referred to the data as being "tortured". The last time I heard this reference was in the context of the suicide analyses but there it was a positive reference. The data there had been tortured but had not surrendered. I believe another factor playing into the skepticism is the magnitude of the number of cases identified in our analyses. On the one hand, the diabetologist, who "know" what a bad glucose is and also "know" the incidence and prevalence of diabetes, probably believe that our cut points are too high (not sufficently sensitive) but on the other hand we find too many cases, even on placebo. Life is difficult when you can't have it both ways.

The group (especially 3 individuals) would feel much more comfortable with an analysis addressing the second question. They want the continuous data (using all data) analyzed over time co-varying for both static (diabetic diagnosis, baseline obesity, etc.) and dynamic co-variates (weight gain, alteration in hypoglycemic dose). Similar to David Allison, 1 or 2 would be happy to take all our data and perform the correct analyses, like we don't have competent statisticians. I will e-mail 2, one US based and the other a Brit, to get there thoughts on methodology. From my crude misunderstanding of methods, these would probably be complex analyses. I will say that I believe we should have a full time, dedicated, sophisticated, statistical resource that does nothing but hyperglycemia, no meetings, no surveys, zilch, until we have completely tortured the data. This would be a small price to pay for this molecule.

With regard to the marketing side of this issue of impaired glucose tollerance / diabetes, the message was clear. Don't get too agressive about denial, blaming it on schizophrenia, or claiming no worse than other agents until we are sure of the facts and sure that we can convince regulators and academicians. W-L with Resulin was the example. Sounds exactly like what Dan Casey was saying.

Charles

---------- Forwarded by Charles M Beasley Jr/AM/LLY on 10/10/2000 07:40 AM ----------

Robert W Baker

10/09/2000 03:42 PM

To: Charles M Beasley Jr/AM/LLY@Lilly, Alan Breier/AM/LLY@Lilly
cc: Christopher C Bomba/AM/LLY@LILLY, Patrizia Cavazzoni/AM/LLY@Lilly, Suni Keeling/AM/LLY@LILLY

Subject: Re: meeting with endocrinologic consultants

FYI. My take was that this board of academic endocrinologists was impressed enough by magnitude of weight gain and number of reports in the spontaneous adverse event database that they were predisposed toward skepticism to any analysis that did not find higher hyperglycemia rates on olanzapine than comparators.

Charles - do you think it appropriate to look at secondary analysis that does not exclude baseline abnormals and another looking at mean changes in glucose?

Alan - I believe that what Tom is referring to as "not the way Lilly typically does business" are suggestions to more vocally assert that olanzapine may have a problem on the glucose issue and, rather than moving forward with our analyses, turning all info over to an independent board for review, conclusions, and dissemination. Neither strikes me as the appropriate step, but this alarmed the Lilly attendees when linked to the Rezulon comparison. Charles did let them know that already we have sent several volumes with all our info to FDA, but I'm not sure that they fully appreciated this.

ZY 2224 249

Exhibit K, Page 3 of 6
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

Thanks,

R

---------- Forwarded by Robert W Baker/AM/LLY on 10/09/2000 03:29 PM ----------

Thomas M Brodie
10/09/2000 03:10 PM

To: Robert W Baker/AM/LLY@Lilly
cc: Eugene R Thiem/AM/LLY@LILLY

Subject: Re: meeting with endocrinologic consultants

Robert.....clearly, this group of Endocrinologists (who spoke up and I would rate those who did speak up as the leaders of the pack) are very concerned with the approach Lilly is taking towards the issue that Zyprexia leads to diabetes. I can only hope that you and all of the team who attended the NADAB meeting are gaining the ear of senior leadership and articulating this finding. Although the boards recommendation is probably not the way Lilly typically does business, I do believe they made a very strong point that unless we come clean on this, it could get much more serious than we might anticipate.

Gene, John and I were very glad to provide you with time in front of this group and if you should need additional time at future meetings (next one is Feb. 2001) please let me know. It was great meeting you as well.

Regards,
Tom

ZY 2224 250

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Zyprexa MDL Plaintiffs' Exhibit No.01453
1453-001 / 4
006044
1453-004

Robert W Baker

10/10/2000 02:40 PM

To: Charles M Beasley Jr/AM/LLY@Lilly, Alan Breier/AM/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, Jamie Dananberg/AM/LLY@Lilly, John H Holcombe/AM/LLY@Lilly, Suni Keeling/AM/LLY@LILLY, Bruce Kinon/AM/LLY@Lilly, John R Richards/AM/LLY@Lilly

cc: Thomas M Brodie/AM/LLY@Lilly, James B Gregory/AM/LLY@Lilly, Bryan Johnstone/AM/LLY@Lilly, Jack E Jordan/AM/LLY@Lilly, Michael B Murray/AM/LLY@LILLY, Eugene R Thiem/AM/LLY@LILLY, Patrick A Toalson/AM/LLY@Lilly, Paula T Trzepacz/AM/LLY@Lilly

Subject: Lilly visit from Sam Dagogojack, M.D.

Please consider meeting with Dr. Dagogojack as your schedule permits during a visit to Lilly on Friday December 8. He is an endocrinologist in Jackson, MS with particular interest in diabetes, clamping, and co-morbidity in psychiatric illnesses. The ML in his area, Pat Toalson, has been working to develop this relationship because of Dr. D.'s interests and expertise, but also because he is interested in working with us, and he has relationships with two psychiatrists who are key drivers of concerns about olanzapine and hyperglycemia: He has been a colleague and co-author with John Newcomer MD, he now is located in the same University as Henry Nasrallah, M.D.

The 12/8 visit will be consultative around marketing and sales force handling of current data. However, I will appreciate any time that you can spare to convey your personal activities and especially updating Sam on our data and ongoing plans. He's had several ideas that others may evaluate better than I, and he likely will be interested in pursuing some studies himself should we be interested. It is I know close to ACNP but has been hard to schedule.

This visit is a supplement to other efforts now underway to strengthen relationships with the Lilly Endocrine academic advisory board and consideration of assembling a board including endos to help us in an ongoing way.

Thanks,

Robert

John H Holcombe
09/08/2000 09:01 AM

To: Christopher C Bomba/AM/LLY@LILLY, Eugene R Thiem/AM/LLY@LILLY
cc: Robert W Baker/AM/LLY@Lilly, Jack E Jordan/AM/LLY@Lilly, Suni Keeling/AM/LLY@LILLY, Paula T Trzepacz/AM/LLY@Lilly
Subject: endo consultants

Gene and Chris
I agree with the names Mel Prince gave you, including Richard Rubin. I know the latter quite well. As a psychologist, he wouldn't be one to put in front of a psych audience to talk about diabetes, HOWEVER, it would be very important to have him as a consultant along with the endocrinologists to get his input on how best to proceed with educating psychiatrists about diabetes. He could do that better than anyone. He's written several books on behavior problems in diabetes, he's internationally recognized, and I likes Lilly. He has a son with type 1 diabetes...

Just about anyone on our NADAB could serve on an olanzapine board as well, with the exception of Gene Wright and Neil Brooks. I say that because neither is an expert in the pathophysiology of diabetes. Of the board members, in order, that I would suggest are the following:
Bernie Zinman
Richard Bergenstal (David Kendall works with him and we might choose David instead to build relationships..)
James Gavin (doesn't come to many NADAB meetings, but might be interested in the olanzapine issue)
Vivian Fonseca (he is incredibly bright)

Others not on the board, but should be considered are
Helmut Steinberg (spelling?) who's at IU doing the insulin clamp study with olanzapine now
Julio Rosenstock (Dallas), good friend of Lilly and a practical endo.
Ralph DeFronzo (Famous diabetologist, has done significant work on insulin resistance)

Of course we can come up with other names as well. I would suggest 10 or fewer for the board, but how many did you guys have in mind?? Endos LOVE to get involved with ad hoc issues, so I anticipate a good response.

I would be delighted to personally call any of the docs whom we'd like to invite.

I'm working from home today.. Call [Redacted] if you have questions.

John

ZY 2224 943

[redacted]

Hyperglycemia/Diabetes: Sell Sheet Implementation

For Internal Use Only
Not For Use In Detailing

Lilly
Answers That Matter.

[redacted]

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Page

Zyprexa MDL Plaintiffs' Exhibit No.01962

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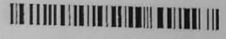

Proper implementation is key!

Our goal and focus is on creating a market with Donna. The competition wins if we are distracted into talking about diabetes. So, stand strong against their ploys and answer the AOC concisely and with confidence!

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Zyprexa MDL 1596: Confidential-Subject to Protective Orde
ZY2000967;
Page 2

Zyprexa MDL Plaintiffs' Exhibit No.01962

Exhibit L, Page 2 of 5
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

Handling the Diabetes AOC:

This is a highly competitive driven issue.

Therefore, we will NOT proactively address the diabetes concern, but rather only when it arises from an MD.

If it does, please do the following:

1. Cushion/Clarify the AOC
2. Handle by providing the verbatim
3. Check for agreement, **if not satisfied then utilize the sell sheet**
4. Restate the verbatim while utilizing the diabetes sell sheet
5. Check for agreement and get back to Donna!

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Zyprexa MDL Plaintiffs' Exhibit No.21952

Zyprexa MDL 1596: Confidential-Subject to Protective Orde
ZY20000677;
Page 8

What are the facts to convey and where do you find them within the sell sheet?

1. Diabetes is common in the general population, even reaching epidemic proportions. Moreover, **patients with mental illness are 2-4 times more likely to develop diabetes**. *(Inside cover, "Diabetes is common" section 3)*
2. As the "Diabetes Care" company, Lilly takes this issue very seriously and will continue to offer solutions. *(Not written on the sell sheet but use as a segue to the next point)*
3. When you look at various agents to treat patients with mental illness, the rate of **treatment-emergent diabetes is comparable across agents.** *(Front cover, "Comparable rates..." section 1)*

Correct tone is everything: Stay Confident and Informative

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Zyprexa MDL Plaintiffs' Exhibit No.01962

Zyprexa MDL 1596: Confidential-Subject to Protective Orde
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Page 4

Exhibit L, Page 4 of 5
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

Handling AOC - Other Risk Factors

For customers who ask about Diabetes as it relates to risk factors such as weight, please provide the following verbatim.

1. While there is a relationship between weight (or specifically obesity) and diabetes, it is not exact and constitutes one of **many** risk factors for diabetes. For example, another is hyperprolactinemia (*Inside cover, "A number of factors…" section 4)*
2. Even among the patients that had substantial weight gain with Zyprexa, over 96% had no glycemic abnormalities at all. (*Inside cover, "Weight gain…." section 2)*

Remember correct tone is critical, Confident and informative!
Our customers just want the facts and reassurance

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Zyprexa MDL Plaintiffs' Exhibit No.01962

Zyprexa MDL 1596: Confidential-Subject to Protective Orde
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Page 6

Exhibit L, Page 5 of 5
SOA Request for Clarification of
the Court's Order re: Other Drugs
Case No. 3AN-06-5630 CI

Case # 06-5630 CI CR/CI

Case Title: Stit v. Eli Lilly + CO

Type of Document Enclosed: Reply

Date Filed: 2/20 Judge: Lindsey

SEALED

No one, including court personnel, may view the contents of this envelope without a written order of the court.

Comments: Reply to motion + memo to exclude Evidence relating to Arctic York Times Article

TF-330 (6/89) (TCS Fl. Pink, 4"x5½")

Filed in the Trial Courts
STATE OF ALASKA, THIRD DISTRICT
FEB 20 2008
Clerk of the Trial Courts
By _____ Deputy

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

Filed in the Trial Courts
STATE OF ALASKA, THIRD DISTRICT
FEB 19 2008
Clerk of the Trial Courts
By _____ Deputy

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

DEFENDANT ELI LILLY AND COMPANY'S NOTICE OF FILING ITS REPLY IN FURTHER SUPPORT OF ITS MOTION IN LIMINE TO EXCLUDE EVIDENCE RELATING TO NEW YORK TIMES ARTICLES UNDER SEAL

COMES NOW Defendant Eli Lilly and Company ("Lilly") and files its Reply in Further Support of Its Motion in Limine to Exclude Evidence Relating to New York Times Articles, under seal, attached to this notice. The subject and contents of the Reply may fall under prior confidentiality rulings.

DATED this 20th day of February, 2008.

PEPPER HAMILTON LLP
Nina M. Gussack, admitted *pro hac vice*
George A. Lehner, admitted *pro hac vice*
John F. Brenner, admitted *pro hac vice*
Andrew R. Rogoff, admitted *pro hac vice*
Eric J. Rothschild, admitted *pro hac vice*
and
LANE POWELL LLC
Attorneys for Defendant

By _____
Brewster H. Jamieson, ASBA No. 8411122
Andrea E. Girolamo-Welp, ASBA No. 0211044

I certify that on February 20, 2008, a copy of the foregoing was served by hand on:

Eric T. Sanders, Esq.
Feldman Orlansky & Sanders
500 L Street, Suite 400
Anchorage, Alaska 99501-5911

009867.0038/163544.1

See Judge Rindner's order dated 6/13/08 pages 15:16 Documents unsealed #5 Lwade 8/11/08

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, v. ELI LILLY AND COMPANY, Defendant.	Case No. 3AN-06-05630 CI **[FILED UNDER SEAL]**

DEFENDANT ELI LILLY AND COMPANY'S REPLY IN FURTHER SUPPORT OF ITS MOTION IN LIMINE TO EXCLUDE EVIDENCE RELATING TO NEW YORK TIMES ARTICLES

I. INTRODUCTION

In response to Lilly's Motion in Limine to Exclude Evidence Relating to New York Times Articles, the State agrees not to offer or reference the articles at trial, however, it does intend to introduce documents referenced in *The New York Times* articles, as well as documents generated as a result of the articles. Lilly agrees that prejudice can be addressed by keeping the articles out of evidence, and can be minimized by redacting – where practicable – references to the articles in otherwise admissible documents. But where documents are so inextricably intertwined with the fact of, and references to, *The New York Times* articles that they cannot stand independent of the articles, such documents should be barred from evidence. Further, where these documents would not exist but for *The New York Times* articles, such documents should be barred, particularly given that the same evidence is available to the State from other sources.

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II. ARGUMENT

A. The Controversy Surrounding The New York Times Articles Should be Barred From Evidence.

The State does not dispute that *The New York Times* articles are unfairly prejudicial to Lilly, and agrees not to offer the articles themselves at trial. However, the State does not reveal whether they agree that reference to *the fact that the articles were written and published* is similarly prejudicial, nor do they indicate whether they agree that evidence about, or reference to, *the controversy surrounding the articles* is similarly prejudicial. Lilly underscores its objection to evidence on these points, and to references to same.

B. Where Redaction of References to The New York Times Articles is Impracticable, Documents Should be Barred From Evidence.

Lilly agrees that the fact that a document is referenced in a *New York Times* article is not a basis for exclusion, assuming the document is otherwise admissible. Lilly and the State agree that admissibility of such documents should be determined without reference to the articles.

The State agrees that prejudice to Lilly can be minimized by redacting references to the articles in documents. It seems that, at this point, disagreement comes down to one document. The State plans to offer into evidence Lilly's February 2007, three-part response submitted in solicited reply to the FDA's inquiry about the allegations in *The New York Times* articles. Parts two and three of this response arguably can be admitted without prejudice through redacting references to *The New York Times*.

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However, there is no way to alleviate the prejudice which would result from admitting part one of Lilly's response to the FDA, even if painstakingly redacted. Part one of Lilly's FDA response is an interwoven point-by-point reply to *The New York Times* allegations. The basis for, and core of, the document is *The New York Times* allegations themselves. In this part of the response, Lilly restates its interpretation of each allegation, and then formulates its response around – tailored to – each of those allegations. *See, e.g.*, Exhibit B, Regulatory Response, 2.7. Allegation #7. *The New York Times'* allegations are so integral a skeleton for part one of the FDA response that the document cannot stand independent of the references to the articles. Carving out the references through redaction would leave behind only half the story, which could be explained to the jury only through discussion of *The New York Times* articles.

The State says Lilly's FDA response demonstrates Lilly's state of mind, admissions or statements against interest, or impeachment evidence because it represents Lilly's views and explanations on particular documents and data at issue in the litigation. But this document, *these explanations*, would not exist but for the fact that unrelated third-parties conspired to violate a court order, but for the fact that *The New York Times* articles were published, and but for the fact that the FDA specifically asked Lilly to respond to *The New York Times'* allegations. The circumstances behind the generation of this document were unique, and do not approximate or resemble that of a typical submission to the FDA which might be prepared in the course of normal business. *The New York Times* allegations were created by a layman journalist using a biased selection of Lilly's internal documents. In

preparing part one of the response to the FDA, Lilly had to presume what documents in the selection the newspaper used for its story, estimate which allegations the writer conjured from which documents, and formulate a response to the allegations based on this effort. Lilly's statements in part one of the FDA response are perhaps Lilly's views and explanations regarding *The New York Times* articles, which were conclusions drawn by a layperson from a biased selection of documents. It would be unfair to offer this unique effort as evidence probative on issues in this litigation. This document is derivative of illegal acts committed by unrelated third-parties. Lilly should not be prejudiced by fruits of this poisonous tree. The unfairness to Lilly is heightened by the fact that the same evidence the State seeks to offer here is available through other admissible documents.

III. CONCLUSION

For the foregoing reasons, Lilly requests this Court enter an Order excluding from evidence *The New York Times* articles, and any references to same.

DATED this 20th day of February, 2008.

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George A. Lehner, admitted *pro hac vice*
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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT AT ANCHORAGE

Filed in the Trial Courts
STATE OF ALASKA, THIRD DISTRICT

FEB 14 2008

Clerk of the Trial Courts
By _____ Deputy

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

ELI LILLY'S NOTICE OF FILING UNDER SEAL

Defendant Eli Lilly, by and through counsel of record, files its Objection to the State of Alaska's Motions in Limine to Exclude Evidence Realting to Zyuprexa's Efficacy or Benefits of Zyprexa for (1) Indicated Uses, and (2) Non-Indicated or "Off-Label" Uses, attached to this notice. Portions of the exhibits may be confidential.

DATED this 14th day of February, 2008.

See Judge Rindner's order 9 6/13/08, page 17 #8 Levade 8/11/08

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Pages 6066A-6146

Case # 06-5680 CF CR/CI

Case Title: State v. Eli Lilly + Co

Type of Document Enclosed: objection to motion in limine

Date Filed: 8/14 Judge: Rindner

*

SEALED

No one, including court personnel, may view the contents of this envelope without a written order of the court.

Comments: Re: Motion in limine to exclude findings relating to Zyprexa's Efficacy

TF-330 (8/99) (TCB Fl. Pink, 4"x5½")

* See Judge Rindner's order of 6/13/08 page 17, #8

Documents unsealed

Wade 8/11/08

Pages 6066A-6146

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

Filed in the Trial Courts
STATE OF ALASKA, THIRD DISTRICT
FEB 20 2008
Clerk of the Trial Courts
By _____ Deputy

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

DEFENDANT ELI LILLY AND COMPANY'S NOTICE OF FILING REPLY IN FURTHER SUPPORT OF ITS MOTION IN LIMINE TO EXCLUDE REFERENCES TO RECENT REGULATORY COMMUNICATIONS AND DEVELOPMENTS UNDER SEAL

COMES NOW Defendant Eli Lilly and Company ("Lilly") and files its Reply in Further Support of Its Motion in Limine to Exclude References to Recent Regulatory Communications and Developments, under seal, attached to this notice. The subject and contents of the Reply may fall under prior confidentiality rulings.

DATED this 20th day of February, 2008.

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See Judge Rindner's order of 6/13/08, page 16 #6 Documents unsealed
Judge 8/11/08

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Pages 6059A-6065

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
v.	)	
	)	
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	Case No. 3AN-06-05630 CI
	)	

SUPPLEMENTAL ORDER REGARDING EVIDENCE OF THE DEFENDANT'S PROFITS, NET WORTH, AND THE PRICE OF ZYPREXA

IT IS HEREBY ORDERED that the parties may not offer evidence that relates to: (1) Lilly's profits, (2) Lilly's net worth, or (3) the price of Zyprexa. The parties may, however, offer argument and evidence that Lilly's profit motive during time periods relevant to this case was, or was not, affected by the expiration of Lilly's patent on Prozac.

DATED this ____ day of _____, 2008.

BY THE COURT

_____
Mark Rindner
Superior Court Judge

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006059A

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

[FILED UNDER SEAL]

DEFENDANT ELI LILLY AND COMPANY'S REPLY IN FURTHER SUPPORT OF ITS MOTION IN LIMINE TO EXCLUDE REFERENCES TO RECENT REGULATORY COMMUNICATIONS AND DEVELOPMENTS

Defendant Eli Lilly and Company ("Lilly") submits this reply to respond to several arguments made by the State in its Response to Defendant's Motion to Exclude References to Recent Regulatory Communications and Developments. As set forth in detail below, the State's arguments are without merit, and Lilly's Motion should be granted.

I. EVIDENCE RELATED TO 2007 REGULATORY COMMUNICATIONS AND DEVELOPMENTS IS NOT "RELEVANT" AS DEFINED BY THE RULES OF EVIDENCE.

The State argues that the March 2007 FDA letter and the October 2007 Zyprexa® label change are "relevant" to this action because they tend to prove that Zyprexa's prior warnings were inadequate, and that Lilly fraudulently failed to reveal a causal link between Zyprexa and diabetes. But the State has not recanted its earlier acknowledgements that Zyprexa's diabetes and hyperglycemia warnings were adequate as of the September 2003

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label change,[1] and that the 2003 label change revealed Lilly's alleged fraud.[2] Moreover, the State has claimed that "the [alleged] link between Zyprexa and diabetes became known" when the 2003 warnings change occurred, and its designee, David Campana, testified that the State knew, by the fall of 2004, that Zyprexa caused diabetes.[3]

If the State was aware, as of the 2003 label change, that the earlier warnings were inadequate, and was aware by the fall of 2004 of the alleged causal link, then the 2007 regulatory evidence has negligible probative value with respect to those facts, and, by definition, its prejudicial effect outweighs its probative value. Under Alaska Rule of Evidence 403, this evidence must be excluded.

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[1] *See, e.g.*, Pl's Memo. Describing Its Claims and Proofs at 15 ("[O]nce adequate warnings were given in the United States regarding Zyprexa's risks, physicians' prescribing practices changed and the number of prescriptions went down"); 16 ("[W]hen adequate warnings were given, the number of prescriptions decreased"); 19 ("Lilly did not provide these warnings until forced to do so by the FDA"); 20 ("The State will show the lack of adequate warning through expert testimony and by demonstrating the 75 percent drop in new prescriptions when proper warnings were given in Japan, as well as the drop-off in prescriptions in the United States after warnings were provided").

[2] Pl's Memo Describing Its Claims And Proofs at 27 ("[W]hen Lilly began to issue adequate warnings, prescriptions decreased, demonstrating that physicians as a whole relied upon the misrepresentations, and altered their prescribing practices once those misrepresentations were revealed").

[3] *See* Transcript of September 19, 2007 Videotaped Deposition of State of Alaska 30(b)(6) Designee David Campana, relevant portions of which are attached as Exhibit F, at 260-69 (testifying that, in fall 2004, or perhaps earlier, he had gathered information he interpreted to be communicating that Zyprexa caused diabetes, yet never required prior authorization for Medicaid reimbursement of Zyprexa prescriptions, implemented a "step-edit" procedure, or created a PDL for antipsychotics).

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II. THE STATE'S "TOO LATE FOR EXPERT TESTIMONY" ARGUMENT IS WITHOUT MERIT.

The State argues that the October 2007 label change and the December 2007 deposition of Lilly's 30(b)(6) designee occurred too late to be built into the reports of the State's warnings experts. Lilly does not dispute that the evidence in question was obtained late in the discovery period. However, as explained in Lilly's Motion in Limine, this Court had made specific provisions for the parties to seek extra time should the need for supplemental expert testimony arise.[4] The State offers no explanation for its failure to avail itself of this process; instead, it merely cites the expiration of the original expert deadline to explain its failure to supplement its reports.

Moreover, it was the State that insisted that this case be rushed to trial under an unprecedented bifurcation scheme, as an antidote to its own production failures. If Zyprexa's label change created the need for additional discovery and amended expert reports, the State should have agreed to the extension Lilly requested (because of continuing problems obtaining the State's Medicaid database). After ensuring that no additional time would be forthcoming, the State can not now complain that it did not have enough time. Under no circumstances should the State's experts be allowed to discuss this evidence at trial, absent the required disclosures in their expert reports.

---

[4] *See* Defendant Eli Lilly and Company's Motion in Limine to Exclude Evidence of Recent Regulatory Communications and Developments ("Lilly Br."), at 5.

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III. THE STATE CANNOT INTRODUCE THE 2007 REGULATORY EVIDENCE WITHOUT EXPERT TESTIMONY.

The State also argues that the 2007 regulatory evidence can be introduced without the testimony of an expert, because it does not require "scientific, technical or other specialized knowledge" for evaluation by the jury. Rather, the State argues, the testimony of Lilly's 30(b)(6) designee and other fact witnesses, as well as the State's fact and expert witnesses testifying about "general scientific issues," will be "more than sufficient" for the jury to "draw appropriate conclusions."[5] The State is effectively attempting to argue that a label change is *per se* evidence of the inadequacy of the prior label. This is not the case, as labels routinely evolve over time as the FDA and prescription drug manufacturers remain abreast of the latest scientific knowledge.

Thus, the State must demonstrate that the 2007 regulatory evidence indicates that the September 2003 label did not adequately disclose known risks of Zyprexa. This cannot be argued by the State, or inferred by the jury, on the present record. Rather, as explained in Lilly's Motion, adequacy of a prescription drug label in a product liability case is a subject that must be introduced to the jury through the testimony of an expert.[6] Because the State has

[5] State's Br. at 7.

[6] *See, e.g., Brown v. SmithKline Beecham Corp.*, 2008 WL 205410, *5 (N.D. Ill. 2008); *Beale v. Biomet, Inc.* 492 F. Supp. 2d 1360, 1369 (S.D. Fla. 2007); *Webster v. Pacesetter, Inc.*, 259 F. Supp. 2d 27, 36 (D.D.C. 2003); *Willard v. Park Industries,* 69 F. Supp. 2d 268, 272 (D.N.H. 1999); *Burton v. Danek Medical, Inc.*, 1999 WL 118020, *8 (E.D. Pa. 1999).

not produced an expert report analyzing this evidence, and therefore has no expert who can testify about it to the jury, it may not introduce the evidence at trial.

IV. EVIDENCE OF THE OCTOBER 2007 LABEL CHANGE SHOULD BE EXCLUDED AS A SUBSEQUENT REMEDIAL MEASURE.

The State argues that, because Alaska Rule of Evidence 407 permits the introduction of evidence of subsequent remedial measures to prove "defective condition in a products liability case," evidence of the 2007 FDA letter and 2007 Zyprexa label change cannot be excluded under this rule.[7] In fact, notwithstanding this exception, the Alaska rule provides that such evidence is "not admissible to prove negligence . . . ."[8] The State still has an active negligence claim in this lawsuit. Accordingly, regardless of whether the so-called "exception" for "defective conditions" would encompass the State's product liability warnings claim, the 2007 regulatory evidence is clearly excluded under Rule 407.

The State also argues that the jury should be allowed to consider the label change because it was directed by the FDA and was not "voluntary" on Lilly's part. This amounts to a concession that the FDA's comprehensive authority over all issues related to prescription drug labeling preempts the State's warnings claims as well as its UTPCPA claims related to Zyprexa's label, and makes clear that the label change should not be considered or weighed by a jury deciding state law claims.

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[7] State's Br. at 7, citing Alaska R. Evid. 407.

[8] Alaska R. Evid. 407.

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V. CONCLUSION

For these reasons, and as set forth in greater detail in Lilly's Motion in Limine, this Court should bar the State of Alaska from introducing into evidence at trial (i) communications to or from the United States Food and Drug Administration ("FDA"), and (ii) other regulatory communications or developments concerning Zyprexa labeling, occurring after March 1, 2004.

DATED this 20th day of February, 2008.

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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

DEFENDANT ELI LILLY AND COMPANY'S OBJECTION TO THE STATE OF ALASKA'S MOTIONS IN LIMINE TO EXCLUDE EVIDENCE RELATING TO ZYPREXA'S EFFICACY OR BENEFITS OF ZYPREXA FOR (1) INDICATED USES, AND (2) NON-INDICATED OR "OFF-LABEL" USES

The State of Alaska's two motions seeking to prohibit Eli Lilly and Company ("Lilly") from introducing evidence of Zyprexa's efficacy or benefits, either for indicated uses or non-indicated uses, should be denied because evidence of efficacy is relevant to the State's claims that Lilly's marketing actions constituted Unfair Trade Practices Consumer Protection Act ("UTPCPA") violations and also relevant to its failure-to-warn claim. There is also a broader relevance argument, as in this case about a prescription medicine that remains an important treatment for mentally ill patients, the State is trying to strip Phase 1 of this trial of any information about what the medication actually does for patients.

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I. EVIDENCE OF ZYPREXA'S EFFICACY IS RELEVANT TO DEMONSTRATE THAT LILLY'S ACTIONS DID NOT CONSTITUTE "UNFAIR TRADE PRACTICES" UNDER THE UTPCPA.

A. The State's Articulation of its Own Claims Prove the Relevance of Evidence of Efficacy, Use or Benefits of Zyprexa.

The State's proposed UTPCPA claims include that Lilly "represented Zyprexa to have characteristics, uses, benefits and/or qualities that it did not have" and "represented that Zyprexa was of a particular standard, quality, and grade suitable for consumption when in fact it was not."[1] The State proposes to prove these claims with "evidence that Lilly through its representatives marketed Zyprexa as safe and effective, both for uses for which it was approved by the FDA and for many uses that were not approved."[2] By attacking the "uses," "benefits," "qualities" and "standard" of Zyprexa, the State directly challenges the asserted efficacy, benefits, or uses of the medication. Evidence of efficacy and benefits is therefore relevant to the State's UTPCPA claims, and for this reason alone should be admitted.

[1] Compl. at ¶53. *See also* Exhibit A, Pl.'s Supplemental Resps to Def.'s Fourth Set of Interrogs. at 6 (alleging that Lilly violated the UTPCPA because its sales representatives "affirmative[ly] misrepresent[ed] . . . Zyprexa's risks, benefits or uses.").

[2] Pl.'s Mem. Describing Claims and Proofs at 22.

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B. Evidence Of Zyprexa's Efficacy, Uses and Benefits also Provides Necessary Context for the State's Claimed UTPCPA Violations.

1. The Evidence Provides Essential Context to the State's Challenges that Lilly's Marketing Concerning Weight Gain or Diabetes Violated the UTPCPA.

The State has challenged Lilly's marketing message concerning the safety profile of Zyprexa. The State's motions attack portions of a marketing message, but seek to deny Lilly the opportunity to discuss the context for the entire message, which includes placing metabolic issues in an overall risk/benefit equation.

For example, the State alleges that Lilly violated the UTPCPA because its "sales representatives were delivering the company message that weight gain was manageable and that any risk of it was far outweighed by Zyprexa's superior efficacy."[3] By attacking the message weighing the risk of weight gain against efficacy, the State seems to acknowledge the contextual role that efficacy plays in Lilly's weight gain messages, but now seeks to deny Lilly the opportunity to explain the rest of the words used as part of the message.

The State also claims that Lilly violated the UTPCPA when its sales representatives "used company messages regarding 'comparable rates [of diabetes] among atypical antipsychotics'" to "reassure physicians and encourage prescribing Zyprexa."[4] This allegation also requires consideration of the full context of Lilly's messages. For instance,

[3] Exhibit A, Pl.'s Supplemental Resps. to Def.'s. Fourth Set of Interrogs. at 6.

[4] *Id.* at 7.

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the State seeks to introduce Lilly's brochure, *Diabetes and patients with mental illness*, as evidence of a UTPCPA violation.[5] This exhibit opens with a risk-benefit scale putting diabetes risks in the context of Zyprexa's benefits, includes a set of charts analyzing the rates of diabetes for commonly prescribed psychotropics, provides information about diabetes risk factors and then closes with a reminder to "consider the whole story" because "treatment selections should be based on the patient's underlying psychiatric condition and the overall risk/benefit profile of the medication." The diabetes message is an inseparable parcel of the messages about Zyprexa's overall risk-benefit profile. Allowing the State to focus on the risk, and preclude Lilly from talking about the benefits, will mislead the jury. Lilly's "message" about comparable rates cannot be extracted from its "message" about the need for efficacious treatment of the patient's psychiatric condition without doing violence to the context of these messages.

The State also wants to introduce the ADA Consensus Statement to support an argument that clozapine and Zyprexa were associated with higher levels of diabetes than other medicines.[6] The State should not, however, be permitted to cherry-pick portions of the Consensus Statement. The Consensus Statement itself qualifies its metabolic discussion with a section on the importance of risk-benefit assessment, acknowledging that

[5] Exhibit B, Lilly Brochure, *Diabetes and patients with mental illness.*

[6] Exhibit C, Deposition of David Thomas Noesges, January 11, 2008, at 125-28.

> [e]ven for those medications associated with an increased risk of metabolic side effects, the benefit to specific patients could outweigh the potential risks. . . [s]ince treatment response in many psychiatric conditions is heterogeneous and unpredictable, physicians and patients can benefit from the availability of a broad array of different therapeutic agents.[7]

Because the State has placed the efficacy of Zyprexa at issue, and because evidence of efficacy provides necessary context to Lilly's sales messages, such evidence is relevant and should not be excluded.

2. Evidence of Efficacy is also Essential to Defend Claims of Alleged Off Label Promotion or Were Otherwise "Unfair."

The State attacks the communications between Lilly sales representatives and physicians concerning off-label topics, alleging that they constitute "violations of the UTPCPA in the form of Lilly's illegal off-label promotion of Zyprexa for symptoms or conditions for which it was never indicated."[8] To support its claims, the State seeks to introduce evidence, such as call notes,[9] that Lilly sales representatives allegedly discussed off-label uses with physicians. At the same time, however, the State seeks to preclude

[7] Exhibit D, American Diabetes Association, et al., *Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes,* 27 Diabetes Care 596 (February 2004).

[8] Exhibit A, Pl.'s Supplemental Resps. to Def.'s. Fourth Set of Interrogs. at 7. *See also* Pl.'s Mem. Describing its Claims and Proofs at 22 ("The State will prove this violation [of the UTPCPA] with evidence that Lilly through its representatives marketed Zyprexa as safe and effective, both for uses for which it was approved by the FDA *and for many uses that were not approved*.") (emphasis added).

[9] *See generally* Call Notes Designated by State (designated as Pl.'s Ex. No. 10144). Lilly is separately objecting to this Exhibit on other grounds, as well.

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evidence of the reason why such discussions may arise in a permissible context: physicians requesting information about Zyprexa's off-label uses because, in their clinical judgment, Zyprexa may help patients suffering from disorders without approved and effective treatments. As Dr. Curtiss explained at her deposition:

> Q. For what kinds of conditions do you use Zyprexa in your practice today?
> A. In my practice today, I have patients that take Zyprexa for schizophrenia, schizoaffective disorder, bipolar disorder, PTSD, and behavioral disturbances associated with dementia.
>
> Q. And for several of those illnesses, the treatment with Zyprexa would be off label; is that correct?
>
> A. Yes.
>
> Q. Why do you use Zyprexa off label?
>
> A. Well, in psychiatry there is very much off-label prescribing; and particularly in the field of geriatric psychiatry, there are no FDA-indicated treatments for behavioral disturbances associated with dementia. All of that prescribing is off label. And so I think as – as a field, we are more comfortable with off-label prescribing than other fields may be.
>
> Q. How about for post-traumatic stress disorder.
>
> A. That is also a diagnosis for which most prescribing is off label.
>
> Q. Have you found in your practice that using Zyprexa for schizoaffective disorder, post-traumatic stress disorder and behavioral disturbances associated with dementia has been effective for your patients?

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A. For some patients, yes.[10]

Physicians may prescribe FDA-approved medications for "any purpose that [they] deem[] appropriate, regardless of whether the [medication] has been approved for that use by the FDA."[11] Although pharmaceutical companies may not market or promote medications for off-label uses,[12] the First Amendment right of free speech allows the companies to disseminate accurate information to physicians about off-label uses of drugs in a non-promotional manner.[13]

The entire context of the off-label communications will depend upon *who* initiated the discussion, *how* and *why* the discussion was conducted, and *what* information or materials were exchanged. Evidence of efficacy for off-label uses is relevant to all of these inquiries. For example, if a physician read or heard about Zyprexa's use to treat an off-label condition from a non-Lilly source, the physician might ask his Lilly sales representative for further information about that use. In response, the sales representative could discuss certain types

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[10] *See* Exhibit E, Deposition of Lucy Ljubicich Curtiss, M.D., December 13, 2007, at 31-32.

[11] *In re Neurontin Marketing & Sales Pract. Litig.*, 244 F.R.D. 89, 92 (D. Mass. 2007); *Washington Legal Foundation v. Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000) ("*WLF IV*").

[12] 21 U.S.C. § 331; *see also, e.g., In re Neurontin Marketing & Sales Pract. Litig.*, 244 F.R.D. at 92; *United States ex rel. Franklin v. Parke-Davis*, 147 F. Supp.2d 39, 44 (D. Mass. 2001).

[13] *Washington Legal Foundation v. Henney*, 56 F. Supp.2d 81 (D.D.C. 1999) (*WLF III*); *Washington Legal Foundation v. Friedman*, 36 F. Supp.2d 16 (D.D.C. 1999) ("*WLF II*"); *Washington Legal Foundation v. Friedman*, 13 F. Supp.2d 51 (D.D.C. 1998) ("*WLF I*"), *vacated as moot sub nom. Washington Legal Foundation v. Henney*, 202 F.2d 331 (D.C. Cir. 2000) ("*WLF IV*").

of off label information. Evidence of efficacy illuminates the reasons for the off-label topics being raised in call notes.[14]

The State also claims that Lilly engaged in off-label promotion by marketing Zyprexa for the treatment of symptoms, rather than for disease states approved by the FDA.[15] In support of these allegations, the State offers various Lilly promotional pieces that discuss symptoms of mental illness. Evidence of efficacy is relevant to show that these promotional materials were not off-label sales aids, but instead were tools to help physicians identify symptoms that characterize diseases for which Zyprexa is approved.

For example, the State seeks to introduce a sample patient profile that concentrates on symptoms of "irritability," "elevated mood," and "poor sleep."[16] These symptoms are all part of the diagnosis of bipolar mania, and therefore do not reflect an "off-label" promotion. This fact will be lost on the jury without evidence of how Zyprexa works to treat these symptoms, as part of the efficacy in the treatment of indicated uses. As one ratings scale demonstrated, improvements in "irritability," "elevated mood" and "sleep" can be used to

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[14] As highlighted by Dr. Curtiss' testimony, these questions are hardly hypothetical, and further make the bifurcation of this trial unwieldy, as the individual physician decision-making is being deferred for a later phase.

[15] Pl.'s Mot. in Limine to Exclude Testimony or Argument Regarding Efficacy or Benefits of Zyprexa for Non-Indicated or "Off-Label" Uses at 4.

[16] Exhibit F, Michael Patient Profile at 1.

evaluate Zyprexa's efficacy in treating bipolar mania.[17] Evidence of efficacy therefore gives context to promotional pieces regarding symptoms, and discredits the State's allegations that they were tools for off-label promotion.

II. EVIDENCE OF ZYPREXA'S EFFICACY IS RELEVANT TO THE THE EVALUATION OF WHETHER LILLY'S WARNINGS WERE ADEQUATE.

For a warning to be adequate,[18] it must be "sufficient to put the physician on notice of the nature and extent of any scientifically knowable risks or dangers inherent in the use of the drug."[19] Like the metabolic messages discussed in the previous section, the adequacy of a medication's warning can only be evaluated in context. For example, whether Zyprexa (olanzapine) is an appropriate choice for diabetics or people at risk for diabetes (and implicitly whether there should be a contraindication in the warnings for Zyprexa in diabetics) requires reference to efficacy. As Lilly physician, Dr. Robert Baker, explained in his deposition:

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[17] *See, e.g.,* Exhibit G, Zyprexa: the novel psychotropic at 7 (graphically representing the improvement in irritability, sleep, and elevated mood, as measured through Y-MRS Individual Item Scores (LOCF), for the proposition that Zyprexa has "proven effective in treating complicated mood symptoms in bipolar mania.").

[18] The State asserts that its UTPCPA claims "focus partly on defendant's failure to warn of Zyprexa's risks" and states that "[t]he issues and evidence [for its UTPCPA claims] are similar to the failure to warn claim and do not in any way implicate evidence regarding the benefits of Zyprexa in treating Schizophrenia and Bipolar I disorder." Pl.'s Mot. in Limine to Exclude Testimony or Argument Regarding Efficacy or Benefits of Zyprexa for Indicated Uses at 3. To the extent that the State's UTPCPA claims mirror its failure-to-warn claim, the foregoing analysis applies to the State's UTPCPA claims as well.

[19] *Shanks v. Upjohn Co.,* 835 P.2d 1189, 1200 (Alaska 1992).

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> We have data on patients who have diabetes coming in to treatment with olanzapine. We have it compared to other medications. I think, certainly, as our label indicates, doctors should pay attention to the diabetes and management of the diabetes. But keep in mind that we're talking about schizophrenia, bipolar mania, conditions that are very acute, sometimes life threatening, and in which doctors have to be making a choice of what, looking at the range of choices and the range of potential benefits and concerns they have are best for them. And in some cases olanzapine would, indeed, be the best.[20]

Alaska law recognizes the importance of including information regarding efficacy when giving an adequate warning. In *Shanks v. Upjohn Co.,* the court commented on a jury instruction stating that adequate warnings were those "that, under the circumstances then existing, provide a doctor with reasonable notice of the intended effects, side effects, and adverse effects of a drug and clear directions for the safe use of that drug."[21] The Court did not disagree with the jury instruction's inclusion of the phrase, "the circumstances then existing," which requires that a warning's adequacy be evaluated in the full context of the case. Lilly should not be precluded from providing the jury the "circumstances," and "intended effects," including the state of scientific knowledge at the time of the warning, the seriousness of the disease state being treated, the medication's efficacy and its risks.

[20] Exhibit H, Deposition of Robert Baker, M.D., July 28, 2006, at 332.

[21] 835 P.2d at 1200, n.16.

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As does Alaska, the FDA considers circumstances and context when evaluating a medication's labeling.[22] The FDA considers benefits along with risks, and efficacy along with safety, when opining on the content of a label and the adequacy of the warnings contained therein. The FDA thus described its role:

> FDA is the expert public health agency charged by Congress with ensuring that drugs are safe and effective, and that their labeling adequately informs users of the risks and benefits of the product and is truthful and not misleading. . . . FDA carefully controls the content of labeling for a prescription drug, because such labeling is FDA's principal tool for educating health care professionals about the risks and benefits of the approved product to help ensure safe and effective use.[23]

Among the reasons why the FDA considers efficacy in its analysis is that efficacy assists the FDA in guarding against "overwarning." For instance, the benefits of a medication help define the magnitude of harm that will ensue if overwarning is allowed to occur:

---

[22] The FDA's status as a national, expert scientific authority makes its analyses and opinions relevant to the determination of whether Lilly adequately warned of Zyprexa's risks. *Carlin v. Superior Court,* 920 P.2d 1347, 1352-53 (Cal. 1996) ("[E]vidence of compliance with FDA requirements is admissible as relevant evidence in a strict tort liability case on the issue whether a pharmaceutical manufacturer failed to provide adequate warnings.") (citing *Hatfield v. Sandoz-Wander, Inc.,* 464 N.E.2d 1105, 1109); *see In re Ephedra Products Liability Litigation,* 393 F. Supp.2d 181, 195-96 (S.D.N.Y. 2005) (admitting into evidence a statement in a Federal Register to bolster expert testimony because the statement showed "the FDA makes the same inferences from good but inconclusive science as [the party's] experts."). The trier of fact may assess the FDA's view of a pharmaceutical warning and accord it "the weight it deserves." *Toner v. Lederle Laboratories,* 732 P.2d 297, 311 n.12 (Idaho 1987).

[23] Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) (emphasis added).

> Exaggeration of risk could discourage appropriate use of a beneficial drug. . . [A]dditional warnings can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products or encouraging inappropriate use and undermining the objectives of the [FDCA].[24]

Efficacy evidence provides context to the State's failure-to-warn claim, and should not be excluded.

III. CONCLUSION

Evidence of Zyprexa's efficacy is relevant to Lilly's defense against the State's UTPCPA claims, and it provides necessary context for the State's warning claims.

DATED this 14th day of February, 2008.

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[24] 71 Fed. Reg. at 3935 (emphasis added). This concern about overwarning comports with a long line of FDA precedent. *See Amicus Curiae* Brief of the United States of America, *Reigel v. Medtronic*, No. 06-0179 (U.S.) (May 23, 2007) at 13 (citing FDA guidance on the topic of overwarning from 1979 through 2006).

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Case No. 3AN-06-05630 CI
	)	
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	
	)	

PLAINTIFF'S SUPPLEMENTAL RESPONSES TO DEFENDANT'S FOURTH SET OF INTERROGATORIES

PRELIMINARY STATEMENT

In response to Lilly's First Interrogatories and Requests for Production, the State provided a general description of the kinds of proof it would offer underlying its claims in this case. In response to Lilly's Fourth Interrogatories and Requests for Production, the State provided a description of similar information with respect to its claims under the Unfair Trade Practices and Consumer Protection Act (UTPCPA). However, the evidence is incomplete at this point because of Lilly's reluctance to produce meaningful discovery in response to the State's discovery requests. Lilly delayed the production of virtually any discovery until ordered by the Discovery Master to produce it. Additionally, at Lilly's request, key depositions have been delayed.[1]

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[1] The recent 30(b)(6) deposition on the issue of Lilly's marketing practices was initially noticed for December 6, 2007, but at Lilly's request was delayed until January 11, 2008.

In accordance with the Discovery Master's order of January 14, 2008, below is a recitation of the specific violations upon which the State bases its UTPCPA claims. This information will be supplemented at the conclusion of discovery, or as otherwise necessary.

Before addressing the specific Alaska violations which are the subject of Lilly's interrogatories, it is important to note that Lilly had a sophisticated, broad-based scheme designed to distort the entire body of public knowledge regarding Zyprexa's risks and benefits. Lilly formulated this scheme at its corporate headquarters in Indianapolis, and it was carried out nationwide. Sales messages and materials all originated in Indianapolis, and the sales representatives were expected to carry those messages nationwide. The scheme was implemented in Alaska, as in all other states.

Lilly's scheme included failing to warn in the product labeling accompanying each prescription about the risks associated with Zyprexa use. However, the scheme also included affirmative misrepresentations which 1) minimized the magnitude and hazards of weight gain with Zyprexa; 2) denied a causal relationship between Zyprexa and hyperglycemia or diabetes; 3) claimed that hyperglycemia or diabetes occurred with Zyprexa use at rates comparable to other antipsychotic medications; and 4) promoted Zyprexa as safe and efficacious for uses not indicated on its labeling.

At the 30(b)(6) deposition of Lilly regarding its marketing practices, deponent David Noesges testified that all sales messages delivered by Lilly sales representatives are

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EXHIBIT A
PAGE 2 OF 16

B C D E F G H

developed in Indianapolis.[2] He further testified that the sales representatives are trained to and expected to deliver those messages, and are prohibited from delivering any messages that have not been approved by Lilly.[3] Sales representatives are provided with a number of sales tools, including brochures, sell sheets and scripted answers to various questions. These materials included messages which, as indicated above, affirmatively misrepresented the risks and benefits of Zyprexa. Clear evidence that Lilly sales representatives delivered these messages is available in the sampling of "call notes" produced by Lilly. A call note is a business record which contemporaneously details a Lilly sales representative's visit to a physician.[4] Sales representatives are expected to accurately detail such visits.[5]

Pursuant to the January 14 order of the Discovery Master, the State provides answers to Lilly's interrogatories below on the basis of information the State currently possesses.

INTERROGATORIES

INTERROGATORY NO. 66: State the number of times that you contend Lilly violated the Alaska Unfair Trade Practices and Consumer Protection Act, AS 45.50.471, et seq., as alleged in the Fifth Claim for Relief in the Complaint by:

(a) "represent[ing] Zyprexa had characteristics, uses, benefits and/or qualities that it did not have;"

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[2] Exhibit 1 (Deposition of David Thomas Noesges, January 11, 2008 at 38).
[3] Id. at 35-36.
[4] Id. at 197-198; Exhibit 2 (Exhibit 9 to Deposition of David Thomas Noesges).
[5] Exhibit 1 at 198; Exhibit 2.

(b) "represent[ing] that Zyprexa was of a particular standard, quality and grade suitable for consumption when in fact it was not;"

(c) "advertis[ing] Zyprexa with an intent not to sell it as advertised;"

(d) "engag[ing] in conduct creating a likelihood of confusion or a misunderstanding and which misled or damaged buyers of Zyprexa, including the State of Alaska;"

(e) "us[ing] misrepresentations or omissions of material facts with the intent that others rely on the misrepresentations or omissions in connection with the sale of Zyprexa;" and/or

(f) "violat[ing] the labeling and advertising provisions of AS 17.20."

ANSWER: The State objects to the foregoing interrogatory in that discovery is ongoing in this case. The State is still in the process of taking depositions of Lilly witnesses with information relevant to the State's claims. The State reserves the right to use any and all evidence produced by any party in discovery in this case or in the Zyprexa Multidistrict Litigation ("MDL"). Subject to and without waiving this objection, it is clear that Lilly engaged in conduct violating the above-referenced provisions of the Alaska statutory law by minimizing the magnitude and hazards of olanzapine-induced weight gain, denying a causal relationship between olanzapine and hyperglycemia and/or diabetes, and by claiming that hyperglycemia and/or diabetes occurring during treatment with olanzapine occurred at rates comparable to other antipsychotic medications. Moreover, Lilly misrepresented that

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Zyprexa was an appropriate treatment for "complicated mood disorders" and other off-label uses. This list is intended to be illustrative and not exhaustive.

At a minimum, Lilly violated the above-referenced provisions of the UTPCPA with each prescription of Zyprexa that was unaccompanied by a product label which adequately conveyed the risks of Zyprexa use, including but not limited to the risks of weight gain, hyperglycemia or diabetes, and other metabolic disturbances.[6] Each and every prescription of Zyprexa to any Alaska resident is a violation of the provisions of the UTPCPA, because each prescription failed to warn of the true nature and extent of Zyprexa's risks. Through the year 2006, there were 208,780 prescriptions to Alaska Medicaid patients alone. The State believes the total number of prescriptions (to both Medicaid and non-Medicaid patients) will be significantly higher but is still in the process of discovering the total number prescriptions to all Alaska residents.

In addition to each prescription without an adequate warning being a separate violation of UTPCPA, it was also a separate violation of the Act for any sales call in which the sales representative minimized the hazards with weight gain and diabetes, misrepresented the facts about the drug, or improperly promoted the drug off-label. Identified herein are a

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[6] It is important to note here that the Discovery Master found that "[t]he State's responses, including all incorporated materials, adequately identify the factual bases for inadequate warnings and Lilly's knowledge of the alleged hazards of Zyprexa."

number of additional violations related to affirmative misrepresentations of Zyprexa's risks, benefits or uses which are detailed in call notes by sales representatives.[7]

Searching the call notes database with specific terms reveals numerous violations of the UTPCPA. The State will provide examples below of such searches and exhibits detailing the results of those searches. These exhibits detail specifically the dates and substance of the UTPCPA violations in response to these interrogatories.

A search of the call notes using the search term "weight gain" reveals 98 instances of Lilly sales representatives discussing the issue of Zyprexa-related weight gain with Alaska physicians between 1999 and 2004.[8] In none of these instances did the Lilly sales representative indicate the true extent and magnitude of Zyprexa weight gain to the physician. Instead, the sales representatives were delivering the company message that weight gain was manageable and that any risk of it was far outweighed by Zyprexa's superior efficacy. Each of these notes establishes a violation of the UTPCPA.

A search of the call notes using the terms "diabetes," "glucose," "no differences," "comparable," "cause" or "causal" reveals 170 instances of Lilly sales representatives discussing high glucose or diabetes with Alaska physicians between 2000 and 2004.[9] Lilly sales representatives did not advise physicians of the true risks of high glucose or diabetes in

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[7] The State has only received a sampling of call notes to date. It will require a full production of all call notes through the present to fully address the spectrum and magnitude of UTPCPA violations in Alaska.

[8] Exhibit 3 (Alaska call notes reflecting discussion of weight gain).

[9] Exhibit 4 (Alaska call notes reflecting discussion of diabetes, glucose or diabetes messages).

these visits, but instead used company messages regarding "comparable rates among atypical antipsychotics" or "no causal link between Zyprexa and diabetes" to reassure physicians and encourage prescribing Zyprexa. Each of these notes establishes a violation of the UTPCPA.

Not only do the call notes establish violations of the UTPCPA for failing to advise of the full nature and extent of weight gain and diabetes risks associated with Zyprexa, they also establish violations of the UTPCPA in the form of Lilly's illegal off-label promotion of Zyprexa for symptoms or conditions for which it was never indicated. For example, using the search term "SSRI" reveals 20 instances between 2002 and 2003 in which a Lilly sales representative promoted Zyprexa as a mood stabilizer for someone whose symptoms were aggravated by an SSRI or in whom SSRI treatment failed.[10] Further, using the search term "elderly" reveals 51 instances between 2001 and 2002 in which Lilly sales representatives promoted Zyprexa for use in elderly patients for various symptoms or disorders such as agitation, hostility, dementia or improved cognition.[11] Searching for "children" or variations thereof reveals 11 instances between 1999 and 2000 of Lilly representatives promoting the use of Zyprexa in adolescents.[12] Finally, searching for the names of various Lilly patient exemplars or "patient types" such as "Martha," "Melvin," "Donna" or "Kelly" reveals 159 instances of Lilly representatives between 2001 and 2002 using these patient exemplars to

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[10] Exhibit 5 (Alaska call notes reflecting discussion of use of Zyprexa in patients treated with SSRI).
[11] Exhibit 6 (Alaska call notes reflecting discussion of use of Zyprexa in elderly patients).
[12] Exhibit 7 (Alaska call notes reflecting discussion of use of Zyprexa in adolescent patients).

promote the use of Zyprexa in patients who were not diagnosed with bipolar disorder or schizophrenia, the only indications for Zyprexa.[13]

All of the call notes above establish numerous violations of the UTPCPA, but not all violations. Until discovery is complete, the State cannot establish with precision the total number of violations.

INTERROGATORY NO. 67: Identify every alleged violation enumerated in response to Interrogatory No. 66 which was the result of Lilly's representing that "Zyprexa had characteristics, uses, benefits and/or qualities that it did not have, in violation of AS 45.50.471(b)(4)," as alleged in paragraph 53(a) of Complaint. For each representation, your response should identify who made the representation, the recipient(s) of the representation, the method of communication, the date of the representation, the content of the representation, and the basis for your contention that the representation was false, including but not limited to identifying what characteristics, uses, benefits and/or qualities Lilly represented Zyprexa to have, which it did not have.

ANSWER: The State objects to the foregoing interrogatory in that discovery is ongoing in this case. The State is still in the process of taking depositions of Lilly witnesses with information relevant to the State's claims. The State reserves the right to use any and all evidence produced by any party in discovery in this case or in the Zyprexa Multidistrict Litigation ("MDL"). See response to Interrogatory No. 66, above.

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[13] Exhibit 8 (Alaska call notes reflecting discussion of various patient types).

By way of further response, there are many instances of Zyprexa sales representatives minimizing the magnitude and risks of weight gain on Zyprexa. For example, Alaska sales representatives told physicians that weight gain was "manageable," provided "strategies" and "solutions" for combating weight gain, and generally touted Zyprexa's "superior" or "broad spectrum" efficacy as a benefit which outweighed the risk of weight gain.[14] This conduct occurred regularly from 1999 to 2004, a time during which Lilly acknowledged internally that it did not know how to effectively manage weight gain, that weight loss programs worked only five percent of the time in healthy – i.e., mentally stable – volunteers, that it was actively attempting to minimize the liability of weight gain while at the same time increasing the focus on Zyprexa's superior efficacy, and that it would be ludicrous to state that some patients who gained clinically significant weight on Zyprexa would not be at long-term increased cardiac risk as a result. Further, Lilly taught its sales representatives to "weaken [the] link" between weight gain and diabetes.[15]

Lilly's Alaska sales representatives also misrepresented to physicians on numerous occasions that there was no causal relationship between Zyprexa and diabetes, or between weight gain on Zyprexa and diabetes. These detailing visits occurred between 2000 and 2004, a time when the company was attempting to eliminate the risk of diabetes from the risk/benefit equation. It is clear from the call notes that when Lilly representatives shared

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[14] Exhibit 3.
[15] Exhibit 1 at 113; Exhibit 9 (Zyprexa MDL Plaintiffs' Exhibit 1901).

diabetes information with physicians in Alaska, it was the same tortured data claiming there was no causal link between Zyprexa and diabetes.[16]

Lilly sales representatives also used the "comparable rates" message with Alaska physicians and denied that there was a causal connection between Zyprexa and diabetes.[17] These messages were designed reduce the perception that diabetes was linked to Zyprexa and to eliminate the diabetes risk from the risk/benefit equation. The message was delivered with frequency to Alaska physicians, beginning in 2001 and continuing through at least January 2004.[18] However, at all times Lilly had relevant information belying the "comparable rates" message that it refused to share with physicians. Even after Lilly was required to change its label in September 2003, Lilly continued to trumpet the message to physicians to minimize the negative effect of the label change on Zyprexa. Not only was this message belied by available data – a point made clearly in 2004 by the ADA Consensus Statement, which ranked the atypicals by weight gain and diabetes risk – but Lilly was forced in October 2007 to acknowledge this in a revised Zyprexa warning label. Internal company documents cited in the State's "backgrounder" make it clear the company knew this for years prior to 2007, and the recent 30(b)(6) deposition of Lilly regarding the label change confirmed the same.

Finally, there are numerous instances in the "call notes" of Lilly sales representatives promoting Zyprexa as safe and efficacious for uses far beyond its approved indications.

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[16] Exhibit 1 at 103-111; Exhibit 10 (Exhibits 4 and 5 from the Deposition of David Thomas Noesges).
[17] Exhibit 1 at 58-60, 63; Exhibit 11 (Zyprexa MDL Plaintiffs' Exhibit 1941).
[18] Exhibit 4.

Often through the use of patient exemplars with names like "Donna," "Martha," "Marty" and "Melvin," the representatives would promote Zyprexa for use in combating non-indicated mood and thought disorders such as depression, anxiety, and "complicated mood disorder," and for use in patient populations such as the elderly and children for whom Zyprexa had not been established as safe or effective.[19] Lilly sales representatives were taught to do this, though the drug was never approved for any of these conditions.[20]

This evidence clearly establishes violations of the above-referenced UTPCPA provision. Lilly's sales representatives in Alaska were carrying out the company's orchestrated national plan to minimize the magnitude and hazards of olanzapine-induced weight gain, deny any causal relationship between olanzapine and hyperglycemia and/or diabetes, convince physicians that hyperglycemia and/or diabetes occurring during treatment with olanzapine occurred at rates comparable to other antipsychotic medications, and promote Zyprexa was an appropriate treatment for "complicated mood disorders" and other off-label uses. Until discovery is complete, however, the State is unable to perform and exhaustive recitation of such evidence and additional violations.

INTERROGATORY NO. 68: Identify every alleged violation enumerated in response to Interrogatory No. 66 which was the result of Lilly's representing that "Zyprexa was of a particular standard, quality and grade suitable for consumption when in fact it was not, in violation of AS 45.50.471(b)(6)," as alleged in paragraph 53(b) of Complaint. For

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[19] Exhibits 4 – 7.

[20] Exhibit 1, p. 164:15 – 177:15. Exhibit 12 (Zyprexa MDL Plaintiffs' Exhibit 4121).

each representation, your response should identify who made the representation, the recipient(s) of the representation, the method of communication, the date of the representation, the content of the representation, and the basis for your contention that the representation was false, including but not limited to identifying what characteristics, standard, quality and grade Lilly represented Zyprexa to have, which it did not have.

ANSWER: See response to Interrogatory Nos. 66 and 67, above.

INTERROGATORY NO. 69: Identify every alleged violation enumerated in response to Interrogatory No. 66 which was the result of Lilly's "advertis[ing] Zyprexa with an intent not to sell it as advertised, in violation of AS 45.50.471(b)(8)," as alleged in paragraph 53(c) of the Complaint. Your response should identify each and every representation you contend constitutes an advertisement, the content of the advertisement, where the advertisement was published, transmitted, or otherwise communicated, the date of the advertisement, who received the advertisement, and the basis for your contention that Lilly's intent contradicted the content of the advertisement.

ANSWER: See response to Interrogatory Nos. 66 and 67, above.

INTERROGATORY NO. 70: Identify every alleged violation enumerated in response to Interrogatory No. 66 which was the result of Lilly's "engag[ing] in conduct creating a likelihood of confusion or a misunderstanding and which misled or damaged buyers of Zyprexa, including the State of Alaska, in violation of AS 45.50.471(b)(11)," as alleged in paragraph 53(d) of the Complaint. Your response should describe in detail each

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incidence of alleged conduct, identify who engaged in the conduct and describe their involvement, identify when the conduct occurred, identify where the conduct occurred, and identify what was confusing or misleading about the conduct, and identify what buyers were misled and/or damaged by the conduct.

ANSWER: See response to Interrogatory Nos. 66 and 67, above.

INTERROGATORY NO. 71: Identify every alleged violation enumerated in response to Interrogatory No. 66 which was the result of Lilly's "us[ing] misrepresentations or omission of material facts with the intent that others rely on the misrepresentations or omissions in connection with the sale of Zyprexa, in violation of AS 45.50.471(b)(12)," as alleged in paragraph 53(e) of the Complaint. For each representation, your response should identify who made the representation, the recipient(s) of the representation, the method of communication, the date of the representation, the content of the representation, and the basis for your contention that the representation was false. For each omission, your response should identify the information that was omitted, the date that the information should have been communicated, and the person(s) to whom the information should have been communicated.

ANSWER: See response to Interrogatory Nos. 66 and 67, above.

INTERROGATORY NO. 72: Identify every alleged violation enumerated in response to Interrogatory No. 66 which was the result of Lilly's "violat[ing] the labeling advertising provisions of AS 17.20, in violation of AS 45.50.471(b)(48)," as alleged in

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paragraph 53(f) of the Complaint. Your response should identify each provision of AS 17.20 that you contend was violated, describe in detail each incidence of alleged conduct resulting in that violation of AS 17.20, identify who engaged in the conduct and describe their involvement, identify when the conduct occurred, and identify where the conduct occurred.

ANSWER: See response to Interrogatory Nos. 66 and 67, above. Additionally, per the Discovery Master's January 14, 2008 order, the State's prior responses and incorporated materials "adequately identify the factual bases for inadequate warnings and Lilly's knowledge of the alleged hazards of Zyprexa."

INTERROGATORY NO. 73: For each individual violation enumerated in response to Interrogatory No. 66, identify the "ascertainable loss of money or property" that you contend resulted from that specific violation.

ANSWER: The State objects to this interrogatory as discovery is ongoing and that any response to this interrogatory is premature in that damages are not at issue in the first phase of trial currently scheduled for March 3, 2008. By way of further response, the State is entitled to any and all damages to be determined by the Court and/or jury at the trial on damages in this case. The State will prove at the first trial that Zyprexa presents serious risks of weight gain, hyperlipidemia, hyperglycemia and/or diabetes, and related health conditions for which the State has the burden of paying the cost of medical treatment. In the second trial, the State will prove the extent of these injuries and the State's damages, and evidence relevant to that proof will be provided to Lilly in accordance with the Court's January 4,

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2008 order regarding discovery unrelated to liability. Additionally, the State will prove in the first trial that Lilly promoted Zyprexa for numerous symptoms and conditions for which Zyprexa had no indication, and the State will prove at the second trial that it suffered damages as a result of increased prescriptions for off-label uses.

Respectfully SUBMITTED and DATED this 24 day of January, 2008.

FELDMAN, ORLANSKY & SANDERS
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Certificate of Service
I hereby certify that a true and correct copy of the foregoing **Plaintiff's Supplemental Responses to Defendant's Fourth Set of Interrogatories** was served by messenger on:

Brewster H. Jamieson
Lane Powell LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648

Barry Boise, via email (boiseb@pepperlaw.com)
Pepper Hamilton

By Annette R. Carter
Date 1-24-08

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B C D E F G H

Diabetes and patients with mental illness

EXHIBIT 13
PAGE 1 OF 10

006094

What do you consider when choosing medications?

What benefits do you associate with ZYPREXA® (olanzapine)?

What risks do you associate with it?

EXHIBIT 5
8-11-1
noesges

Diabetes is common.

- As many as 6.2% of American adults have diabetes.[1]
- One half of them may not know it.[1]
- 6.9% more have fasting blood glucose levels that are above normal.[1]

But your patients are at an even greater risk.

- People with serious mental illness are 2 to 4 times more likely to develop diabetes.[2-5]
- There have been reports linking antipsychotics and certain mood stabilizers with hyperglycemia since the 1950s.[4-9]

For additional safety profile and other important prescribing considerations for ZYPREXA, see inside and the full Prescribing Information.

The Adverse Reactions section of the full Prescribing Information for ZYPREXA includes hyperglycemia (infrequent), glycosuria (infrequent), diabetes mellitus (infrequent), diabetic acidosis (rare), and ketosis (rare) as well as postintroduction reports of diabetic coma.

Lilly

Zyprexa Plaintiff's Exhibit 10093

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Study methodology

Studies included patients aged 18 to 65 years, with a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, or acute bipolar mania. Diagnosis of treatment-emergent diabetes was based on the clinical discretion of the investigator. For this analysis, all randomized patients were considered.

ZYPREXA vs haloperidol: Three randomized, double-blind studies compared ZYPREXA (5 to 20 mg/day) with haloperidol (5 to 20 mg/day). After the initial 6-week phase, further double-blind observations were conducted following exposure for up to 52 weeks.

Comparisons also include a haloperidol-controlled study of 33 subjects receiving ZYPREXA (1 mg/day).

ZYPREXA vs risperidone: One 28-week, double-blind study compared ZYPREXA (5 to 20 mg/day) with risperidone (4 to 12 mg/day).

ZYPREXA vs divalproex: One 47-week, double-blind study compared ZYPREXA (5 to 20 mg/day) with divalproex (500 to 2500 mg/day).

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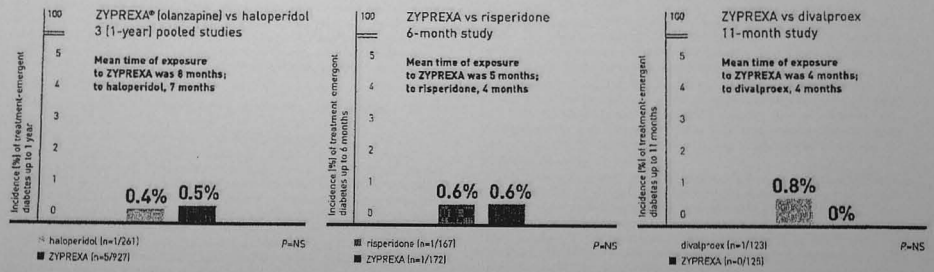
006095

EXHIBIT 8
PAGE 2 OF 12

How do the medications you use compare?

Rates of diabetes were comparable for commonly prescribed psychotropics during longer-term clinical trials.*

Incidence of diagnosed treatment-emergent diabetes in longer head-to-head schizophrenia and bipolar mania trials*



* These trials were not designed specifically to evaluate glycemic effects. Fasting glucose levels were not determined.

For safety information on haloperidol, risperidone, or divalproex, see the manufacturers' respective package inserts.
For additional safety profile and other important prescribing considerations for ZYPREXA, see inside and the full Prescribing Information.

The Adverse Reactions section of the full Prescribing Information for ZYPREXA includes hyperglycemia (infrequent), glycosuria (infrequent), diabetes mellitus (infrequent), diabetic acidosis (rare), and ketosis (rare) as well as postintroduction reports of diabetic coma.

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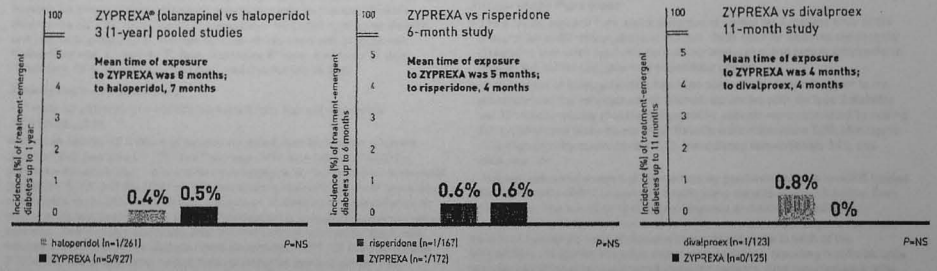
EXHIBIT 8
PAGE 3 OF 10

Page 3 of 10

How do the medications you use compare?

Rates of diabetes were comparable for commonly prescribed psychotropics during longer-term clinical trials.*

Incidence of diagnosed treatment-emergent diabetes in longer head-to-head schizophrenia and bipolar mania trials*



* These trials were not designed specifically to evaluate glycemic effects. Fasting glucose levels were not determined.

For safety information on haloperidol, risperidone, or divalproex, see the manufacturers' respective package inserts.
For additional safety profile and other important prescribing considerations for ZYPREXA, see inside and the full Prescribing Information.

The Adverse Reactions section of the full Prescribing Information for ZYPREXA includes hyperglycemia (infrequent), glycosuria (infrequent), diabetes mellitus (infrequent), diabetic acidosis (rare), and ketosis (rare) as well as postintroduction reports of diabetic coma.

Answers T

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EXHIBIT B
PAGE 4 OF 10

Study methodologies

Lilly Advance PCS Study

- Incidence among all patients combined on typical antipsychotics was 1.6% (307/19,782)
- Hazard ratio was significantly elevated for all treatment groups vs control patients not receiving antipsychotic medications

A 2-year retrospective, pharmacoepidemiological study of an independent prescription claims database (Advance PCS) containing over 50 million members. Patients who had been prescribed a diabetes medication at any point during the 12-month period prior to enrollment or who had been prescribed an antipsychotic during the 6-month period prior to enrollment were excluded. Diabetes mellitus was identified by oral hypoglycemic or insulin prescription claims in both the study and control groups. Patients in the antipsychotic study group were prescribed a single typical or atypical antipsychotic during the 6 months of follow-up. Out of this database, 5.8 million patients receiving a prescription medication that was not an antipsychotic served as the reference group. Hazard ratio was determined by Cox proportional hazard regression controlling for age, gender, and accounting for time to event. Incidence of new antidiabetic prescription was haloperidol 133/8476, thioridazine 62/3133, clozapine 7/277, olanzapine 194/13,863, quetiapine 40/4196, and risperidone 400/20,633. Average duration of treatment with antipsychotic medications was: clozapine 137 days, olanzapine 89 days, quetiapine 89 days, risperidone 90 days, haloperidol 68 days, and thioricazine 76 days

Janssen Quebec Medicare Study

- *P*-value for olanzapine vs risperidone hazard ratio was not reported by the investigators

A Janssen-sponsored analysis of patients identified from the Quebec Medicare database between January 1997 and December 1999. One cohort consisted of patients who had at least 1 prescription for olanzapine but not clozapine during that period (n=19,153) and the other of patients receiving risperidone but not olanzapine or clozapine (n=14,792). Patients with a diagnosis of diabetes or a prescription for insulin or an oral hypoglycemic agent before beginning antipsychotic therapy were excluded. New diabetes diagnoses after the first antipsychotic prescription were tabulated. Incidence of new diabetes were olanzapine 319/19,153 and risperidone 217/14,792. Cox proportional hazard ratio adjusting for age and gender was calculated and reported relative to risperidone group. Duration of treatment with antipsychotic medicines was not reported by the investigators.

Lilly IMS Study

- Odds ratio for olanzapine- and risperidone-treated patients was not significantly different vs patients receiving typical antipsychotic medication

A retrospective analysis of the IMS LifeLink™ claims database identified patients aged 18-65 initiated on antipsychotic medicine between October 1996 and December 1998. The study included only patients with no antipsychotic use for 6 months prior and no diagnosis of diabetes or receipt of any diabetic medication for 1 year prior to antipsychotic initiation. Observed diabetes incidences were typical antipsychotics 68/3208, olanzapine 32/1530, and risperidone 43/1598. Logistic regressions were used to estimate odds ratios (OR) of a diagnosis of diabetes or use of any diabetic medication in the 1-year post-initiation compared to patients on typical antipsychotics; controlling for age, gender, mental health comorbidities, and regional differences. This analysis tabulated all diabetes incidences during 1 year subsequent to antipsychotic prescription irrespective of duration of the treatment episode.

Sernyak Study

A 4-month retrospective analysis included 38,632 outpatients listed in the Veterans Health Administration database with schizophrenia who were treated with typical or atypical antipsychotics. Using the same database, patients with a diagnosis of diabetes were also identified and used to calculate the prevalence of diabetes mellitus among patients receiving prescriptions for antipsychotic agents. Of the total number of patients included in the study, 15,984 received typical neuroleptics and 22,648 received atypical neuroleptics; 1,207 received clozapine; 10,970 olanzapine; 955 quietapine; and 9,903 risperidone.

Janssen Health Plans Study*

- The analysis depicted here is of a subgroup observed for 4 months prior to the prescription of the antipsychotic of interest. Odds ratio for diabetes significantly elevated vs untreated psychotic patients for olanzapine and typical antipsychotic groups, but not for clozapine and risperidone groups.
- In an analysis of a subgroup that had been observed for 8 months prior to the prescription of the antipsychotic of interest, estimated odds for type 2 diabetes per 12 months relative to untreated psychotic patients were calculated by raising the monthly odds to the power of 12. Results were risperidone 0.88, olanzapine 3.10, high-potency conventionals 2.13, low-potency conventionals 3.46, and clozapine 7.44.

A Janssen-sponsored analysis of claims data for psychosis patients (n=4,331 treated, 3,061 untreated) within 2 unspecified health plans encompassing 2.5 million lives. Patients reporting pre-existing diabetes diagnosis or claim for antidiabetic medication up to 4 months prior to observation were excluded. Logistic regression models compared the odds of diabetes based on exposure to each of the antipsychotic categories and other explanatory variables, reporting results as odds ratio per month relative to untreated psychotic patients. Also reported were odds ratios of 1.05 high-potency typicals and 1.06 low-potency typicals. Characteristics reported for the group observed for 4 months prior to the antipsychotic treatment episode of interest were: Number of observed treatment episodes—clozapine 64, olanzapine 1,047, risperidone 1,368, high-potency typical antipsychotics 1,376, and low-potency typical antipsychotics 480. Average duration of antipsychotic treatment episodes were: clozapine 6.8 months, olanzapine 5.6 months, risperidone 6.4 months, high-potency typical antipsycholics 6.7 months, and low-potency typical antipsycholics 6.8 months. The investigators did not provide these details for the subset observed for 8 months prior to the antipsychotic treatment episode.

* Control group is psychotic patients not treated with antipsychotic medication.

EXHIBIT 8
PAGE 5 OF 10
000698

Incidence and odds ratios of developing diabetes during treatment with antipsychotics.

Findings from 5 epidemiological studies show no consistent differences regardless of the agent studied.

	Lilly[10] Advance PCS Database	Janssen[11] Quebec Medicare Database	Lilly[12] IMS Database*	Sernyak[13] Veterans Database	Janssen[14] Health Plans Study
N	58,751	33,945	6,440	38,632	4,308
Control	0.8%*	–	–	–	1.00‡
Clozapine	2.5%	–	–	1.25	1.08
Quetiapine	1.0%	–	–	1.31	–
Risperidone	1.9%	1.5%	2.7%	1.05	1.02
Olanzapine	1.4%	1.7%	2.1%	1.11	1.08
Typical antipsychotics	1.6-2.0%	–	2.1%	–	1.05-1.06
	†OBSERVED INCIDENCE			‖CALCULATED ODDS RATIO/MONTH	

(-) Drug not studied or value not supplied.

N=Number of antipsychotic-treated subjects studied.

* Control group is general population patients receiving prescriptions other than antipsychotic medications.
† Data on file, Lilly Research Laboratories.
‡ Control group is psychotic patients not receiving prescriptions for antipsychotic medication.

§ Observed incidence is the percentage of patients taking the medication of interest who have new onset of diabetes mellitus. It does not control for potentially important factors such as patient age or duration of treatment.
‖ Odds ratio refers to probability of becoming diabetic relative to control group. An odds ratio of 1.05 means that for every 100 cases seen in the control group, no more than 105 would be expected to develop diabetes in the comparison group.

For safety information on clozapine, quetiapine, or risperidone, see the manufacturers' respective package inserts.
For additional safety profile and other important prescribing considerations for ZYPREXA, see inside and the full Prescribing Information.

The Adverse Reactions section of the full Prescribing Information for ZYPREXA includes hyperglycemia (infrequent), glycosuria (infrequent), diabetes mellitus (infrequent), diabetic acidosis (rare), and ketosis (rare) as well as postintroduction reports of diabetic coma.

Answers TI

Lilly

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EXHIBIT 8
PAGE 6 OF 10

Important safety information

The most common treatment-emergent adverse event associated with ZYPREXA® (olanzapine) in 6-week schizophrenia trials vs placebo was somnolence (26% vs 15%). Also observed (ZYPREXA vs placebo) were:

postural hypotension (5% vs 2%)	akathisia (5% vs 1%)
dizziness (11% vs 4%)	constipation (9% vs 3%)
personality disorder* (8% vs 4%)	weight gain (6% vs 1%)

The most common treatment-emergent adverse event associated with ZYPREXA in placebo-controlled bipolar mania trials was somnolence† (35% vs 13% for placebo). Also observed (ZYPREXA vs placebo) were:

dry mouth† (22% vs 7%)	dizziness‡ (18% vs 6%;
dyspepsia (11% vs 5%)	asthenia† (15% vs 6%)
constipation (11% vs 5%;	increased appetite (6% vs 3%)
tremor (6% vs 3%)	

Transient, asymptomatic elevations of hepatic transaminase

In placebo-controlled schizophrenia studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to ZYPREXA compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

No baseline ECG required

No difference in clinically significant QTc prolongation with ZYPREXA compared to placebo in premarketing clinical trials.

Orthostatic hypotension

In premarketing trials of oral ZYPREXA, some patients may have experienced orthostatic hypotension associated with dizziness‡; tachycardia‡; and in some cases, syncope (15/2500, 0.6%).

Low potential for drug interactions

Coadministration of diazepam or ethanol with ZYPREXA may potentiate orthostatic hypotension. Lower doses of ZYPREXA should be considered in patients receiving concomitant therapy with fluvoxamine.

Tardive dyskinesia—as with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD. If its signs and symptoms appear, discontinuation should be considered.

Seizures—occurred infrequently in premarketing clinical trials (22/2500, 0.9%). Confounding factors may have contributed to many of these occurrences. ZYPREXA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

* COSTART term for nonaggressive objectionable behavior.

† In bipolar mania trials, 4 adverse events occurred with statistically significantly higher incidence with ZYPREXA than with placebo—none of these resulted in discontinuation.

‡ In acute-phase, placebo-controlled schizophrenia trials (n=366), dizziness (11% vs 4%) and tachycardia (4% vs 1%) were reported; these events were not always associated with hypotension.

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2. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry.* 1996;37:68-73.
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15. American Diabetes Association Screening for type 2 diabetes. *Diabetes Care.* 2000;23 (suppl 1).
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C D E F G H

006100

EXHIBIT 8
PAGE 7 OF 10

Page 7 of 10

Important safety information

The most common treatment-emergent adverse event associated with ZYPREXA® (olanzapine) in 6-week schizophrenia trials vs placebo was somnolence (26% vs 15%). Also observed (ZYPREXA vs placebo) were:

postural hypotension (5% vs 2%)
dizziness (11% vs 4%)
personality disorder* (8% vs 4%)
akathisia (5% vs 1%)
constipation (9% vs 3%)
weight gain (6% vs 1%)

The most common treatment-emergent adverse event associated with ZYPREXA in placebo-controlled bipolar mania trials was somnolence† (35% vs 13% for placebo). Also observed (ZYPREXA vs placebo) were:

dry mouth† (22% vs 7%)
dyspepsia (11% vs 5%)
constipation (11% vs 5%)
tremor (6% vs 3%)
dizziness‡ (18% vs 6%)
asthenia† (15% vs 6%)
increased appetite (6% vs 3%)

Transient, asymptomatic elevations of hepatic transaminase

In placebo-controlled schizophrenia studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to ZYPREXA compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

No baseline ECG required

No difference in clinically significant QTc prolongation with ZYPREXA compared to placebo in premarketing clinical trials.

Orthostatic hypotension

In premarketing trials of oral ZYPREXA, some patients may have experienced orthostatic hypotension associated with dizziness‡; tachycardia‡; and in some cases, syncope (15/2500, 0.6%).

Low potential for drug interactions

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Tardive dyskinesia—as with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD. If its signs and symptoms appear, discontinuation should be considered.

Seizures—occurred infrequently in premarketing clinical trials (22/2500, 0.9%). Confounding factors may have contributed to many of these occurrences. ZYPREXA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

* COSTART term for nonaggressive objectionable behavior.

† In bipolar mania trials, 2 adverse events occurred with statistically significantly higher incidence with ZYPREXA than with placebo—none of these resulted in discontinuation.

‡ In acute-phase placebo-controlled schizophrenia trials (n=266), dizziness (11% vs 4%) and tachycardia (6% vs 1%) were reported; these events were not always associated with hypotension.

References

1. NHS Direct. Diagnosis, risk factors for diabetes. Available at: http://www.psychiatry.ox.ac.uk/diabetes/patient/diagnosis/risk.html. Accessed March 7, 2003.
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4. Keskiner A, Toumi AE, Bousquet T. Psychotropic drugs, diabetes, and chronic mental patients. *Psychosomatics.* 1973;14:175-181.
5. Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. *Am J Psychiatry.* 1999;156:1417-1420.
6. Charatan FBE, Bartlett NG. The effect of chlorpromazine ["Largactil"] on glucose tolerance. *J Mental Sci.* 1955;101:351-353.
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8. Garland EJ, Remick RA, Zis AP. Weight gain with antidepressants and lithium. *J Clin Psychopharmacol.* 1988;8:323-330.
9. Mellerup ET, Dam H, Wildschiodtz G, Rafaelsen OJ. Diurnal variation of blood glucose during lithium treatment. *J Affective Dis.* 1983;5:341-347.
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11. Caro JJ, Ward A, Levinton C, Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry.* 2002;63(12):1135-1139.
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13. Sernyak M-J, Leslie DL, Alarcon RD, et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry.* 2002; 159:561-566.
14. Gianfrancesco FD, Grogg A-L, Mahmoud RA, et al. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on Type 2 diabetes: findings from a large health plan database. *J Clin Psychiatry.* 2002;63(10):920-930.
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17. Foss MC, Paula FJ, Paccolla GM, et al. Peripheral glucose metabolism in human hyperprolactinaemia. *Clin Endocrinol.* 1995;43:721-726.

EXHIBIT 8 PAGE 8 OF 10

C D E F G H

0019001

The diabetes risk your patients face may be even greater if they:[15-17]

- ☑ Are African American, Native American, Asian American/Pacific Islander, or Hispanic.
- ☑ Are 45 years of age or older.
- ☑ Have a body mass index ≥25 kg/m^2.
- ☑ Have dyslipidemia.
- ☑ Do not get enough exercise.
- ☑ Are hypertensive.
- ☑ Have polycystic ovary syndrome.
- ☑ Have a previous history of glucose intolerance.
- ☑ Have a family history of diabetes.
- ☑ Have a history of gestational diabetes or delivered a baby weighing >9 lbs.

For additional safety profile and other important prescribing considerations for ZYPREXA, see inside and the full Prescribing Information.

The Adverse Reactions section of the full Prescribing Information for ZYPREXA includes hyperglycemia (infrequent), glycosuria (infrequent), diabetes mellitus (infrequent), diabetic acidosis (rare), and ketosis (rare) as well as postintroduction reports of diabetic coma.

Lilly
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C D E F G H

006102

EXHIBIT 8
PAGE 9 OF 10

Consider the whole story.

EXHIBIT 8
PAGE 10 OF 10

006103

- Diabetes is **common**, and people with serious **mental illness** are at an even **greater risk**
- Among patients treated with different antipsychotics, clinical trial and epidemiological data show **no consistent differences** in rates of diabetes
- **Assess** patients for **risk factors** of diabetes, irrespective of which psychotropic is prescribed
- Treatment selection should be based on the patient's underlying **psychiatric condition** and the overall **risk/benefit profile** of the medication

For additional safety profile and other important prescribing considerations for ZYPREXA, see inside and the full Prescribing Information.

The Adverse Reactions section of the full Prescribing Information for ZYPREXA includes hyperglycemia (infrequent), glycosuria (infrequent), diabetes mellitus (infrequent), diabetic acidosis (rare), and ketosis (rare) as well as postintroduction reports of diabetic coma.

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Lilly
Answers That Matter.

C D E F G H

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, vs. ELI LILLY AND COMPANY, Defendant.	CASE NO. 3AN-06-5630 CIV

The videotaped deposition upon oral examination of DAVID THOMAS NOESGES, a witness produced and sworn before me, Carolyn L. Smith, CSR, RPR, Notary Public, in and for the County of Hamilton, State of Indiana, taken on behalf of Plaintiff, at the offices of Ice Miller, One American Square, Suite 3100, Indianapolis, Indiana, on January 11, 2008, at 9:31 a.m., pursuant to all applicable rules.

marked as Plaintiffs' Exhibit 2368, which for the record is the consensus statement, an article titled "Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes." It was published in Diabetes Care in February of 2004 and it's been previously marked as Plaintiffs' Exhibit 2368.

Sir, if I could direct your attention to Table 2 of this article, which is on the second page on the bottom right-hand corner.

There is a table there rating various second generation antipsychotics and their association with metabolic abnormalities, correct?

A Yes.

Q And the assessments that they give there are for Weight gain, Risk for diabetes, and Worsening lipid profile, correct?

A Yes.

Q In the legend at the bottom they note that a plus sign indicates that there is an increased effect; a minus sign indicates there is no effect and a D indicates that there is discrepant results, correct?

A Yes.

Q And with respect to Weight gain, it shows that

Olanzapine and Clozapine are given three pluses and the others have lesser numbers, correct?

A Yes.

Q And it also shows that there is pluses for the Risk of diabetes for Olanzapine and Clozapine, but not for any of the other drugs, correct?

MR. BOISE: Object to the form.

THE WITNESS: Could you repeat that question for me?

QUESTIONS BY MR. SUGGS:

Q I'll restate the question.

With respect to the Risk for diabetes, it shows that there are pluses, meaning that there is an increased effect, shown in this table for Clozapine and Olanzapine and there are no pluses besides -- beside any of other drugs, correct?

A For risk for diabetes, that's correct.

Q Exactly. Okay. The same thing holds true with respect to Worsening lipid profile, there are plus signs given for Clozapine and Olanzapine, but not for any of the other drugs, correct?

A Yes.

Q If I could direct your attention to the fifth page which is also page 600 in the article.

That is the page that has the Summary in the

right-hand column?

A Yes.

Q I would like to direct your attention to the second full paragraph in the fourth line down on that paragraph it states, quote, Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine appear to have immediate effects. Aripiprozole and ziprasidone are associated with little or no significant weight gain, diabetes, or dyslipidemia. Do you see that language, sir?

A Yes.

THE VIDEOGRAPHER: Excuse me, I have a couple of minutes left.

QUESTIONS BY MR. SUGGS:

Q And that conclusion of the American Diabetes Association and the American Psychiatric Association contradicts Lilly's claims of comparable rates --

MR. BOISE: Object to the form.

QUESTIONS BY MR. SUGGS:

Q -- of diabetes, correct?

MR. BOISE: Object to the form of the question, mischaracterizes the document.

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

AMERICAN DIABETES ASSOCIATION
AMERICAN PSYCHIATRIC ASSOCIATION
AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
NORTH AMERICAN ASSOCIATION FOR THE STUDY OF OBESITY

Antipsychotic medications are an important component in the medical management of many psychotic conditions. With the introduction of the second-generation antipsychotics (SGAs) over the last decade, the use of these medications has soared. Although the SGAs have many notable benefits compared with their earlier counterparts, their use has been associated with reports of dramatic weight gain, diabetes (even acute metabolic decompensation, e.g., diabetic ketoacidosis [DKA]), and an atherogenic lipid profile (increased LDL cholesterol and triglyceride levels and decreased HDL cholesterol).

Because of the close associations between obesity, diabetes, and dyslipidemia and cardiovascular disease (CVD), there is heightened interest in the relationship between the SGAs and the development of these major CVD risk factors. To gain a better understanding of this relationship, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity convened a consensus development conference 19–21 November 2003 on the subject of antipsychotic drugs and diabetes. An eight-member panel heard presentations from 14 experts drawn from the areas of psychiatry, obesity, and diabetes. Presentations were also made by a representative from the U.S. Food and Drug Administration (FDA) and by representatives from the AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, and Pfizer pharmaceutical companies. In addition, before the conference, the consensus panel was given copies of most of the known peer-reviewed, English language clinical studies published in this area, as well as additional articles from animal studies; other papers and abstracts were reviewed at the conference.

With this information, the panel developed a consensus position on the following questions:

1. What is the current use of antipsychotic drugs?
2. What is the prevalence of obesity, prediabetes, and type 2 diabetes in the populations in which the SGAs are used?
3. What is the relationship between the use of these drugs and the incidence of obesity or diabetes?
4. Given the above risks, how should patients be monitored for the development of significant weight gain, dyslipidemia, and diabetes, and how should they be treated if diabetes develops?
5. What research is needed to better understand the relationship between these drugs and significant weight gain, dyslipidemia, and diabetes?

1. WHAT IS THE CURRENT USE OF ANTIPSYCHOTIC DRUGS?

— Antipsychotic medications (Table 1) are the mainstay of treatment for psychotic illnesses and are also widely used in many other psychiatric conditions. Introduced ~50 years ago, these medications have helped millions of people manage their symptoms. For people who respond well, antipsychotics can mean the difference between leading an engaged, fulfilling community life and being severely disabled.

The first-generation antipsychotics (FGAs) are still widely available and are effective at treating positive symptoms of psychosis, such as hallucinations and delusions. FGAs do not, however, adequately alleviate many other common and important aspects of psychotic illness, such as negative symptoms (e.g., withdrawal, apathy, poverty of speech), cognitive impairment, and affective symptoms. In addition, all FGAs can produce significant extrapyramidal side effects at clinically effective doses. These side effects, which include dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia, can make treatment intolerable for some people, leading to subjective distress, diminished function, stigma, and nonadherence.

The effort to find more effective medications with fewer and less-severe side effects led to the development of the SGAs, often referred to as the "atypical antipsychotics." SGAs have fewer or no extrapyramidal side effects at clinically effective doses. Many of these newer medications are also more effective than the older agents at treating the negative, cognitive, and affective symptoms of psychotic illnesses.

The six currently available SGAs vary in their efficacy, formulation, biochemistry, receptor binding, and side effect profiles. One of them, clozapine, is clearly the most effective antipsychotic. However, clozapine is only indicated after other medications have failed or in patients at high risk for suicidal behavior, largely because it can cause agranulocystosis.

In general, SGAs are better tolerated and more effective than the FGAs. Aside from clozapine, they have become the first-line agents for their indicated use and

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Abbreviations: CVD, cardiovascular disease; DKA, diabetic ketoacidosis; FDA, Food and Drug Administration; FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics.

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EXHIBIT D
PAGE 1 OF 6
Zyprexa MDL Plaintiffs' Exhibit No 02368
006109
ZY200381764
Page 1
E F G H

Table 1—*Antipsychotic medications*

	Generic name	Trade name	Year approved
Commonly used FGAs	Chlorpromazine	Thorazine	—
	Perphenazine	Trilafon	—
	Trifluoperazine	Stelazine	—
	Thiothixene	Navane	—
	Haloperidol	Haldol	—
	Fluphenazine	Prolixin	—
SGAs	Clozapine	Clozaril	1989
	Risperidone	Risperdal	1993
	Olanzapine	Zyprexa	1996
	Quetiapine	Seroquel	1997
	Ziprasidone	Geodon	2001
	Aripiprazole	Abilify	2002

are increasingly being used off-label. In current practice, people who are likely to be treated with an SGA include those with schizophrenia spectrum disorders, bipolar disorder, dementia, psychotic depression, autism, and developmental disorders and, to a lesser extent, individuals with conditions such as delirium, aggressive behavior, personality disorders, and posttraumatic stress disorder. These psychiatric conditions are common and often require lifelong treatment. In the U.S., the prevalence of schizophrenia and related conditions is ~ 1%, the prevalence of bipolar disorders is ~ 2%, and the prevalence of major depression is ~ 8%. The SGAs are therefore widely used medications, and their use has important public health ramifications.

2. WHAT IS THE PREVALENCE OF OBESITY, PRE-DIABETES, AND TYPE 2 DIABETES IN THE POPULATIONS IN WHICH THE SGAs ARE USED?

It is difficult to determine whether the prevalence of these metabolic disorders is increased in these psychiatric populations independent of drug treatment. Most of the available data are derived from studies of individuals with schizophrenia, and even in this condition, the evidence is very limited. Data from most studies suggest that the prevalence of both diabetes and obesity among individuals with schizophrenia and affective disorders is ~1.5–2.0 times higher than in the general population. Many characteristics of people with schizophrenia, such as sedentary behavior, may contribute to the apparently higher prevalence of metabolic abnormalities. However, none of these studies controlled for all of the major diabetes risk factors. For example, BMI and family history of diabetes were rarely determined, nor were the control populations appropriately matched for these and other variables. Thus, it is unclear whether psychiatric conditions per se, independent of other known diabetes risk factors, account for the increased prevalence.

There are limited data evaluating the metabolic profile and diabetes risk of drug-naive subjects with schizophrenia. In a small cohort of adults with schizophrenia untreated with medications, visceral fat content (which is correlated with insulin resistance) was threefold higher than in age- and BMI-matched control subjects. In another study, the same investigators found that drug-naive patients presenting with their first episode of schizophrenia had an increased prevalence of impaired fasting glucose, were more insulin resistant, and had higher plasma levels of glucose, insulin, and cortisol than did matched control subjects.

Overall, the limited amount of epidemiological data suggest an increased prevalence of obesity, impaired glucose tolerance, and type 2 diabetes in people with psychiatric illness. Whether this is a function of the illness itself versus its treatment is unknown. Studies using the proper diagnoses of glucose intolerance and more complete risk factor characterization are necessary in order to resolve this issue.

3. WHAT IS THE RELATIONSHIP BETWEEN THE USE OF THESE DRUGS AND THE INCIDENCE OF OBESITY OR DIABETES?

Recognition of an association between SGAs and diabetes was first derived from case reports of severe, sometimes fatal, acute diabetic decompensation, including DKA. Subsequent drug surveillance and retrospective database analyses suggest there is an association between specific SGAs and both diabetes and obesity. This potential relationship is of considerable clinical concern because obesity and diabetes are important risk factors for CVD, and the relative risk of CVD mortality is significantly greater in people with psychiatric disorders than in the general population. High rates of smoking and physical inactivity may also contribute to the excess mortality. Therefore, if SGA therapy further increases the risk for obesity and type 2 diabetes, this should be of major clinical concern.

Although there are significant shortcomings in many of the studies examining the relationships between the SGAs and obesity or diabetes, clear-cut trends can be identified.

Obesity

There is considerable evidence, particularly in patients with schizophrenia, that treatment with SGAs can cause a rapid increase in body weight in the first few months of therapy that may not reach a plateau even after 1 year of treatment. There is, however, considerable variability in weight gain among the various SGAs (Table 2). At 10 weeks of therapy, estimated average weight gain with drug treatment compared with placebo varies from ~0.5 to 5.0 kg. Limited data suggest that in humans, most of the weight gained

Table 2—*SGA's and metabolic abnormalities*

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/–	–	–
Ziprasidone*	+/–	–	–

+ = increase effect; – = no effect; D = discrepant results. *Newer drugs with limited long-term data.

EXHIBIT D
PAGE 2 OF 6

Zyprexa MDL Plaintiffs' Exhibit No.02368
006110
ZY200381765
Page 2

is fat. Data derived from a canine model indicated that certain SGAs increase total visceral fat mass and intrahepatic lipid content.

The mechanism(s) responsible for weight gain associated with SGA therapy are unknown. Weight gain occurs when more energy is ingested than is expended. Therefore, weight gain is due to increased energy intake, decreased energy expenditure, or both. Even a small, chronic imbalance between energy intake and expenditure can lead to large changes in body weight over time. For example, ingestion of ~500 kcal/day more than is expended can account for the largest average weight gain reported with SGA therapy (4.5 kg at 10 weeks). This amount of daily increase in energy intake represents the calories in a normal-size candy bar plus a soda or in an ice cream dessert. Hunger and satiety may be altered in people taking SGAs because of the known binding affinities of these drugs to serotonin, norepinephrine, dopamine, and particularly histamine-H1 receptors. All of these receptors have been implicated in the control of body weight.

Weight gain and changes in body composition may account for many of the purported metabolic complications associated with SGA therapy, e.g., insulin resistance, pre-diabetes, diabetes, and dyslipidemia. A possible direct effect of SGAs on β-cell function and insulin action in liver and muscle tissue could also be involved, as discussed below.

Diabetes

Numerous case reports have documented the onset or exacerbation of diabetes, including the occurrence of hyperglycemic crises, following initiation of therapy with many of the SGAs.

Several of these events occurred within a few weeks of initiating drug treatment. In some, but not all cases, hyperglycemia promptly resolved after the medication was discontinued. Several reports documented recurrent hyperglycemia after another challenge with the same drug. Additional cases of diabetes or hyperglycemia have been reported through MedWatch into the FDA's Adverse Event Reporting System.

Large retrospective cohort studies have been reported that estimate the prevalence of diabetes in patients using SGAs. These reports relied on a variety of methods for determining the diagnosis of diabetes, such as ICD-9 codes and data on prescriptions for diabetes medications. In addition, several cross-sectional studies of patients taking different SGAs, "switch studies" of patients changed from one medication to another, and one prospective randomized controlled trial evaluating SGA therapy on parameters of insulin sensitivity and glycemic control have been conducted. Despite limitations in study design, the data consistently show an increased risk for diabetes in patients treated with clozapine or olanzapine compared with patients not receiving treatment with FGAs or with other SGAs. The risk in patients taking risperidone and quetiapine is less clear; some studies show an increased risk for diabetes, while others do not. The two most recently approved SGAs, aripiprazole and ziprasidone, have relatively limited epidemiological data, but available clinical trial experience with these drugs has not shown an increased risk for diabetes (Table 2).

One possible mechanism for hyperglycemia is impairment of insulin action (i.e., insulin resistance). Drug-induced insulin resistance may occur because of weight gain or a change in body fat distribution or by a direct effect on insulin-sensitive target tissues. Patients treated with olanzapine and clozapine have higher fasting and postprandial insulin levels than patients treated with FGAs, even after adjusting for body weight. To date, studies in humans have not shown adverse effects of any antipsychotic medication on β-cell function, but this issue has not been adequately studied in individuals with psychiatric illnesses.

Dyslipidemia

An additional related consequence of SGA use is their effect on serum lipids. Although the data are limited, the available evidence suggests that changes in serum lipids are concordant with changes in body weight. Clozapine and olanzapine, which produce the greatest weight gain, are associated with the greatest increases in total cholesterol, LDL cholesterol, and triglycerides and with decreased HDL cholesterol. Aripiprazole and ziprasidone, which are associated with the least amount of weight gain, do not seem to be associated with a worsening of serum lipids. Risperidone and quetiapine appear to have intermediate effects on lipids (Table 2).

Risk-benefit assessment

Despite the adverse effects cited above, a number of factors should be considered when choosing among the antipsychotic medications. These include the nature of the patient's psychiatric condition, specific target signs and symptoms, past history of drug response (both therapeutic and adverse), patient preference, history of treatment adherence, medication effectiveness, psychiatric and medical comorbidities, availability of appropriate formulations (e.g., fast-dissolving oral, short- or long-acting intramuscular), need for special monitoring, and cost of and access to medications. Nonetheless, the risks of obesity, diabetes, and dyslipidemia have considerable clinical implications in this patient population and should also influence drug choice.

Even for those medications associated with an increased risk of metabolic side effects, the benefit to specific patients could outweigh the potential risks. For example, clozapine has unique benefits for treatment-refractory patients and those at significant risk for suicidal behavior. Since treatment response in many psychiatric conditions is heterogeneous and unpredictable, physicians and patients can benefit from the availability of a broad array of different therapeutic agents.

4. GIVEN THE ABOVE RISKS, HOW SHOULD PATIENTS BE MONITORED FOR THE DEVELOPMENT OF SIGNIFICANT WEIGHT GAIN, DYSLIPIDEMIA, AND DIABETES, AND HOW SHOULD THEY BE TREATED IF DIABETES DEVELOPS? —

Given the serious health risks, patients taking SGAs should receive appropriate baseline screening and ongoing monitoring. Clinicians who prescribe SGAs for patients with psychiatric illnesses should have the capability of determining a patient's height and weight (BMI) and waist circumference. These values should be recorded and tracked for the duration of treatment. Clinicians should also encourage patients to monitor and chart their own weight. It is particularly important to monitor any alteration in weight following a medication change. The patients' psychiatric illness should not discourage clinicians from addressing the metabolic

EXHIBIT D
PAGE 3 OF 6
Zyprexa MDL Plaintiffs' Exhibit No.02368
006111
ZY200381766
Page 3

Table 3—*Monitoring protocol for patients on SGAs**

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

*More frequent assessments may be warranted based on clinical status

complications for which these patients are at increased risk.

Baseline monitoring

The panel recommends that baseline screening measures be obtained before, or as soon as clinically feasible after, the initiation of any antipsychotic medication (Table 3). These include

- Personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease
- Weight and height (so that BMI can be calculated)
- Waist circumference (at the level of the umbilicus)
- Blood pressure
- Fasting plasma glucose
- Fasting lipid profile

These assessments can determine if the patient is overweight (BMI 25.0–29.9) or obese (BMI ≥30), has pre-diabetes (fasting plasma glucose 100–125 mg/dl) or diabetes (fasting plasma glucose ≥126 mg/dl), hypertension (blood pressure >140/90 mmHg), or dyslipidemia. If any of these conditions are identified, appropriate treatment should be initiated. Psychiatrists should not hesitate to refer the patient to the appropriate health care professional or specialist knowledgeable about these disorders.

The panel recommends that nutrition and physical activity counseling be provided for all patients who are overweight or obese, particularly if they are starting treatment with an SGA that is associated with significant weight gain. Referral to a health care professional or program with expertise in weight management may also be appropriate.

Health professionals, patients, family members, and caregivers should be aware of the signs and symptoms of diabetes and especially those associated with the acute decompensation of diabetes such as DKA (Table 4). The latter is a life-threatening condition and always requires immediate treatment. Patients, family members, and caregivers also need to know that treatment with some SGAs may be associated with significant weight gain and a heightened risk of developing diabetes and dyslipidemia. For patients with, or at higher risk for, diabetes and in those treated with other medications that may increase these risks (e.g., valproate, lithium, Depo-Provera), it may be preferable to initiate treatment with an SGA that appears to have a lower propensity for weight gain and glucose intolerance (Table 2). Potential for weight gain should also be considered in the choice of other psychiatric and nonpsychiatric medications.

Table 4—*DKA clinical presentation*

Rapid onset of:
- Polyuria, polydipsia
- Weight loss
- Nausea, vomiting
- Dehydration
- Rapid respiration
- Clouding of sensorium, even coma

Follow-up monitoring

The patient's weight should be reassessed at 4, 8, and 12 weeks after initiating or changing SGA therapy and quarterly thereafter at the time of routine visits (Table 3). If a patient gains ≥5% of his or her initial weight at any time during therapy, one should consider switching the SGA. In such a situation, the panel recommends cross-titration to be the safest approach; abrupt discontinuation of an antipsychotic drug should generally be avoided. When switching from one antipsychotic drug to another, it is preferable to discontinue the current medication in a gradual fashion. The profile of the subsequent drug will determine the initial dose and escalation strategy. Particular consideration should be given before discontinuing clozapine because of the potential for serious psychiatric sequelae.

Fasting plasma glucose, lipid levels, and blood pressure should also be assessed 3 months after initiation of antipsychotic medications. Thereafter, blood pressure and plasma glucose values should be obtained annually or more frequently in those who have a higher baseline risk for the development of diabetes or hypertension. In those with a normal lipid profile, repeat testing should be performed at 5-year intervals or more frequently if clinically indicated.

Although limited data are available in children and adolescents regarding the risks of diabetes when SGAs are given, these patients should have their height, in addition to weight, measured at regular intervals and their BMI calculated. BMI percentile adjusted for age and sex should be used to determine if excessive weight gain has occurred, and if present, a change in therapy should be considered.

For people who develop worsening glycemia or dyslipidemia while on antipsychotic therapy, the panel recommends considering switching to an SGA that has not been associated with significant weight gain or diabetes (Table 2). All patients with diabetes should be referred to an American Diabetes Association–recognized diabetes self-management education program, if available. Referral to a clinician with experience treating people with diabetes is recommended. These patients should carry diabetes identification.

Immediate care or consultation is required for patients with symptomatic or severe hyperglycemia (glucose values >300 mg/dl), symptomatic hypoglycemia, or glucose levels <60 mg/dl, even in the absence of symptoms. The presence of

EXHIBIT D
PAGE 4 OF 6
Zyprexa MDL Plaintiffs' Exhibit No.02368
006112
ZY200381767
Page 4

symptoms of DKA (Table 4), requires immediate evaluation and treatment.

Blood pressure, lipid, and glycemic goals of therapy for people with diabetes apply equally to those who also have psychiatric disorders. However, all goals need to be individualized. The benefits and risks of different therapeutic agents used in the treatment of diabetes and its comorbidities should be considered in the context of the patient's psychiatric condition and treatment.

In summary, the panel recommends the following:

- Consideration of metabolic risks when starting SGAs
- Patient, family, and care giver education
- Baseline screening
- Regular monitoring
- Referral to specialized services, when appropriate

5. WHAT RESEARCH IS NEEDED TO BETTER UNDERSTAND THE RELATIONSHIP BETWEEN THESE DRUGS AND SIGNIFICANT WEIGHT GAIN, DYSLIPIDEMIA, AND DIABETES? — Evidence for weight gain and abnormalities of glucose and lipid metabolism in patients taking SGAs is in part derived from case-control studies, pharmacovigilance (e.g., through MedWatch), and database reviews. Many of these studies suffer from their retrospective nature, heterogeneity of methodology, selection or ascertainment bias, and absence of appropriate or well-characterized control subjects. Comparison studies among SGAs are also limited by relatively short periods of study, by failure to control for a possible treatment sequence bias in "switchover" studies, and by not always using clinically equivalent dosages of the medications.

Trials with SGAs should be randomized and controlled, preferably using drug-naive subjects. Weight gain and measures of glucose and lipid metabolism should be thoroughly evaluated. Study subjects should be well-characterized in terms of their baseline risk factors for diabetes, obesity, and lipid disorders and their degree of baseline impairment in insulin sensitivity and β-cell function. The duration of exposure to the various SGAs should be carefully controlled. Future research studies should focus on the following:

- Baseline body composition in untreated patients with psychiatric disorders and changes that occur during treatment with SGAs need to be better characterized. This would include measures of fat versus fat-free mass and visceral and subcutaneous adipose stores, using valid methods to measure body fat (e.g., magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry).
- The contribution of altered neuroendocrine function (e.g., hypothalmic-pituitary-adrenal axis activation) to alterations in body composition and abnormalities in glucose and lipid metabolism needs further study to distinguish the acute effects of stress from the underlying disease process.
- Studies are needed that examine glucose and lipid metabolism as they relate to alterations in insulin sensitivity in peripheral and hepatic tissues (e.g., euglycemic-hyperinsulinemic clamp with labeled glucose infusions), alterations in β-cell function (hyperglycemic clamp or frequently sampled intravenous glucose tolerance test), and alterations in lipid metabolism (using tracer infusions).
- Large prospective studies should be conducted to identify baseline and early treatment factors that predict the later occurrence of abnormalities in body weight and composition and disorders of glucose and lipid metabolism during treatment with these drugs.
- Additional studies are needed to identify whether there are baseline characteristics that predict acute, life-threatening complications (e.g., DKA, pancreatitis).
- Additional data are needed to determine whether the risks of therapy are increased in certain ethnic groups (e.g., African Americans).
- Studies determining the effect of SGAs in various psychiatric disorders are needed to clarify the disease-related risk for the development of weight gain and metabolic disturbances.
- Alterations in energy intake and expenditure as contributors to weight gain in the psychiatric population and how these processes are altered by treatment with SGAs should be studied.
- Studies are needed to determine whether the disorders of body weight and glucose and lipid metabolism are due to central nervous system or peripheral tissue actions of the SGAs. Valuable information on the direct effects of SGAs on different body tissue compartments might be obtained from studies in appropriate animal models.
- Studies of the genetic markers that are associated with, and may be causally related to, the metabolic disturbances occurring in treated patients with psychiatric disorders (e.g., 5-HT_{2C}, histamine-H1 receptor alleles) are needed.

SUMMARY — The SGAs are of great benefit to a wide variety of people with psychiatric disorders. As with all drugs, SGAs are associated with undesirable side effects. One constellation of adverse effects is an increased risk for obesity, diabetes, and dyslipidemia. The etiology of the increased risk for metabolic abnormalities is uncertain, but their prevalence seems correlated to an increase in body weight often seen in patients taking an SGA. Direct drug effects on β-cell function and insulin action could also be involved, since there is insufficient information to rule out this possibility. In the general population, being overweight or obese also carries a much higher risk of diabetes and dyslipidemia.

These three adverse conditions are closely linked, and their prevalence appears to differ depending on the SGA used. Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine appear to have intermediate effects. Aripiprazole and ziprasidone are associated with little or no significant weight gain, diabetes, or dyslipidemia, although they have not been used as extensively as the other agents.

The choice of SGA for a specific patient depends on many factors. The likelihood of developing severe metabolic disease should also be an important consideration. When prescribing an SGA, a commitment to baseline screening and follow-up monitoring is essential in order to mitigate the likelihood of developing CVD, diabetes, or other diabetes complications.

EXHIBIT D
PAGE 5 OF 6

Zyprexa MDL Plaintiffs' Exhibit No.02368

006113

ZY200381768
Page 6

E F G H

APPENDIX

Consensus panel

Eugene Barrett, MD, PhD, Chair; Lawrence Blonde, MD, Stephen Clement, MD, John Davis, MD, John Devlin, MD, John Kane, MD, Samuel Klein, MD, William Torrey, MD.

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Presenters at the conference

David Allison, PhD, Richard Bergman, PhD, John Buse, MD, PhD, Patrizia Cavazzoni, MD, Fred Fiedorek, MD, Rohan Ganguli, MD, Andrew Greenspan, MD, David Kendall, MD, Ron Leonge, MD, Antony Loebel, MD, Patrick Lustman, PhD, Herbert Meltzer, MD, John Newcomer, MD, Judy Racoosin, MD, Bryan Roth, MD, Michael Sernyak, MD, Jogin Thakore, MB, Donna Wirshing, MD, William Wirshing, MD.

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EXHIBIT D
PAGE 6 OF 6
Zyprexa MDL Plaintiffs' Exhibit No.02368
006114
ZY200381769
Page 6
E F G H

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

vs.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

VIDEOTAPED DEPOSITION OF LUCY LJUBICICH CURTISS, M.D.

December 13, 2007
1:35 p.m.

Taken at:
Anchorage Community Mental Health
4020 Folker Street, Conference Room C
Anchorage, Alaska

Reported by: Sandra M. Mierop, CRR, CPP, CBC

EXHIBIT E
PAGE 1 OF 4

patient against his or her will?

A. Not directly. No.

Q. Have you ever sought a court order to medicate somebody?

A. No. We don't do that in the outpatient setting. If we think that someone is at imminent risk, we seek hospitalization; we would never seek a court order to medicate someone in the community.

Q. And the hospitalization would be typically in this community at API?

A. At API.

Q. For what kinds of conditions do you use Zyprexa in your practice today?

A. In my practice today, I have patients that take Zyprexa for schizophrenia, schizoaffective disorder, bipolar disorder, PTSD, and behavioral disturbances associated with dementia.

Q. And for several of those illnesses, the treatment with Zyprexa would be off label; is that correct?

A. Yes.

Q. Why do you use Zyprexa off label?

A. Well, in psychiatry there is very much

off-label prescribing; and particularly in the field of geriatric psychiatry, there are no FDA-indicated treatments for behavioral disturbances associated with dementia. All of that prescribing is off label. And so I think as -- as a field, we are more comfortable with off-label prescribing than other fields may be.

Q. How about for post-traumatic stress disorder?

A. That is also a diagnosis for which most prescribing is off label.

Q. Have you found in your practice that using Zyprexa for schizoaffective disorder, post-traumatic stress disorder and behavioral disturbances associated with dementia has been effective for your patients?

A. For some patients, yes.

MR. STEELE: Is there a "T" in that word?

MR. ROGOFF: Yes, no, does not have a T in it.

MR. STEELE: He's got a "T" in his "schizo," "schizo."

MR. ROGOFF: No.

MR. JAMIESON: It's the German

articulate a percentage, first of all, from second-generation versus first generation?

A. I would say the majority is second-generation. Beyond that, no.

Q. Can't break it down among the second-generation anti-psychotics?

A. I use all of them.

Q. Has your use of them varied over the years? And I'm talking about the atypicals.

A. Yes.

Q. For what reasons has your usage varied?

A. Availability. And they weren't all available at the same time. My experience and comfort in prescribing them. It takes probably a couple of years to really have a good feel for an agent and how to use it, when to use it, who is most likely to benefit from it. Side effect profiles. All of the concerns about metabolic effects, definitely we think more about that now than we did in the past.

Q. When did your concern about metabolic side effects change?

A. Again, I can't tell you what year, but it has been within the last few years.

Q. Do you recall a classwide label change

EXHIBIT E
PAGE 4 OF 4

F G H

Know your patients.

- Michael is in his mid-30s, highly functional, has been your patient for years, and is in good general health
- He reports a decreased need for sleep
- You've ruled out substance abuse and possible organic causes
- He strongly resists your attempt to refer him for psychiatric treatment

His wife has shared her concerns with you...

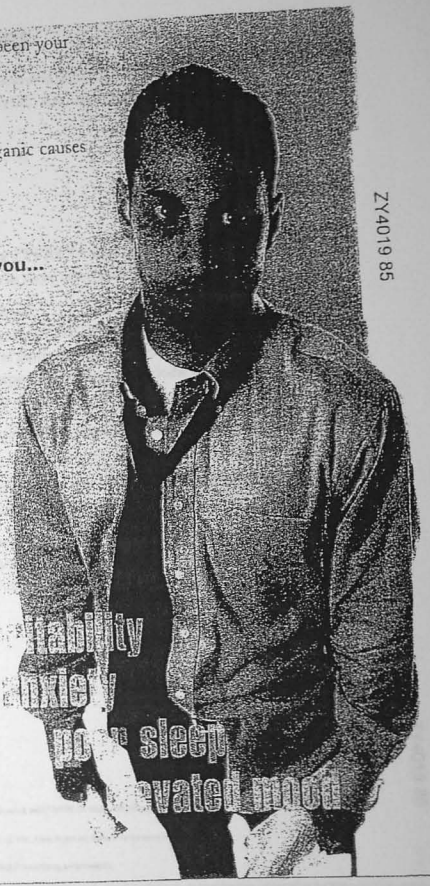
"He has these sudden mood swings—I never know what to expect."

"He talks so quickly, bouncing from subject to subject."

"He's being so erratic. He's spending money we just don't have."

Goals of treatment may include:

- Stabilize mood
- Reduce agitation



Know **ZYPREXA.**

zyprexa Olanzapine

EXHIBIT F
PAGE 1 OF 4

Lilly

G H

Other prescribing considerations

The most common treatment-emergent adverse event associated with ZYPREXA in placebo-controlled bipolar mania trials was somnolence* (35% vs 13% for placebo). Also observed (ZYPREXA vs placebo) were:

dry mouth* (22% vs 7%)
dizziness* (18% vs 6%)
asthenia* (15% vs 6%)
constipation (11% vs 5%)
dyspepsia (11% vs 5%)
increased appetite (6% vs 3%)
tremor (6% vs 3%)

Orthostatic hypotension
In premarketing schizophrenia trials, some patients taking ZYPREXA may have experienced orthostatic hypotension associated with dizziness,† tachycardia,† and, in some cases, syncope (15/2500, 0.6%).

Transient, asymptomatic elevations of hepatic transaminase
In placebo-controlled schizophrenia studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to ZYPREXA compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

As with all antipsychotic medications, the following considerations should be taken into account when prescribing ZYPREXA:

Tardive dyskinesia (TD)—as with all antipsychotic medications, prescribing should be consistent with the need to minimize TD. If its signs and symptoms appear, discontinuation should be considered.

Seizures—occurred infrequently in premarketing clinical trials (22/2500, 0.9%). Confounding factors may have contributed to many of these occurrences. ZYPREXA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Such conditions may be more prevalent in patients age 65 years or older.

ZY4019 86

* In bipolar mania trials, 4 adverse events occurred with statistically significantly higher incidence with ZYPREXA than with placebo—none of these resulted in discontinuation.
† In acute-phase schizophrenia trials (n=366), dizziness (11% vs 4%) and tachycardia (4% vs 1%) were reported; these events were not always associated with hypotension.

For additional safety profile and other important prescribing considerations, see the full Prescribing Information.

zyprexa Olanzapine

Lilly

EXHIBIT F
PAGE 2 OF 4

G H

ZY4019 87

Favorable safety profile

- **No black-box or bolded warnings**
- **No baseline ECG required**
  - No difference in clinically significant QTc prolongation with ZYPREXA compared to placebo in premarketing clinical trials
- **No routine blood monitoring required**
- **The most common treatment-emergent adverse event associated with ZYPREXA in placebo-controlled clinical trials for acute mania was somnolence (35% vs 13% for placebo)**

ZYPREXA has been used by more than 6 million patients worldwide.

ZY4019 88

ge see inside for additional safety information and full Prescribing Information.
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ZEXA is a registered trademark of Eli Lilly and Company.

Zyprexa Olanzapine

www.ZYPREXA.com

Lilly

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Zyprexa MDL Plaintiffs' Exhibit No.00229
006122
EXHIBIT F
PAGE 4 OF 4
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G H

zyprexa
Olanzapine

ZY 4026 87

Lilly

EXHIBIT 6
PAGE 1 OF 22

ZYPREXA
the novel psychotropic

ZYPREXA is the only psychotropic agent approved for all of the following:

- Short-term treatment of bipolar mania
- Short-term treatment and maintenance of treatment response in schizophrenia

Favorable safety profile

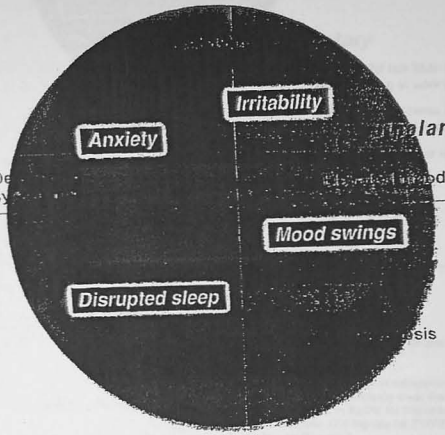
Mood

- Extrapyramidal symptoms (EPS) comparable to placebo
  - In only one analysis of a placebo-controlled study, only one specific form of EPS, akathisia, was reported significantly more often with ZYPREXA at any specific dose (10.0±2.5 or 15.0±2.5 mg/day) compared with placebo
- Effect on prolactin comparable to placebo
  - In 6-week, acute-phase trials involving schizophrenia patients, modest elevations of prolactin were seen, although mean changes from baseline to endpoint were not statistically significantly different between ZYPREXA and placebo. A small number of patients experienced asymptomatic elevations of hepatic transaminase; none of these patients developed jaundice or drug-induced hepatitis.
- Low potential for harmful drug interactions
- No significant change in QT interval compared to placebo
  - No difference in clinically significant QTc prolongation with ZYPREXA compared to placebo in premarketing clinical trials
- No routine blood monitoring

5 years on the market, used by more than 8 million patients worldwide

zy 4036 88

EXHIBIT 6
PAGE 2 OF 22



Mood

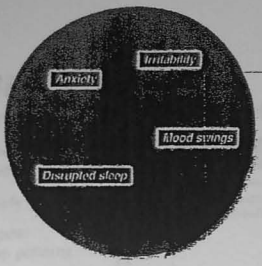
Schizophrenia

ZY 4036 89

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information.

Zyprexa Olanzapine

EXHIBIT 6
PAGE 3 OF 22



Donna

Single mom in her mid-30s, presents in drab clothing and seems ill at ease

"I feel so anxious and irritable lately."

History

- Reports she has been sleeping more than usual, has trouble concentrating at work and at home
- Several appointments earlier, she was talkative, elated, and reported little need for sleep
- You have treated her with various medications including antidepressants

- **Change in appearance**
- **Decreased energy**
- **Decreased concentration**

Favorable safety profile

- **Incidence of EPS significantly lower than Risperdal® (risperidone)[1]**
  - Incidence of treatment-emergent extrapyramidal symptoms (EPS) was significantly lower than Risperdal (12.5% for ZYPREXA vs 22.3% for Risperdal; $P=.034$, Mean modal doses: 17.2 mg/day for ZYPREXA, 7.2 mg/day for Risperdal)
- **Incidence of prolactin elevation significantly lower than Risperdal[1]**
  - Potential complications of prolactin elevation may include sexual dysfunction, amenorrhea, galactorrhea, gynecomastia, and risk of osteoporosis[2-5]
- **Pregnancy category C**
  - No evidence of teratogenicity was observed in preclinical trials; there are no adequate and well-controlled trials with ZYPREXA in pregnant women

1 See Study 2 on pages 18-20 for Methodology and Study Limitations.

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.
2. Hamner MB, et al. *CNS Drugs.* 1996;10(3):209-222.
3. Marken PA, et al. *Clin Pharm.* 1992;11:851-856.
4. Halbreich U, et al. *Schizophr Bull.* 1996;22(3):447-454.
5. Ataya K, et al. *Fertil Steril.* 1988;50(6):876-881.

ZY-1036-90

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information. For safety information on Risperdal or Depakote, see manufacturers' package inserts.

EXHIBIT G
PAGE 4 OF 22

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Zyprexa MDL Plaintiffs' Exhibit No.00284
006126
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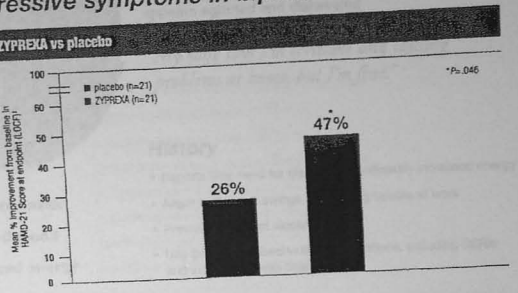
Page 4

Reliable...

Improves depressive symptoms in bipolar manic or mixed patients

- Depressed mood
- Anxiety
- Irregular sleep patterns



Improvement compared with placebo at week 3 in manic and mixed patients with substantial depressive symptoms (defined as HAMD≥20)

1 HAMD-21 is Hamilton Rating Scale for Depression, consisting of 21 items.

LOCF is Last Observation Carried Forward.

See Studies 3 and 4 on pages 18-20 for Methodology and Study Limitations.

ZYPREXA is not approved for the treatment of bipolar depression

Works as early as day 2

ZYPREXA was statistically significantly better (LOCF) in Y-MRS Total Score[1] compared with Depakote® (divalproex sodium) ($P=.031$) as early as day 2

Mean modal doses were 17 mg QD for ZYPREXA and 1400 mg BID or TID for Depakote

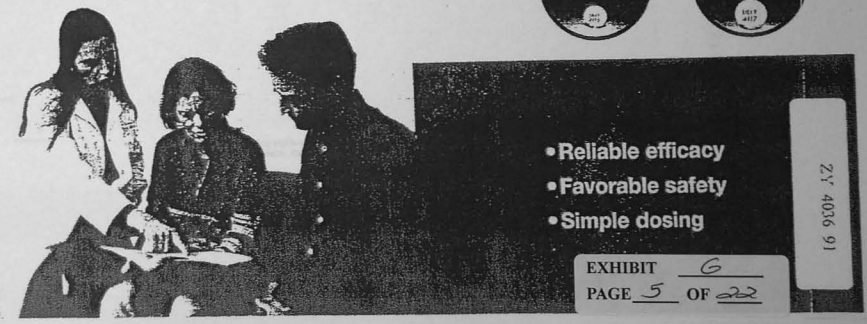
1 Y-MRS is Young Mania Rating Scale, consisting of 11 items.

Y-MRS Total Score was measured at days 1, 2, 3, 4, 5, 6, 7, 14, and 21 (endpoint).

See Study 5 on pages 18-20 for Methodology and Study Limitations.

Simple...

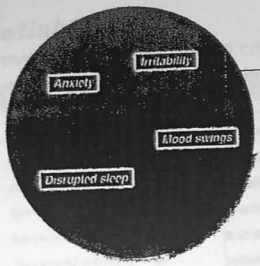
Once-daily dosing at bedtime



ZY 4036 91

EXHIBIT 6
PAGE 5 OF 22

ZYPREXA



Mark

Middle-aged male brought in by his wife, appears agitated and disheveled

"My wife says I'm irritable and causing problems at home, but I'm fine."

- **Erratic behavior**
- **Elevated mood**
- **Increased energy**

History

- Reports little need for sleep and significantly increased energy
- Anger and mood swings are causing trouble at work
- Previous history of alcohol abuse
- Has been prescribed various medications, including SSRIs and anxiolytics, with little success

Favorable safety profile

- **No black-box or bolded warnings**
- **No routine blood monitoring required**
- **Incidence of prolactin elevation significantly lower than Risperdal® (risperidone)[1]**
  - Potential complications of prolactin elevation may include sexual dysfunction, amenorrhea, galactorrhea, gynecomastia, and risk of osteoporosis[2-5]

1 See Study 2 on pages 18-20 for Methodology and Study Limitations.

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.
2. Hamner MB, et al. *CNS Drugs.* 1998;10(3):209-222.
3. Marken PA, et al. *Clin Pharm.* 1992;11:851-856.
4. Halbreich U, et al. *Schizophr Bull.* 1995;22(3):447-454.
5. Ataya K, et al. *Fertil Steril.* 1988;50(6):875-881.

ZY-1036-02

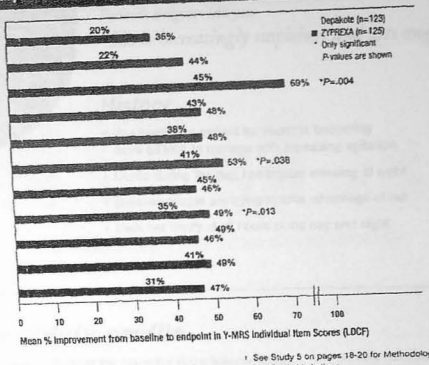
For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information. For safety information on Risperdal or Depakote, see manufacturers' package inserts.

EXHIBIT 6
PAGE 6 OF 22

Reliable...

Proven effective in treating complicated mood symptoms in bipolar mania†

ZYPREXA vs Depakote® (divalproex sodium)



† See Study 5 on pages 18-20 for Methodology and Study Limitations.

Works as early as day 2

ZYPREXA was statistically significantly better (LOCF) in Y-MRS Total Score‡ compared with Depakote ($P=.031$) as early as day 2

‡ Y-MRS Total Score was measured at days 1, 2, 3, 4, 5, 6, 7, 14, and 21 (endpoint).

See Study 5 on pages 18-20 for Methodology and Study Limitations.

Simple...

Once-daily dosing at bedtime

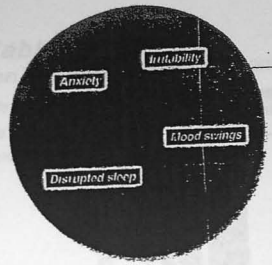
- **Reliable efficacy**
- **Favorable safety**
- **Simple dosing**

ZY 4036 93

zyprexa Olanzapine

Mark

EXHIBIT 6
PAGE 7 OF 22



Martha

Widow, living independently near her family

Patient's daughter tells you:
"She is increasingly suspicious and gets angry easily."

History

- Has been your patient for years; is becoming more difficult to manage with increasing agitation
- Dozes during the day, has trouble sleeping at night
- Believes people are trying to take advantage of her
- Calls her family at all hours of the day and night

- **Agitation**
- **Hostility**
- **Suspicion**

Favorable safety profile

- **Low potential for harmful drug interactions**
- **Low potential for anticholinergic side effects[†]**
  - Incidence of serious anticholinergic events not statistically different from placebo in schizophrenia trials
- **Incidence of EPS significantly lower than Risperdal® (risperidone)[‡1]**
  - Incidence of treatment-emergent extrapyramidal symptoms (EPS) was significantly lower than Risperdal (12.5% for ZYPREXA vs 22.3% for Risperdal; $P=.034$. Mean modal doses: 17.2 mg/day for ZYPREXA, 7.2 mg/day for Risperdal)

† See Study 1 on pages 18-20 for Methodology and Study Limitations.

‡ See Study 2 on pages 18-20 for Methodology and Study Limitations.

1. Tran PV, et al. J Clin Psychopharmacol. 1997;17:407-418.

ZY 4036 94

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information. For safety information on Risperdal, see manufacturer's package insert.

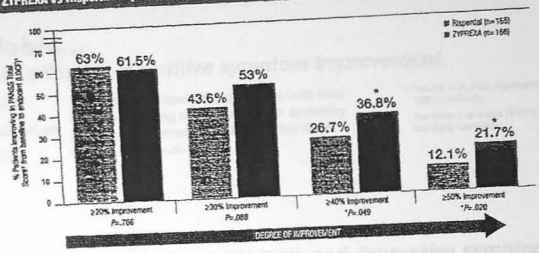
EXHIBIT 6
PAGE 8 OF 22

Reliable...

Proven effective in total symptom improvement

- Hostility
- Anxiety
- Suspiciousness

ZYPREXA vs Risperdal in patients with schizophrenia



A significantly greater percentage of patients treated with ZYPREXA achieved an improvement of ≥40% in PANSS Total Score as compared with Risperdal-treated patients[1]

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.

† PANSS is Positive and Negative Syndrome Scale, consisting of 30 items.

See Study 2 on pages 18-20 for Methodology and Study Limitations.

Martha

Simple...

Once-daily dosing at bedtime

- Reliable efficacy
- Favorable safety
- Simple dosing

LY 4036 95

zyprexa
Olanzapine

EXHIBIT 6
PAGE 9 OF 202

ZYPREXA is the only agent indicated for both bipolar mania and schizophrenia

Reliable...

Proven effective in positive symptom improvement

- Delusions
- Suspiciousness
- Hostility

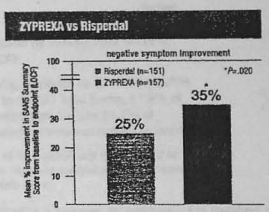
ZYPREXA and Risperdal® (risperidone) both were effective in treating positive symptoms according to mean improvement in PANSS Positive Score (32% vs 31%, $P=.654$)[1]

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.

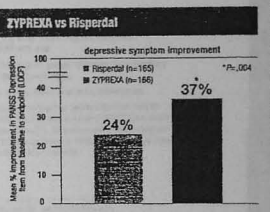
See Study 2 on pages 18-20 for Methodology and Study Limitations.

Improvement in negative symptoms and depressive symptoms[1]

- Lack of motivation
- Social withdrawal
- Sadness
- Hopelessness



ZYPREXA was significantly more effective than Risperdal in treating negative symptoms



ZYPREXA was significantly more effective than Risperdal in improving depressive symptoms associated with schizophrenia

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.

SANS is Scale for Assessment of Negative Symptoms, consisting of 24 items.

See Study 2 on pages 18-20 for Methodology and Study Limitations.

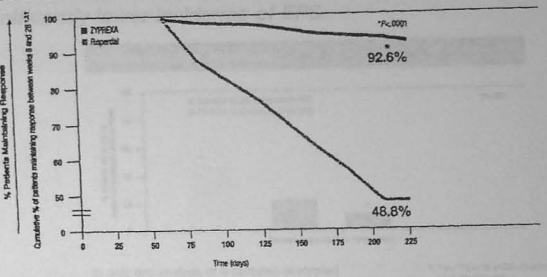
ZY 4036 96

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information.
For safety information on Risperdal, see manufacturer's package insert.

EXHIBIT 6
PAGE 10 OF 22

Superior maintenance of treatment response for patients achieving ≥40% improvement

ZYPREXA vs Risperdal



Relapse measured by PANSS Total Score at endpoint (LOCF)†

When measuring response as defined by ≥20% improvement in PANSS Total Score, 87.9% of ZYPREXA-treated patients and 67.7% of Risperdal-treated patients maintained response

Patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.

   See Study 2 on pages 18-20 for Methodology and Study Limitations.
2. Data on file, Lilly Research Laboratories.

† Response defined as ≥40% improvement in PANSS Total Score at week 8 (ZYPREXA n=44, Risperdal n=37). Symptom worsening defined as ≥20% worsening in PANSS Total Score plus CGI-S ≥3 after 8 weeks.

ZYPREXA is approved for maintenance of treatment response in schizophrenia

- **Reliable efficacy**
- **Favorable safety**
- **Simple dosing**

ZY 4036 97

zyprexa Olanzapine

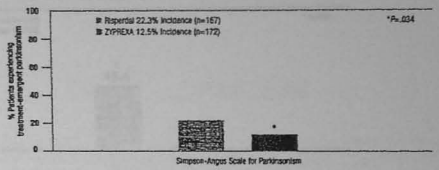
ZYPREXA vs Risperdal

EXHIBIT 6
PAGE 11 OF 22

ZYPREXA is the only agent indicated for both bipolar mania and schizophrenia

Significantly lower incidence of EPS

ZYPREXA vs Risperdal® (risperidone)



In only one analysis of a placebo-controlled study, only one specific form of EPS, akathisia, was reported significantly more often with ZYPREXA at any specific dose (10.0±2.5 or 15.0±2.5 mg/day) compared with placebo

Mean modal dose was 17.2 mg/day for ZYPREXA and 7.2 mg/day for Risperdal

EPS symptoms include:

- tremors
- rigidity
- spasms
- restlessness
- inability to sit still

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-408.

See Study 2 on pages 18-20 for Methodology and Study Limitations.

ZY 4036 98

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information. For safety information on Risperdal, see manufacturer's package insert.

EXHIBIT 6
PAGE 12 OF 22

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Zyprexa MDL Plaintiffs' Exhibit No.00284 006134
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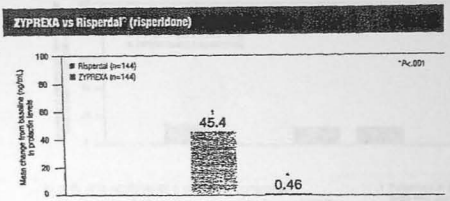
Significantly lower incidence of prolactin elevation[1†]

Potential consequences of hyperprolactinemia:

- Sexual dysfunction[2,3]
- Amenorrhea[2-4]
- Galactorrhea[2-4]
- Gynecomastia[2]
- Risk of osteoporosis[4,5]



ZYPREXA induced significantly lower prolactin elevations vs Risperdal (0.46 ng/mL, 45.4 ng/mL)[1]

Modest elevations in prolactin were seen with ZYPREXA in acute-phase trials (incidence, 34% vs 13% with placebo). However, mean changes from baseline to endpoint were not statistically significantly different between ZYPREXA and placebo.[6]

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.
2. Hamner MB, et al. *CNS Drugs.* 1998;10(3):209-222.
3. Marken PA, et al. *Clin Pharm.* 1992;11:851-856.
4. Halbreich U, et al. *Schizophr Bull.* 1995;22(3):447-454.
5. Ataya K, et al. *Fertil Steril.* 1998;50(6):876-881.
6. Data on file, Lilly Research Laboratories.

† Upper limit of normal prolactin levels for males, 18.77 ng/mL; for females, 24.2 ng/mL.

See Study 2 on pages 18-20 for Methodology and Study Limitations.

- Reliable efficacy
- Favorable safety
- Simple dosing

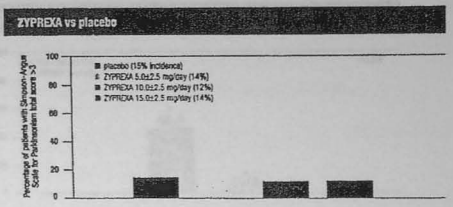
ZY 4036 99

ZYPREXA® Olanzapine

EXHIBIT 6
PAGE 13 OF 22

Favorable safety profile

Treatment-emergent EPS comparable to placebo at all dose ranges†

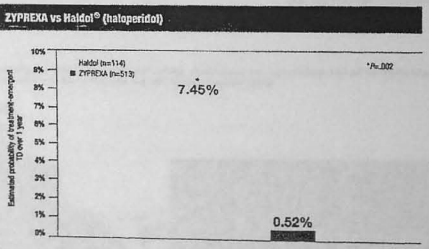


In only one analysis of a placebo-controlled schizophrenia study, only one specific form of EPS, akathisia, was reported significantly more often with ZYPREXA at any specific dose (10.0±2.5 or 15.0±2.5 mg/day) compared with placebo

† Percentage of patients with Simpson-Angus Scale total score >.3. No statistically significant differences vs placebo.

See Study 1 on pages 18-20 for Methodology and Study Limitations.

Incidence of tardive dyskinesia (TD) significantly lower than Haldol



Projected incidence of treatment-emergent TD over 1 year in schizophrenia patients treated with ZYPREXA was significantly lower than in those treated with Haldol[1†]

When these data were extended for a total of 700 days, the incidence with ZYPREXA remained low

Prescribing should be consistent with the need to minimize the risk of TD

1. Beasley CM, et al. *Br J Psychiatry*. 1999; 174:23-30.

† Estimated 1-year risk following an initial 6-week observation period.

See Study 7 on pages 18-20 for Methodology and Study Limitations.

ZY 4036 100

EXHIBIT 6
PAGE 14 OF 22
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prexa MDL Plaintiffs' Exhibit No.00284
006136
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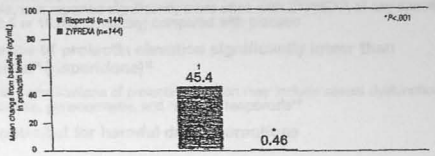
Page 14

Significantly lower incidence of prolactin elevation[1†]

Potential consequences of hyperprolactinemia:

- Sexual dysfunction[2,3]
- Amenorrhea[2-4]
- Galactorrhea[2-4]
- Gynecomastia[2]
- Risk of osteoporosis[4,5]

ZYPREXA vs Risperdal® (risperidone)



ZYPREXA induced significantly lower prolactin elevations vs Risperdal (0.46 ng/mL, 45.4 ng/mL)[1]

Modest elevations in prolactin were seen with ZYPREXA in acute-phase trials (incidence, 34% vs 13% with placebo). However, mean changes from baseline to endpoint were not statistically significantly different between ZYPREXA and placebo.[6]

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.
2. Hamner MB, et al. *CNS Drugs.* 1998;10(3):209-222.
3. Marken PA, et al. *Clin Pharm.* 1992;11:851-856.
4. Halbreich U, et al. *Schizophr Bull.* 1995;22(3):447-454.
5. Ataya K, et al. *Fertil Steril.* 1988;50(6):876-881.
6. Data on file, Lilly Research Laboratories.

† Upper limit of normal prolactin levels for males, 18.77 ng/mL; for females, 24.2 ng/mL.

See Study 2 on pages 18-20 for Methodology and Study Limitations.

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information.
For safety information on Haldol or Risperdal, see manufacturers' package inserts.

- Reliable efficacy
- Favorable safety
- Simple dosing

ZY 4026 101

Side effect profile

zyprexa® Olanzapine

Favorable safety profile

- **Incidence of extrapyramidal symptoms (EPS) comparable to placebo[†‡]**

  In only one analysis of a placebo-controlled study, only one specific form of EPS, akathisia, was reported significantly more often with ZYPREXA at any specific dose (10.0±2.5 or 15.0±2.5 mg/day) compared with placebo

- **Incidence of prolactin elevation significantly lower than Risperdal® (risperidone)[1§]**

  Potential complications of prolactin elevation may include sexual dysfunction, amenorrhea, galactorrhea, gynecomastia, and risk of osteoporosis[2-5]

- **Low potential for harmful drug interactions**

- **Low potential for anticholinergic side effects[‡]**

  Incidence of serious anticholinergic events not statistically different from placebo in schizophrenia trials

- **No black-box or bolded warnings**

- **No routine blood monitoring required**

- **Pregnancy category C**

  No evidence of teratogenicity was observed in preclinical trials; there are no adequate and well-controlled trials with ZYPREXA in pregnant women

- **The most common treatment-emergent adverse event associated with ZYPREXA in placebo-controlled clinical trials for acute mania was somnolence (35% vs 13% for placebo)[‖]**

- **Potential for increased appetite and/or weight gain**

  Early reports suggest behavioral and adjunctive pharmacological strategies can blunt/reduce weight gain[6]

† Based on percentage of patients with Simpson-Angus Scale Total Score >3. No statistically significant differences vs placebo.

‡ See Study 1 on pages 18-20 for Methodology and Study Limitations.

§ See Study 2 on pages 18-20 for Methodology and Study Limitations.

‖ In bipolar mania trials, 4 adverse events occurred with statistically significantly higher incidence with ZYPREXA than with placebo—none of these resulted in discontinuation. See Studies 3 and 4 on pages 18-20 for Methodology and Study Limitations.

1. Tran PV, et al. *J Clin Psychopharmacol*. 1997;17:407-418.
2. Hamner MB, et al. *CNS Drugs*. 1996;10(3):209-222.
3. Marken PA, et al. *Clin Pharm*. 1992;11:851-856.
4. Halbreich U, et al. *Schizophr Bull*. 1996;22(3):447-454.
5. Ataya K, et al. *Fertil Steril*. 1988;50(6):875-881.
6. Adapted from: Wirshing DA, et al. *J Clin Psychiatry*. 1999;60(6):358-363.

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information.
For safety information on Risperdal, see manufacturer's package insert.

ZY 4036 102

EXHIBIT 6
PAGE 16 OF 22

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'prexa MDL Plaintiffs' Exhibit No.00284
006138
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Page 16

Simple dosing

ZYPREXA tablets

- Once-daily dosing, with or without food
- Any time of day
- No mandatory titration
- Available in 2.5-, 5-, 7.5-, 10-, 15-, and 20-mg tablets for flexible dosing

ZYPREXA® Zydis® (Olanzapine) Orally Disintegrating Tablets

Where clinically indicated (for example, patients who have difficulty swallowing pills, those who cheek or spit their medication)

- Disintegrates rapidly in the mouth
- No crushing pills
- No difficult liquid dosing
- Available in 5- and 10-mg tablets

Phenylketonurics: ZYPREXA Zydis contains phenylalanine.
Zydis is a registered trademark of R.P. Scherer Corporation.

ZY 4036 103

17

ZYPREXA® Olanzapine

EXHIBIT 6
PAGE 17 OF 22

Methodology and study limitations

Study 1

A double-blind, randomized, placebo-controlled, 6-week study conducted at 23 sites in the US and Canada to compare the efficacy and safety of ZYPREXA 5.0±2.5, 10.0±2.5, and 15.0±2.5 mg/day with Haldol, 15.0±5.0 mg/day. The study involved 335 patients with a DSM-III-R diagnosis of schizophrenia.

Study 2

A double-blind, randomized, multicenter, international study to compare the efficacy and safety of ZYPREXA vs Risperdal. The study involved 339 patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder, randomized to receive a dose range of 10-20 mg/day of ZYPREXA or 4-12 mg/day of Risperdal. Patients had the opportunity to complete 28 weeks of treatment; a total of 178 patients (52.5%) completed the study (ZYPREXA 57.6%; Risperdal 47.3%; $P=.059$).

- Patients treated with ZYPREXA initiated therapy at 15 mg/day for the first 7 days of treatment. Thereafter, investigators could adjust dose by 5 mg/day every 7 days (range 10-20 mg). The mean modal dose for ZYPREXA was 17.2 mg/day. Consistent with product labeling, patients treated with Risperdal began titration at a dose of 1 mg BID on day 1, 2 mg BID on day 2, and 3 mg BID on days 3 through 7. Thereafter, investigators could adjust dose by 2 mg/day every 7 days (range 4-12 mg/day). The mean modal dose for Risperdal was 7.2 mg/day.
- Treatment-emergent EPS was identified based on the following criteria: Simpson-Angus Scale total score >3 at any post-baseline visit for subjects with baseline ≤3; Barnes Akathisia Scale global score ≥2 at any post-baseline visit for subjects with baseline <2.
- Patients who were previously exposed to Risperdal were not excluded from this study, whereas patients previously exposed to ZYPREXA were.

Study 3

A double-blind, placebo-controlled, 4-week study conducted at 26 US sites to evaluate the efficacy and safety of ZYPREXA in the treatment of mania. Patients with a DSM-IV diagnosis of bipolar I disorder, manic or mixed, with or without psychotic symptoms, were randomized to receive a dose range of 5, 10, 15, or 20 mg/day of ZYPREXA or placebo for a 4-week period. Lorazepam use was permitted at 2 mg/day on days 1 to 4, 1 mg/day on days 5 to 10, and none thereafter. Starting dose of ZYPREXA was 15 mg/day. Patients had a baseline Young-Mania Rating Scale (Y-MRS) Total Score >20.

Study 4

A double-blind, placebo-controlled, 3-week study conducted at 8 US sites to evaluate the efficacy and safety of ZYPREXA in the treatment of mania. Patients with a DSM-IV diagnosis of bipolar I disorder, manic or mixed, with or without psychotic symptoms, were randomized to receive a dose range of 5, 10, 15, or 20 mg/day of olanzapine or placebo for a 3-week period. Lorazepam use was permitted at 4 mg/day on days 1 to 7, 2 mg/day on days 8 to 10, and none thereafter. Starting dose of ZYPREXA was 10 mg/day. Patients had a baseline Y-MRS Total Score >20.

ZY 4096 104

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information. For safety information on Haldol, Risperdal, lorazepam, or Depakote, see manufacturer's package inserts.

EXHIBIT 6
PAGE 18 OF 22

Study 5

A double-blind, randomized, 3-week study conducted at 44 US sites to compare the efficacy and safety of ZYPREXA vs Depakote. The study involved 251 patients with a DSM-IV diagnosis of bipolar I disorder experiencing acute manic or mixed episodes (baseline Y-MRS total score >20), with or without psychotic features, with or without rapid cycling courses.

Dosing ranges were 5-20 mg/day for ZYPREXA and 500-2500 mg/day (divided doses) for Depakote, with starting doses at 15 mg QD for ZYPREXA and 750 mg BID or TID for Depakote. Mean ending doses were 17 mg QD for ZYPREXA and 1500 mg BID or TID for Depakote. Dosing adjustments could be made after 2 days and were based on clinical response and plasma levels. Plasma levels were measured to assess whether Depakote trough levels were maintained within the targeted therapeutic range of 50-125 µg/mL. Up to 4 blood samples were obtained per patient (mean, 2.7 samples); the mean value of all levels obtained was 79.4 µg/mL.

Study 6

A double-blind, randomized, placebo-controlled, 6-week study conducted at 12 sites to evaluate the efficacy and safety of ZYPREXA 1.0 and 10.0 mg/day. The study involved 152 patients with a DSM-III-R diagnosis of schizophrenia.

Study 7

Three independent studies were pooled to evaluate the treatment-emergent incidence of tardive dyskinesia (TD) in patients treated with double-blind, randomized, Haldol or ZYPREXA therapy for up to 2.6 years. A total of 1192 ZYPREXA-treated patients and 522 Haldol-treated patients with a DSM-III-R diagnosis of schizophrenia participated in one of three multicenter, double-blind, randomized studies. The first of these studies compared several dose ranges of ZYPREXA (5.0±2.5, 10.0±2.5, and 15.0±2.5 mg/day) with one dose range of Haldol (15.0±5.0 mg/day) and with placebo over six weeks. The second of these studies evaluated the same dose ranges of ZYPREXA and Haldol, but included a low dose of ZYPREXA (1.0 mg/day) in lieu of placebo. The third of these studies compared ZYPREXA (5.0 to 20.0 mg/day) with Haldol (5.0 to 20.0 mg/day) over six weeks. Patients responding to treatment in this study continued for up to 19 months thereafter, and ZYPREXA-treated patients completing the 19-month extension entered an open-label study.

- **HAMD-21 Total Score** is a 21-item observer-rated scale that assesses depressive symptoms. HAMD-21 individual items include: depressed mood, guilt, suicide, early insomnia, middle insomnia, late insomnia, work and activities, retardation, agitation, anxiety (psychic), anxiety (somatic), somatic symptoms (gastrointestinal), somatic symptoms (general), genital symptoms, hypochondriasis, loss of weight (history), loss of weight (actual), insight, diurnal variation (present), diurnal variation (severity), depersonalization/derealization, paranoid symptoms, and obsessional/compulsive symptoms. Items are rated finely (on a 5-point scale) or coarsely (on a 3-point scale). Scores on the 5-point scale range from 1 (absent) to 5 (severe).

ZY 4096 105

EXHIBIT 6
PAGE 19 OF 22

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Zyprexa MDL Plaintiffs' Exhibit No.00284

006141

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- **Y-MRS Total Score** is an 11-item instrument used to assess the severity of mania. Depressive symptoms are not assessed. Y-MRS individual items include: elevated mood, increased motor activity/energy, sexual interest, sleep, irritability, speech (rate and amount), language/thought disorder, thought content, disruptive/aggressive behavior, appearance, and insight. Items are rated on a 5-point scale, with varying descriptions for each.

- **PANSS Total Score** is a 30-item rating instrument that evaluates the positive, negative, and overall symptoms of schizophrenia. PANSS individual items include: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, hostility, blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking, somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance. The items are rated on a 7-point scale from 1 (absent) to 7 (extreme).

- **SANS** obtains clinical ratings of negative symptoms in patients with schizophrenia across 5 subscales, including affective blunting, alogia, avolition/apathy, anhedonia/asociality, and disturbance of attention. The 24 total items in these subscales are each rated using a 6-point scale (0=not at all, 5=severe).

- **Simpson-Angus Scale for Parkinsonism:** The Extrapyramidal Side Effects Rating Scale, commonly referred to as the Simpson-Angus Scale, is a 10-item instrument used to measure drug-induced parkinsonism. Simpson-Angus individual items include: gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabellar tap, tremor, and salivation. Items are rated on a 5-point scale from 0 (complete absence of the condition) to 4 (presence of the condition in extreme form).

ZY 4036 106

For additional safety profile and other important prescribing considerations, see the full Prescribing Information.
For safety information on Risperdal or Depakote, see manufacturers' package inserts.

EXHIBIT 6
PAGE 20 OF 22

H

Additional prescribing considerations

The most common treatment-emergent adverse event associated with ZYPREXA vs placebo in 6-week schizophrenia trials was somnolence (26% vs 15%). Also observed (ZYPREXA vs placebo) were:

postural hypotension (5% vs 2%)
akathisia (5% vs 1%)
constipation (9% vs 3%)
personality disorder* (8% vs 4%)
dizziness (11% vs 4%)
weight gain (6% vs 1%)

The most common treatment-emergent adverse event (reported in ≥10% of patients) with ZYPREXA vs risperidone in a schizophrenia trial was somnolence (26% vs 24%). Also observed (ZYPREXA vs risperidone) were:

anxiety (19% vs 17%)
insomnia (11% vs 14%)
nausea (4% vs 10%)
weight gain (16% vs 8%)
depression (6% vs 11%)
headache (15% vs 11%)
rhinitis (9% vs 14%)

The most common treatment-emergent adverse event associated with ZYPREXA vs placebo in short-term, placebo-controlled bipolar mania trials was somnolence† (35% vs 13%). Also observed (ZYPREXA vs placebo) were:

dry mouth† (22% vs 7%)
increased appetite (6% vs 3%)
constipation (11% vs 5%)
dyspepsia (11% vs 5%)
asthenia† (15% vs 6%)
dizziness† (18% vs 6%)
tremor (6% vs 3%)

Common and significantly different adverse events ($P<.01$) in a bipolar mania trial of ZYPREXA vs divalproex were:

somnolence (39.2% vs 20.6%)
nausea (10.4% vs 28.6%)
increased appetite (12.0% vs 2.4%)
dry mouth (33.6% vs 6.3%)

Other treatment-emergent adverse events reported in ≥5% of patients and significantly greater for ZYPREXA vs divalproex included tremor (9.6% vs 3.2%), neck rigidity (7.2% vs 1.6%), speech disorder (8.0% vs 0.8%), and sleep disorder (5.6% vs 0.8%).

Hemodynamic effects
In premarketing trials, some patients taking ZYPREXA experienced orthostatic hypotension associated with dizziness‡; tachycardia‡; and, in some cases, syncope (15/2500, 0.6%).

ZY 4036 107

* COSTART term for nonaggressive objectionable behavior.

† In bipolar mania trials, 4 adverse events occurred with statistically significantly higher significance with ZYPREXA than with placebo—none of these resulted in discontinuation.

‡ In acute-phase trials (n=368), dizziness (11% vs 4%) and tachycardia (4% vs 1%) were reported; these events were not always associated with hypotension.

ZYPREXA Olanzapine

EXHIBIT 6
PAGE 21 OF 22

H

Transient, asymptomatic elevations of hepatic transaminase
In placebo-controlled schizophrenia studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to ZYPREXA compared to none (0/115) of the placebo patients. None of these patients experienced jaundice or drug-induced hepatitis. Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

Effect on prolactin comparable to placebo
Modest elevations in prolactin were seen with ZYPREXA in acute-phase schizophrenia trials (incidence, 34% vs 13% with placebo). However, mean changes from baseline to endpoint were not statistically significantly different between ZYPREXA and placebo.

As with all antipsychotic medications, the following considerations should be taken into account when prescribing ZYPREXA:

Tardive dyskinesia (TD)—prescribing should be consistent with the need to minimize TD. If its signs and symptoms appear, discontinuation should be considered.

Seizures—occurred infrequently in premarketing clinical trials of ZYPREXA (22/2500, 0.9%). Confounding factors may have contributed to many of these occurrences. ZYPREXA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Such conditions may be more prevalent in patients age 65 or older.

Use in patients with concomitant illness—in a clinical study involving nursing home patients having various psychiatric symptoms in association with Alzheimer's disease, somnolence, abnormal gait, fever, dehydration, and back pain were observed more often with ZYPREXA than with placebo. In two placebo-controlled studies in Parkinson's patients with drug-induced (dopamine agonist) psychosis, the following events occurred more often with ZYPREXA than with placebo: worsening of parkinsonian symptoms, hallucinations, somnolence, increased salivation, asthenia, and peripheral edema. As with other CNS-active drugs, ZYPREXA should be used with caution in elderly patients with dementia and/or Parkinson's disease.

ZY 4036 108

For additional safety profile and other important prescribing considerations, see the full Prescribing Information.

EXHIBIT 6
PAGE 22 OF 22

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: MDL-1596

ZYPREXA PRODUCTS

LIABILITY LITIGATION

THIS DOCUMENT RELATES TO:

ALL CASES

C O N F I D E N T I A L

- - -

July 28, 2006

- - -

Videotape deposition of

ROBERT BAKER, M.D.

- - -

GOLKOW LITIGATION TECHNOLOGIES
1600 John F. Kennedy Boulevard
Suite 1210
Philadelphia, Pennsylvania 19103
(877) DEPS-USA

the patients to, for whom Zyprexa would be a good choice wouldn't get it, so I agree with you there.

Q. Sir, that wasn't my question. My question was: If you had told the doctors here in the United States what you were forced to tell them in Japan you would have lost sales. It's just as clear as day, isn't it?

A. Well, I, what I'm saying I think is in agreement, would be that patients who would, for whom Zyprexa would be an excellent choice, if they were arbitrarily excluded from that and didn't get it then that would be fewer patients on it.

Q. You think that people with diabetes, or history of diabetes, use of Zyprexa would be an excellent choice; is that your testimony?

A. For some of those individuals, yes. Certainly not for all of them.

Q. Despite the fact the consensus statement, that there's an

Fold Rap Over Line

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COUNSELORS AT LAW
500 L STREET, FOURTH FLOOR
ANCHORAGE, ALASKA 99501

IN THE SUPERIOR COURT FOR THE STATE OF
ALASKATHIRD JUDICIAL DISTRICT
AT ANCHORAGE

State of Alaska v. Eli Lilly and Company
Case No. 3AN-06-05630 CI

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See Judge Rindner 6/13/08 order
page 17, #9 Documents unsealed
Order 8/11/08

Pages 6147B-6165

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STATE OF ALASKA
THIRD DISTRICT

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

BY DEPUTY CLERK

STATE OF ALASKA,

Plaintiff,

vs.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-5630 CIV

NOTICE OF FILING UNDER SEAL

On this date the State of Alaska is filing a pleading titled "Plaintiff's Response to Defendant's Motion in Limine to Exclude References to Foreign Regulatory Action." Because one or more exhibits filed with this pleading may be confidential documents under the Court's April 6, 2007 oral ruling, the State of Alaska is submitting this pleading and the attached exhibits under seal.

DATED this 14 day of February, 2008.

FELDMAN ORLANSKY & SANDERS
Counsel for Plaintiff

BY _____
Eric T. Sanders
AK Bar No. 7510085

See Judge Rindner's order
of 6/13/08, page 17, #9
Documents unsealed
Linda 8/11/08

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Pepper Hamilton

By Peggy S Crowe
Date 2/14/08

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Pages 006147B-006165

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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Case No. 3AN-06-05630 CI
	)	
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	
	)	

PLAINTIFF'S RESPONSE TO DEFENDANT'S MOTION IN LIMINE TO EXCLUDE REFERENCES TO FOREIGN REGULATORY ACTION

Defendant Eli Lilly and Company ("Lilly") has moved to exclude from the trial of this case any evidence relating to foreign regulatory action regarding Zyprexa. Lilly argues such evidence is irrelevant and that it will result in unfair prejudice, confusion of the issues, misleading the jury and wasting time.

I. FACTS

The State intends to offer evidence of foreign regulatory action in this case. The State *does not* intend to offer evidence of foreign laws, regulations or standards. An example of the nature of the evidence the State intends to offer is the April 2002 requirement by Japanese regulatory authorities that Lilly change its Zyprexa label and issue an emergency letter to physicians regarding diabetic ketoacidosis, diabetic coma

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and increased blood glucose during Zyprexa use.[1] This action occurred after nine serious cases of hyperglycemia, diabetic ketoacidosis and coma – including two deaths – occurred in less than a year of Zyprexa's marketing in Japan.[2] Notably, the emergency letter to physicians states that a "causal relationship" between the events and Zyprexa "cannot be denied."[3] Several months later, the impact of this label change could not have been clearer to Lilly.

In a July 2002 memo reporting on a trip to Japan several months after the Japanese label change warning about diabetes, Dr. Alan Breier, the head of Lilly's Zyprexa Product Team, stated that there "appears to be a decrease in hyperglycemic [adverse events] since the label changes" and that there had been a 75% drop in new patients being prescribed Zyprexa.[4] Thus, Lilly recognized that providing this important safety information to physicians actually reduced the number of injuries occurring in patients. Further, Dr. Breier stated that the company would "ensure that we promote the use of the drug *within the label*, which would by design dramatically reduce the number of [adverse] events."[5] In other words, Lilly recognized that warning doctors and patients

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1 Exhibit A, Zyprexa MDL Plaintiffs' Exhibit No. 320 (English translation of Japanese Emergency Safety Information letter and revised Zyprexa label).

2 *Id.*

3 *Id.*

4 Exhibit B, Zyprexa MDL document ZY203332491 (July 1, 2002 Japan Trip Summary).

5 *Id.* (emphasis added).

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about the risk of diabetes and requiring blood glucose monitoring would "by design" reduce the number of patients who developed diabetes.

This evidence is relevant and admissible on the issues of Lilly's notice of the risk of diabetes and that a warning could reduce the risk to patients as well as being relevant to demonstrate Lilly's state of mind and motivation.

II. ARGUMENT

"Relevant evidence means evidence having any tendency to make, the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence."[6] The State's burdens of proof in this case require it to show, among other things, that Zyprexa posed a risk of injury to one who used the product in a reasonably foreseeable manner and that Lilly had notice of the risks presented by Zyprexa, i.e., that those risks were foreseeable.[7] Further, Lilly's available defenses allow it to avoid liability if it shows the risks posed by Zyprexa were scientifically unknowable.[8] Lilly has not conceded liability for failure to warn or indicated it is not going to present such a defense. The evidence described above is relevant and probative on these issues and others.

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6 Alaska R. Evid. 401.

7 *Shanks v. Upjohn Co.*, 835 P.2d 1189, 1199-1200 (Alaska 1992).

8 *Shanks*, 835 P.2d at 1200.

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Contrary to Lilly's arguments in support of exclusion of this evidence, the question of liability in this case does not turn "solely upon United States regulatory action."[9] In fact, in another of its evidentiary motions, Lilly seeks to exclude certain evidence of United States regulatory action.[10] The question of liability in this case turns on whether Zyprexa posed a risk of harm, whether Lilly knew or could have known of those risks, and whether Lilly adequately warned of the known or knowable risks. Alaska law and standards will determine whether Lilly's Zyprexa label was adequate.

Presenting evidence of a foreign product label or regulatory action does not require an examination of foreign law or an application of it. The evidence is being presented to show that a particular risk existed and that Lilly had notice of it. That Lilly's Zyprexa label carried a warning of a particular risk in a foreign jurisdiction certainly makes it more probable that such a risk indeed existed, and that Lilly itself had notice of that risk or that the risk was scientifically knowable.[11] The evidence further demonstrates that Lilly had notice of the effect of this warning on physician prescribing practices and

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9 Def. Mot. in Limine to Exclude References to Foreign Regulatory Action, 4.

10 Def. Mot. in Limine to Exclude References to Recent Regulatory Communications and Developments.

11 Under federal regulations governing Lilly's Zyprexa label or package insert, a manufacturer is obligated to "include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." *See* 21 C.F.R. § 201.57(c)(6). The Japanese regulatory action and label also provided further notice to Lilly of "reasonable evidence of an association of a serious hazard" with Zyprexa.

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that it would likely reduce sales. In addition, the evidence also demonstrates that Lilly knew that providing a warning similar to what was provided in Japan would increase patient safety. Indeed, Dr. Breier admitted that promoting Zyprexa in accordance with the provisions of the Japanese warning would "by design" reduce the number of adverse events.

The cases cited by Lilly in support of its motion to exclude this evidence are largely distinguishable. Some stand for the proposition that the examination or application of a foreign jurisdiction's laws, regulations or standards is inappropriate in an action in this country.[12] As noted above, the State is not seeking the application of any foreign law, nor seeking to have Lilly's actions measured by any foreign standards. In the two cases which actually bear upon an evidentiary dispute similar to that between the parties, the courts involved granted the exclusionary motions with little or no explanation and the opinions are therefore of limited utility.[13] Clearly, this Court has the discretion to exclude otherwise relevant evidence if its probative value is outweighed by other considerations.[14] However, evidence of foreign regulatory action, events or even

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[12] *Hurt v. Coyne Cylinder Co.*, 956 F.2d 1319 (6th Cir. 1992); *Harrison v. Wyatt Laboratories, et al.*, 510 F. Supp. 1, 4-5 (E.D. Pa. 1980); *Garmon v. Cincinnati, Inc.*, 1993 WL 190923 (Tenn. Ct. App. June 4, 1993).

[13] *In re Baycol Prods. Liab. Litig.*, 495 F. Supp. 2d 977 (D. Minn. 2007); *Colangelo v. Novartis Pharmaceuticals Corp.*, 2002 WL 32153354 (Ill. Cir. Ct. Dec. 17, 2002).

[14] Alaska R. Evid. 403.

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standards is not per se inadmissible.[15] In fact, courts have found such evidence admissible.[16] Judge Weinstein, in ruling on summary judgment motions filed by Lilly in the Zyprexa multidistrict litigation discussed evidence of foreign Zyprexa labeling, thus implicitly recognizing it as relevant and admissible evidence.[17]

The purposes for which the State seeks the admission of this evidence do not present any of the risks argued by Lilly. The jury will not have to examine foreign laws, regulations or standards, nor will it have to apply them to Lilly's conduct. The jury will simply be asked to apply Alaska law and standards to the facts in this case, including the fact that Japanese regulatory authorities required Lilly to issue the warning in Exhibit A. Examining this fact does not require an examination of foreign law or standards, much less political or social customs as Lilly suggests. Whether the foreign regulators' actions

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[15] *See In re Rezulin Prods. Liab. Lit.*, 309 F. Supp. 2d 531, 552 (S.D.N.Y. 2004) (refusing to find evidence of foreign regulatory action irrelevant as a matter of law); *Sherry v. Massey-Ferguson, Inc.*, 1997 WL 480893 (W.D. Mich. 1997) (finding neither *Hurt* nor *Deviner, supra,* held foreign legal standards inadmissible as a matter of law); *Slisze v. Stanley-Bostich*, 979 P.2d 317, 322 (Utah 1999) (rejecting a bright-line rule against admitting foreign safety standards).

[16] *See Sherry, supra,* *2 (finding evidence of a foreign tractor design relevant to feasibility of design alternative and defendant's knowledge of such alternatives); *Orjias v. Stevenson*, 31 F.3d 995, 1000 (10th Cir. 1994) (affirming admission under Rule 404(b) of evidence of foreign state's letters to defendant regarding environmental violations as probative on the issue of defendant's notice or knowledge of issues therein); *Larue v. National Union Electric Corp.*, 571 F.2d 51, 57 (1st Cir. 1978) (affirming admission of evidence regarding safety shield required by foreign regulations).

[17] *In re Zyprexa Prods. Liab. Lit.*, 489 F. Supp. 2d 230, 250 (E.D.N.Y. 2007).

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were appropriate is not at issue nor is it relevant. What is relevant is that the actions occurred and that Lilly had knowledge of them and reacted in specific ways to them.

For the reasons stated above, the Court should deny Defendant's Motion in Limine.

Respectfully submitted this 14 day of February, 2008.

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Certificate of Service

I hereby certify that true and correct copies of **Plaintiff's Response to Defendant's Motion in Limine to Exclude References to Foreign Regulatory Action and (Proposed) Order** were served by messenger on:

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Barry Boise, via email (boiseb@pepperlaw.com)
Pepper Hamilton

By Peggy S. Crowe
Date 2/14/08

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EXHIBIT A
TO STATE OF ALASKA'S RESPONSE TO LILLY'S MOTION IN LIMINE REGARDING FOREIGN REGULATORY ACTIVITY

006155

Appendix 6.
Japanese Dear Doctor Letter

ZY 4051 1633

Eli Lilly - Zyprexa Products Liability Litigation
Zyprexa MDL Plaintiffs' Exhibit No.00320
Confidential and Subject to Protective Order

006156

IMPORTANT

April 2002
No. 02-1

Emergency Safety Information

Regarding diabetic ketoacidosis and diabetic coma due to increased blood glucose during administration of an antipsychotic agent, Zyprexa® Tablets (Olanzapine)

Since the marketing of this product in June 2001, 9 serious cases (including 2 cases of death) with hyperglycemia, diabetic ketoacidosis, and diabetic coma have been reported for which causal relationship with this product cannot be denied (estimated number of patients treated with this product: about 137,000, as of the end of December 2001). (Possible development of) hyperglycemia has been included in "Precautions" to raise awareness. However, as the result of the assessment of these serious cases, the "Precautions" section has been revised and "Contraindications" and "Warnings" have been added. For use of this product, special cautions should be taken regarding the following matters. In the event of hyperglycemia, please contact the medical representatives of Eli Lilly Japan K.K.

1. Do not administer to patients with diabetes mellitus and those who have a history of diabetes mellitus.

In patients with diabetes mellitus and those who have a history of diabetes mellitus, blood glucose may increase and metabolic status may be deteriorated acutely, thus do not administer this product to these patients.

2. During administration of this product, observe sufficiently with such as measurement of blood glucose.

With the administration of this product, from marked increase in blood glucose, serious adverse reactions such as diabetic ketoacidosis, diabeteic coma etc. may appear leading potentially to death. Thus, observe sufficiently with such as measurement of blood glucose during administration of this product.

3. Explain sufficiently to the patient and family members.

Upon administration of this product, explain sufficiently to the patient and family members possible occurrence of serious adverse reactions, such as diabetic ketoacidosis and diabetic coma etc. Provide guidance to them to see a physician suspending administration if such symptoms as thirst, polydipsia, polyurea or frequent urination etc. appear.

We also report the revisions made to the "Warnings," "Contraindications" and "Precautions" as shown on the back of this overleaf.

Where to contact: Medical Information Services, Eli Lilly Japan K.K.
7-1-5 Isogamidoori, Chuo-ku, Kobe 651-0086
Tel: 0120-360-605 **Fax :078-242-9299**

ZY 4051 1634

Exhibit A, Page 3 of
SOA Response to Lilly Motion in Limine to Exclude
References to Foreign Regulatory Action
Case No. 3AN-06-5630 CI

Eli Lilly - Zyprexa Products Liability Litigation
Zyprexa MDL Plaintiffs' Exhibit No.00320

Confidential and Subject to Protective Order

006157

<Case Presentation>

No.	Sex, age, reason for use (complications)	Clinical course and treatment
1	Male, in 20's Schizophrenia (Hyperlipidemia, hepatic disorder)	**Diabetic coma** The patient was diagnosed as having schizophrenia about 10 years ago. He was obese with 170 cm in height and 90 kg in body weight. Came to the hospital about 2 years ago, and had a tendency for weight gain and overeating. Receiving diet therapy for pre-existing hyperlipidemia. About 3 months before administration: Treated with fenofibrate. Triglyceride decreased temporarily. About 2 months before administration: Switched to quetiapine fumarate. Triglyceride increased again. Administration initiation day: Initiated treatment with olanzapine at a daily dose of 10 mg. The body weight was more than 100 kg, and the blood glucose was normal. Day 15 of treatment: Casual blood glucose was 230 mg/dL. Triglyceride increased to 555 mg/dL. Diabetes mellitus was suspected. The dose of olanzapine increased to 15 mg. Day 29 of treatment: Further increased appetite. The patient and his family were instructed to follow strictly the diet therapy and life style modification. Day 43 of treatment: Weight loss of 6 kg in 2 weeks. The patient insisted that he had been on a diet. No particular complaint other than thirst and consumption of a large quantity of juice. The blood tests revealed blood glucose of 723 mg/dL, HbA1c of 10%, triglyceride of 960 mg/dL, total cholesterol of 362 mg/dL, urine glucose of 1 g/dL, and urine ketone body of (+++). Day 45 of treatment: Brought into a critical care center of another hospital due to cardiopulmonary arrest. At the 2nd cardiopulmonary resuscitation, the spontaneous heart beat was resumed. The blood glucose level was 854 mg/dL. Following resuscitation, treatment for encephalopathy and hyperglycemia was started. CT revealed prominent cerebral edema. Day 48 of treatment: The patient died.

	About 3 months before administration	Day 15 of treatment	Day 43 of treatment	Day 45 of treatment
Casual blood glucose (mg/dL)	137	230	723	854
HbA1c (%)			10.0	
Urine glucose (g/dL)	Negative		1	

Concomitant medications: timiperone, biperiden hydrochloride, cloxazolam, quetiapine fumarate, fenofibrate, haloperidol, and bromperidol.

ZY 4051 1635

Exhibit A, Page 4 of 7
SOA Response to Lilly Motion in Limine to Exclude
References to Foreign Regulatory Action
Case No. 3AN-06-5630 CI

Eli Lilly - Zyprexa Products Liability Litigation
Zyprexa MDL Plaintiffs' Exhibit No.00320

Confidential and Subject to Protective Order
006158
Page 3

No.	Sex, age, reason for use (complications)	Clinical course and treatment
2	Male, in 30's Schizophrenia (No complication)	**Diabetic coma** About 8 months before administration: Inpatient treatment started. At the admission, the patient was 170 cm in height and 83 kg in body weight, with the fasting blood glucose of 80 mg/dL. About 4 months before administration: Body weight was 88.5 kg. Tendency for overeating, weight gain, and consumption of a large quantity of soft-drings. About 3 months before administration: After hospital discharge, the patient was followed as an outpatient. Administration initiation day: Initiated treatment with olanzapine at a daily dose of 10 mg. Day 15 of treatment: The patient had thirst, but treatment was continued. The amount of drinking was 2 L per day. Day 17 of treatment: Because of a feeling of swollen throat, visited the otolaryngology department of a general hospital. White spots in oral mucosa and swollen tonsils on both sides were noted and the patient was diagnosed as having acute tonsillitis. Piperacillin 4 g and 500 mL of glucose added solution were administered. Day 18 of treatment: The patient, showing no sign of improvement, was hospitalized into the otolaryngology department of the general hospital. The body weight was 96 kg. Piperacillin 4 g, 1000 mL of glucose added solution, and hydrocortisone 300 mg were administered. The patient had consumed 10 cans of juice on the day. Day 19 of treatment: The patient was found to be in disturbed consciousness, incontinence, and sursumversion on his feet. With the blood glucose of 1655 mg/dL and blood osmotic pressure of 405, a diagnosis of hyperosmolar diabetic coma was given. Treatment was initiated with physiological saline and insulin. About 7 hr after discovery, the blood glucose improved to 980 mg/dL, and the patient regained consciousness. About 10 hr after discovery, the patient developed convulsive seizure and impaired consciousness, and was transferred to ICU. At the admission to ICU, the patient had the blood glucose of 901 mg/dL, HbA1c of 13.6%, hypernatremia, hypokalemia, elevated creatinine, and metabolic acidosis. Thereafter, the systemic conditions of the patient was exacerbated (progress of renal failure), followed by death.
	Concomitant medications: risperidone, lormetazepam, mianserin hydrochloride, nilmazafone hydrochloride, levomepromazine maleate, flunitrazepam, zotepine, biperiden hydrochloride, and triazolam.	

ZY 4051 1636

Eli Lilly - Zyprexa Products Liability Litigation
Zyprexa MDL Plaintiffs' Exhibit No.00320
Confidential and Subject to Protective Order

006159

No.	Sex, age, reason for use (complications)	Clinical course and treatment
3	Male, in 30's Schizophrenia [Psychosis due to central nervous system stimulant, bilateral blepharospasm (tardive dyskinesia), and gout]	**Non-insulin dependent diabetic mellitus, weight gain** Family history of diabetic mellitus (parents) 160 cm in height and 80 kg in body weight. About 6 months before administration: Casual blood glucose was 92 mg/dL. Administration initiation day: Initiated treatment with olanzapine at a daily dose of 20 mg. No other symptoms than the primary disease and the complications. Day 22 of treatment: Lassitude and numbness of feet were developed and worsened. Day 37 of treatment: The patient visited another hospital, and hyperglycemia (casual blood glucose: 298 mg/dL) and HbA1c of 7.0% were detected. Increased appetite and weight gain were observed. The body weight was 95 kg. Day 39 of treatment: The patient came to this hospital, and the olanzapine treatment was discontinued. 7 days after discontinuation: Admitted to another hospital. Casual blood glucose was 162 mg/dL, and HbA1c was 7.0%. 12 days after discontinuation: Hospital discharge. 14 days after discontinuation: An improvement in diabetic mellitus and weight gain. The body weight was 89 kg.
	Concomitant medications: risperidone, nitrazepam, sodium valproate, and allopurinol.	

No.	Sex, age, reason for use (complications)	Clinical course and treatment
4	Female, in 40's Schizophrenia (No complication)	**Hyperglycemia** Unknown history of diabetic mellitus. No familiy history. Prior acute pancreatitis. The patient was 157 cm in height and 66 kg in body weight. 4 months before administration: Although abnormal fasting blood glucose (126 mg/dL) was detected, no close examination such as glucose tolerance test was performed. Therfore, the presence/absence of glucose tolerance abnormality was unknown. Administration initiation day: Initiated treatment with olanzapine at a daily dose of 10 mg. A tendency for polydipsia. Coadministered with haloperidol. Day 50 of treatment: Hyperglycemia (postprandial blood glucose: 521 mg/dL) was detected. The body weight was 67.5 kg. Day 59 of treatment: Olanzapine was switched to risperidone. The blood glucose was 241 mg/dL. The patient was instructed to reduce the consumption of meals and not to eat between meals. 11 days after discontinuation: Fasting blood glucose was 302 mg/dL, and HbA1c was 10.1%. Glibenclamide and voglibose were administered. 17 days after discontinuation: Postprandial blood glucose was 311 mg/dL. 18 days after discontinuation: Fasting blood glucose was 226 mg/dL, and HbA1c was 9.6%. Urine glucose was (+++). The dose of glibenclamide was increased. 25 days after discontinuation: Fasting blood glucose was 214 mg/dL.
	Concomitant medications: brotizolam, sennoside, trihexyphenidyl hydrochloride, and haloperidol.	

ZY 4051 1637

MPORTANT

Emergency Safety Information

"WARNINGS", "CONTRAINDICATIONS"and "PRECAUTIONS"

The revisions made to the "Warnings," "Contraindications" and "Precautions" are as shown below. These revisions are made based on the post marketing case reports of hyperglycemia.

[WARNINGS]

1. From marked increase in blood glucose, serious adverse reactions such as diabetic ketoacidosis, diabetic coma etc may appear leading potentially to death. Observe sufficiently with such as measurement of blood glucose during the olanzapine administration.
2. Upon administration, explain sufficiently in advance to the patient and family members possible occurrence of above adverse reactions. Provide guidance to them to pay attention to such abnormalities as thirst, polydipsia, polyurea, frequent urination, etc., and to see a physician suspending administration immediately if such symptoms appear. See the section on "Important

[CONTRAINDICATIONS(Do not administer to following patients.)]

5. Patients with diabetes mellitus and those who have a history of diabetes mellitus

[PRECAUTIONS]

1. Careful Administration (Administer with caution to following patients.)

(6) Patients with risk factors for diabetes mellitus such as family history of diabetes mellitus, hyperglycemia, obesity, etc. (See the section on "Important Precautions").

2. Important Precautions

(1) By administration of this drug, marked increase in blood glucose may appear leading to fatal clinical course such as diabetic ketoacidosis, diabetic coma, etc. Observe sufficiently with such as measurement of blood glucose, (appearance of) thirst, polydipsia, polyurea, and frequent urination during the olanzapine administration. In particular, patients with risk factors for diabetes mellitus such as hyperglycemia, obesity, etc., blood glucose may increase, leading to acute worsening of metabolic state.

(2) Upon administration, explain sufficiently in advance to patients and family members possible occurrence of above adverse reactions. Provide guidance to them to pay attention to such abnormalities as thirst, polydipsia, polyurea, frequent urination, etc., and to see a physician suspending administration immediately, if such symptoms appear.

(3) As olanzapine may increase body weight, pay attention to obesity, and take appropriate measures such as the diet therapy and exercise therapy, etc. if any sign of obesity is noted.

4. Adverse Reactions

(1) Clinically significant adverse reactions

1) Hyperglycemia, Diabetic ketoacidosis, Diabetic coma: Hyperglycemia may develop leading to fatal clinical course, such as diabetic ketoacidosis and diabetic coma leading to death. Thus, make a close observation, with such as blood glucose measurement, (appearance of) thirst, polydipsia, polyurea and frequent urination. If any abnormalities are noted, discontinue administration and take an appropriate measure(s) such as administration of insulin.

(Shown revised part only.)

ZY 4051 1638

EXHIBIT B
TO STATE OF ALASKA'S RESPONSE TO LILLY'S MOTION IN LIMINE REGARDING FOREIGN REGULATORY ACTION

006162

Memo

Lilly

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

Neuroscience Products

July 1, 2002

Dr. J. Lechleiter
Mr. G Mayr
cc. Mr. A. Mascarenhas

JAPAN TRIP SUMMARY – JUNE 23-27, 2002

This is a summary of issues and proposed actions in follow up to our previous update on Japan. It is clear that the impact of the label change in Japan has been very profound. We concluded we have lost substantial ground and trust in our relationships with the MHLW. Market research shows we have also lost quite a bit of credibility with prescribers and opinion leaders, basically because they felt left in the dark with what they perceived as the late sharing of safety information. As a result, there has been a 75% drop in new patients who are being put on the drug, and a continuing fairly high drop-out rate. That's going to lead to a significant performance impact, probably over and above the 10% assumed on the sales line in the short term, although we think we will be able to stem the tide and turn this around.

Another area of concern is in the sales force. As a result of the label changes, there is substantial lack of alignment and integration in the internal organization. There is a disparity of views on how to address the safety issues and how to integrate marketing, sales, market research, medical, regulatory, etc. Andrew Mascarenhas is staying very close to this himself in the short term, and is considering making a change in the business unit leadership role to get a more integrative leader in place. We have pointed this out to the Japanese leadership team and gotten agreement that obtaining enhanced internal integration is crucial. For the time being, he will take personal responsibility for leading that integration effort.

A further issue is team motivation and turnover in the sales organization and lack of trust both from a sales force and a customer level. We have recommended, in line with the affiliate's proposal, to adjust promotional strategy to reflect the reality of the new label in Japan, enhance confidence by our message for the appropriate use of the product within the label, and point out how to specifically address concerns about hyperglycemia and the potential use of the product in patients with diabetes. We need to also revise our forecast for the year to reflect the post label change environment and discuss how to communicate it to the sales force because it is very unlikely the affiliate will make plan. This is an issue that needs to be resolved with sales management very quickly.

Exhibit B,Page 2 of 4
SOA Response to Lilly Motion in Limine to Exlcude
References to Foreign Regulatory Action
Case No. 3AN-06-5630 CI
Zyprexa MDL 1596: Confidential-Subject to Protective Order
ZY203332491
006163

Memo

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

July 1, 2002

Another major issue, apart from the lack of integration, sales demotivation, and lack of trust is the apparent lack of competency and capability to formulate a pharmacoviligence strategy and approach to the Ministry of Health. Our recommendation is that Andrew Wood assume personal leadership for the time being while recruiting a high-powered new director of this field. We've asked him to continue to utilize the existing capabilities of Charles Beasley and Patrizia Cavazzoni in the short term and consider recruiting a former Ministry of Health employee as a consultant to help us with the subtleties and some of the leg work in starting to build a better relationship and network with the Ministry of Health. There is also an assessment of the filter we (and other US pharmaceutical companies compared to Japanese firms) use in reporting AEs to the Ministry. Further benchmarking is clearly desirable.

There is a need for strong endocrinology support to the Japanese Zyprexa team in the office but also at the field level. We recommend adding a diabetologist to the team who can focus primarily on Zyprexa and the metabolic and endocrinological issues. We've also recommended looking at the diabetes nurses that are currently part of Lilly's diabetes organization, offering their help to prescribing physicians, enabling a rapid evaluation of metabolic and glycemic status of the patients who are being considered for Zyprexa or for monitoring purposes. That's an easy switch we can make for that organization.

Another capacity limitation is in the physician-to-physician promotion. Gerhart, as you and Gus had discussed, the medical representatives may not be considered the appropriate people to provide all scientific information. The current physician, Ann Biele, is working very hard but is just unable to cope with the demands for physician-to-physician communications. We recommend an additional psychiatrist to be involved in the medical-to-medical conversation on a day-by-day basis. This can enable us to communicate more scientific background data to prescribers to again reassure them about the merits and safe handling of Zyprexa.

The last point is regarding opinion leaders. redacted
redacted
We think Fujisawa and Janssen are both quite strong in this field, while we have a very limited base to work from. We need to invest more in advisory boards and involve Japanese psychiatrists in our global advisory boards as a community-building exercise to make sure that we get more traction and more credibility from the scientific point of view to start building a bigger Lilly network.

Zyprexa MDL 1596: Confidential-Subject to Protective Order

Memo

Lilly

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

July 1, 2002

Regarding the further emergence of AEs and label changes, we believe that with deeper expertise and leadership in pharmacoviligence, stronger ties (formal and informal) with the MHLW and improved positioning and education, the occurrence and impact of AEs will be lessened. Moreover, as patients with diabetes are shifted away from Zyprexa to Risperidal and Seroquel, there should be a balancing of the playing field on this issue over time. There appears to be a decrease of hyperglycemic AEs since the label changes. Again, we will make every effort through promotional efforts and physician-to-physician and medical communications to ensure that we promote the use of the drug within the label, which would by design dramatically reduce the number of events.

If you have questions or concerns, please feel free to contact one of us.

Bert van den Bergh
7-6845

Alan Breier
7-9222

Exhibit B,Page 4 of 4
SOA Response to Lilly Motion in Limine to Exlcude
References to Foreign Regulatory Action
Case No. 3AN-06-5630 CI
Zyprexa MDL 1596: Confidential-Subject to Protective Order
006165
ZY203332493

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IN THE SUPERIOR COURT FOR THE STATE OF
ALASKA THIRD JUDICIAL DISTRICT
AT ANCHORAGE

State of Alaska v. Eli Lilly and Company
Case No. 3AN-06-05630 CI

CONFIDENTIAL
AND FILED UNDER SEAL

See Judge Rindner's 6/13/08 order, pages 17:18, #10 Documents unsealed 8/11/08 Jude

Pages 6166B-6178

FILED
STATE OF ALASKA
THIRD DISTRICT

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

BY DEPUTY CLERK

STATE OF ALASKA,

Plaintiff,

vs.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-5630 CIV

NOTICE OF FILING UNDER SEAL

On this date the State of Alaska is filing a pleading titled "Plaintiff's Response to Defendant's Motion in Limine to Exclude Testimony and Call Notes of Non-Alaska Based Sales Representatives." Because one or more exhibits filed with this pleading may be confidential documents under the Court's April 6, 2007 oral ruling, the State of Alaska is submitting this pleading and the attached exhibits under seal.

DATED this 14 day of February, 2008.

FELDMAN ORLANSKY & SANDERS
Counsel for Plaintiff

BY _____
Eric T. Sanders
AK Bar No. 7510085

See Judge Rindner's 6/13/08 Order, pages 17, 18, #10

Documents unsealed per Order 8/11/08

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006166

#64

Pages 6166B-6178

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Pepper Hamilton

By Peggy J. Crowl
Date 2/14/08

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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Case No. 3AN-06-05630 CI
	)	
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	
	)	

PLAINTIFF'S RESPONSE TO DEFENDANT'S MOTION IN LIMINE TO EXCLUDE TESTIMONY AND CALL NOTES OF NON-ALASKA BASED SALES REPRESENTATIVES

Defendant Eli Lilly and Company ("Lilly") has moved to exclude from evidence in the trial of this case any testimony given by Lilly sales representatives who work in states other than Alaska and call notes generated by Lilly sales representatives who work in states other than Alaska.

"Relevant evidence" means evidence having any tendency to make, the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence.[1] Testimony of sales representatives and sales call notes, even those from other States, are relevant in this case.

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[1] Alaska R. Evid. 401.

Lilly had a sophisticated, broad-based plan designed to distort the entire body of public knowledge regarding Zyprexa's risks and benefits. Lilly formulated this plan at its corporate headquarters in Indianapolis, and it was carried out nationwide. There were not state-specific sales messages. Sales messages and materials all originated in Indianapolis, and the sales representatives were expected to carry those messages nationwide. The plan was implemented in Alaska, as in all other states.

Lilly's plan included a number of issues falling within the ambit of the State's claims in this case, including failing to warn in the product labeling accompanying each prescription about the risks associated with Zyprexa use. The plan also included affirmative misrepresentations which 1) minimized the magnitude and hazards of weight gain with Zyprexa; 2) denied a causal relationship between Zyprexa and hyperglycemia or diabetes; 3) claimed that hyperglycemia or diabetes occurred with Zyprexa use at rates comparable to other antipsychotic medications; and 4) promoted Zyprexa as safe and efficacious for uses not indicated on its labeling.

Lilly 30(b)(6) witness David Noesges testified that all sales messages delivered by Lilly sales representatives are developed in Indianapolis.[2] He further testified that the sales representatives are trained to and expected to deliver those messages, and are prohibited from delivering any messages that have not been approved by Lilly.[3] Sales

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[2] Exhibit A (Deposition of David Thomas Noesges, January 11, 2008 at 38).

[3] *Id.* at 35-36.

representatives are provided with a number of sales tools, including brochures, sell sheets and scripted answers to various questions. These materials included messages which, as indicated above, affirmatively misrepresented the risks and benefits of Zyprexa. Clear evidence that Lilly sales representatives delivered these messages is available in the sampling of "call notes" produced by Lilly. A call note is a business record which contemporaneously details a Lilly sales representative's visit to a physician.[4] Sales representatives are expected to accurately detail such visits.[5]

Call notes and testimony of sales representatives, whether within or without Alaska, are relevant proof of the State's claims in this case. While the actual number of UTPCPA violations in Alaska cannot be determined by reference to call notes or testimony involving non-Alaska based sales representatives, such call notes and testimony are certainly probative evidence of actual unfair or deceptive acts within Alaska. Further, they are evidence of Lilly's motive, intent and plan.

For the reasons stated above, the Court should deny Defendant's Motion in Limine.

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[4] *Id.* at 197-198; Exhibit B (Exhibit 9 to Deposition of David Thomas Noesges).

[5] Exhibit A at 198; Exhibit B.

Respectfully submitted this 14 day of February, 2008.

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Certificate of Service

I hereby certify that true and correct copies of **Plaintiff's Response to Defendant's Motion in Limine to Exclude Testimony and Call Notes of Non-Alaska Based Sales Representatives and (Proposed) Order** were served by messenger on:

Brewster H. Jamieson
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Barry Boise, via email
(boiseb@pepperlaw.com)
Pepper Hamilton

By Peggy S. Crowe
Date 2/14/08

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EXHIBIT A

TO STATE OF ALASKA'S RESPONSE TO LILLY'S MOTION IN LIMINE TO EXCLUDE TESTIMONY AND CALL NOTES OF NON-ALASKA BASED SALES REPRESENTATIVES

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA	)	
	)	
Plaintiff,	)	
	)	
vs.	)	CASE NO.
	)	3AN-06-5630 CIV
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	

The videotaped deposition upon oral examination of DAVID THOMAS NOESGES, a witness produced and sworn before me, Carolyn L. Smith, CSR, RPR, Notary Public, in and for the County of Hamilton, State of Indiana, taken on behalf of Plaintiff, at the offices of Ice Miller, One American Square, Suite 3100, Indianapolis, Indiana, on January 11, 2008, at 9:31 a.m., pursuant to all applicable rules.

Page 34

Q Oh, really?
A I'm not sure how long she's been with Lilly.
Q Okay. Where are the sales reps trained?
A Depends on what phase of their training and where that would take place.
Q Tell me about the different phases that there are.
A Every new Lilly representative starts with an entry level sales school that we call ID school. It's initial training school which is conducted in Indianapolis.
Q How long does that last?
A It varies, depending on the products they have in a different time frame, but it's typically anywhere from a four- to six-week initial program.
Q And what programs follow after that?
A After that we currently have a three-month school which is done typically regionally in a decentralized fashion and they now come back for a nine-month school again which is a week-long program conducted again in Indianapolis.
Q When you said a "three-month school," is that how long the schooling lasts or does that take place after they have been a sales rep for three months?
A Takes place after three months as a sales representative.

Page 35

Q How long is that training session?
A The program is approximately two to three days.
Q Okay. And then the nine-month school, I would presume, also does not last nine months but occurs after they have been a sales rep for nine months, correct?
A Yes, that is correct.
Q And how long does that take place?
A That's currently a week-long program.
Q Does the training process differ by state?
A Every representative goes through the comprehensive program I outlined and then we do a lot of ongoing training for our representatives throughout the country.
Q Is it fair to say that sales reps are expected to say particular things about Zyprexa and not say other things when they are selling the product?
MR. BOISE: Objection, vague.
THE WITNESS: Our sales representatives are required to follow our promotional guidelines and the promotional message that we establish for them.
QUESTIONS BY MR. SUGGS:
Q And that -- those promotional guidelines and the message that you establish are for the product throughout the United States and they are not

Page 36

particular for any given state or region, correct?
A Yes, that's correct. We have one promotional message throughout the United States.
Q It's not left up to the individual sales reps to decide what the appropriate representations are, correct?
MR. BOISE: Object to the form.
Representations?
MR. SUGGS: Let me restate the question.
Q It's not left up to the individual sales reps to decide what the appropriate messages are with respect to Zyprexa, correct?
THE WITNESS: Each of the sales representatives are required to use the messages that we establish for them nationally and then to determine, based on the customer needs, how to appropriately utilize those messages.
QUESTIONS BY MR. SUGGS:
Q In fact, sales reps are prohibited from developing their own promotional materials, correct?
A That's correct. The sales representatives can't develop homemade materials.
Q I'm going to hand you what we'll mark as Exhibit 3.
(Deposition Exhibit 3 marked for identification.)

Page 37

QUESTIONS BY MR. SUGGS:
Q Which for the record is a document entitled "Lilly USA, SALES GOOD PROMOTIONAL PRACTICE, Promotional Materials GPP 02, dash, 003."
Do you recognize this document, sir?
A Yes, I do.
Q What is it?
A This is a portion of our good promotional practices, appears effective November of 2004, based on the version number at the end of the document.
Q Says it was updated in November 2004, correct?
A Yes, it does.
Q It states that the policy is that "All promotional materials must be approved by a Brand Team before they may be used with any customer," correct?
A Yes, it does.
Q Okay. Was that policy in effect throughout the time that you have been involved with sales at Lilly?
A Throughout the time that I have been involved in sales with Lilly we have always had an approval process for all promotional materials that included a cross-functional team, referred to as the brand team here, that would be medical, legal, regulatory

Page 38

and our marketing organization.
Q And that brand team is located in Indianapolis and develops promotional materials and messages that are to be applicable throughout the U.S., correct?
A Yes, that's correct.
Q Then below that under the policy there is a heading, Information and Procedures, and then listed on the left are some materials that were apparently available from something called "E-order," and what is E-order?
A E-order means electronically ordering. So a sales representative can order a new promotional tool through the E-ordering system.
Q And this list includes such things as core sales aids, something called "slim jims," what were those?
A A slim jim is just a smaller version of the core sales aid.
Q And a core sales aid, would that be a brochure?
A It could be a brochure. It's basically the primary promotional tools that the representatives are using.
Q Okay. And such things as promotional star reprints, those are published medical literature that have been approved for distribution, correct?

Page 39

A Promotional star reprint is an approved peer review, reprint of a general article that has been approved for promotional use.
Q And those articles only address on-label indications of the drug, correct?
A Yes, promotional reprints would only address on-label uses of the product.
Q Also available from E-order were such things as pens and note pads, calendars, coffee mugs, anatomical models, CD ROMs, videos, DVDs, posters, badge holders, brochures, correct?
A Yes.
Q And all of those would have been generated in Indianapolis for use nationally, correct?
A Yes.
Q And then on the right-hand side under Information and Procedures, it says "From KM."
Am I correct that KM stands for knowledge management database?
A Yes, that's correct.
Q What is the knowledge management database?
A Knowledge management is a database available for the sales representatives to receive communications from Indianapolis and information and tools.
Q Okay. And would sales representatives be alerted

Page 40

that there was so[illegible] the database that they have to be aware [illegible]e, would they receive an E-mail or something telling them that something was on the --
A Yes, oftentimes there's something on knowledge management --
MR. BOISE: Let me interpose an objection. Vague.
You can answer the question.
THE WITNESS: Yes, oftentimes they would be notified if there was something new in knowledge management that they needed to access.
QUESTIONS BY MR. SUGGS:
Q Okay. And would sales representatives be expected to be aware of what was on the knowledge management database?
A There is not an expectation that they know everything on the database.
Q Would it be fair to say that anytime that something was posted on the knowledge management database that was new, the sales reps would be informed of that?
MR. BOISE: Objection, vague.
THE WITNESS: No, not in every case.
QUESTIONS BY MR. SUGGS:

Page 41

Q And the materials that were available on the knowledge management database included such things as Lilly business cards, promotional speaker program invitations, templates, package inserts, sell sheets, approved textbook lists, preprinted prescription pads, cake and cookie templates, special brand initiatives and formulary tools, correct?
MR. BOISE: This time frame?
THE WITNESS: In this time frame, yes.
QUESTIONS BY MR. SUGGS:
Q Okay. And what are sell sheets?
A Sell sheets is another form of a promotional material.
Q These documents that I handed you earlier were sell sheets, were they not?
MR. BOISE: Do you want to show him both? Compound question.
THE WITNESS: Yes, these would be an example of sell sheets.
MR. SUGGS: Okay.
MR. BOISE: Give me a moment to make objections along the way.
QUESTIONS BY MR. SUGGS:
Q And when it refers to "formulary tools," what does

Page 194

sales support personnel in LillyUSA and all sales activities that take place in the United States or with US Healthcare Professionals," correct?
A Yes, sir, that's correct.
Q And the policy statement was that, quote, It is the policy of LillyUSA that all sales personnel appropriately document sales calls with Healthcare Professionals in the call tracking system; is that correct?
A Yes, that's what it says.
Q What was the call tracking system?
A This is referring to basically the sales representatives' computer database that was available to them in this time frame, which would have been effective June 1st, is what this document is referring to -- to put their -- to document calls they were making on healthcare providers.
MR. BOISE: just so the record is clear it's June 1st, 2004.
Q And, in fact, this call system existed before 2004, correct?
A Yes, it did.
Q Okay. Can you describe for us, generally, what is involved in this call system or call note system?
A Depends on the time frame. While that system has

Page 195

been in place, the process of gathering call notes has changed over time.
Q Okay. Well, is it fair to say that the sales rep is expected to -- shortly after his calling on a particular physician is expected to go to a computer database and enter information about the particular sales call that he had?
A Yes, that's correct.
Q And all of that information is to go into a centralized database, correct?
A The sales representative inputs the data into their computer laptop which then is stored centrally, but I don't know the details of how -- how that information gets stored.
Q Okay. Again, I'm not asking for the details; but it's fair to say that there is a database of call notes that describes the -- or that lists the -- who the sales rep was, the doctors that they called on, the products that they discussed and what was said during the sales call, correct, or what information was presented at the sales call?
MR. BOISE: Object to the form of the question, compound.
THE WITNESS: No. It's important to note two things: One, it depends on the time frame, what

Page 196

got documented and, secondly, the call notes are not a comprehensive description. It won't describe everything that happened on the call or everything that was said on the call. To the contrary, it's more of a summary and notes taking process for the sales representatives to use for themselves.
QUESTIONS BY MR. SUGGS:
Q Understood; but -- and management can access the database quite easily, correct?
A Certainly the sales representative, sales managers can access their call notes.
Q If, for example, you wanted to go to get all of the call notes with respect to a particular sales representative, that could be easily retrieved from the call note system, correct?
MR. BOISE: Object to the form of the question.
THE WITNESS: I would have to work with our IT folks to get that, but I certainly could pull data from the call notes. Now, what I don't know is how far back the data goes at any time.
QUESTIONS BY MR. SUGGS:
Q I understand. There's a limitation on anything.
But I mean since whatever system is present now, you could certainly go to -- go to that

Page 197

database and make a query to pull up all of the call notes from Representative Harry Jones, for example?
A I'm assuming I would be able to. It's not something I have done in management. We don't routinely pull together data from the call notes.
Q Okay. And similarly if you wanted to get all of the call notes with respect to a particular doctor, the call note database would permit you do so, correct?
MR. BOISE: Object to the form.
THE WITNESS: Again, you are outside of my expertise in exactly what we can retrieve from the database.
QUESTIONS BY MR. SUGGS:
Q Okay. Directing your attention back to Exhibit 9.
A Yes.
Q There is a Definitions section there and sales call is defined as a face-to-face discussion about Lilly products between a healthcare professional and a Lilly sales representative, correct?
A Yes, it is.
Q And a call note is defined as a business record documented within a call system that accurately reflects all aspects of the sales call, correct?

A Yes.
Q Okay. And then below that there is a section entitled "Information and Procedures" and there's some bulleted points below that, correct?
A Yes.
Q The second bulleted point states, "The goal of the sales call is to appropriately influence a Healthcare Professional using the approved Lilly product information to allow him or her to choose the best therapy for his or her patients and ultimately to increase" the "sales of Lilly products," correct?
A Yes, that's correct.
Q And then on the following page there is a bullet point which states, "For each sales call and/or sample drop, the sales representative must accurately document the interaction in the Structured Call Note system in Premier."
Do you see that language?
A Yes, I do.
Q What is "Premier"?
A Looks like this was a typo here. It's probably referring to Premier Force which is the name of the sales representatives' computer database to enter calls, again, in this time frame, 2004.

Q And the structured call note system, was that a particular program within that Premier that is being referred to there?
A Yes.
Q And it goes on to say, "If applicable, unsolicited questions or medical letter requests must be documented within the SCN," or structured call note, "system according to policy, GPP 02-004 Unsolicited Questions on Off-Label Information or Unapproved Products."
Did I read that correctly?
A Yes, you did.
Q And that is the good promotional practice that we referred to earlier in Exhibit -- trying to find the number here. If you find it before I do, let me know.
A Exhibit 8.
Q Exhibit 8, very good. Thank you.
I would also like to show you some --
MR. BOISE: Dave, is there a question pending?
MR. SUGGS: I'm in the process of stating it.
MR. BOISE: Fair enough. Lots of shuffling of paper. I didn't know if I missed a question, if there was one.
MR. SUGGS: I was working on one.

MR. BOISE: Keep on working on it.
QUESTIONS BY MR. SUGGS:
Q I would like to show you some call notes that have been produced to us in the Alaska litigation, and I'll mark this next as Exhibit 10.
(Deposition Exhibit 10 marked for identification.)
QUESTIONS BY MR. SUGGS:
Q Which I'll represent to you is a page of call notes pulled from the sample that Lilly has produced to us in the Alaska litigation. And it would appear this particular page has call notes that were generated by Margaret Williams, several by her, and also by a Thea Jung.
Do you see that?
A Yes, I do.
Q It appears that this call note database has various fields that include the name of the sales rep, the call date, the call ID, the prescriber last name, the prescriber first name, the city in which the prescriber is, the state, and then it has action, reaction, follow up. And the rest of the information I think probably comes from this litigation.
Were you -- what's your understanding of what

the Action field was for?
A As I mentioned to you before, in this time frame this tool is really used for the reps to describe in shorthand notes to themselves as to the notes they wanted to record from their conversation with the doctor.
Q And then what is the Reaction supposed to be?
A The Reaction was designed to describe, kind of, a customer reaction to the calls. And my experience with these field notes is often it's not what you find in those fields. It all ends up really being shorthand notes to the representatives.
Q Is it the policy and practice of Lilly management to also review the call notes of the sales reps?
A No, we don't routinely review the call notes from the sales representatives.
Q Do you periodically do so?
A The district managers are able to access the call notes and if they choose to they can take a look at a call note or discuss it with a sales representative.
Q Do you know who Margaret Williams was?
A No, I do not know Margaret.
MR. SUGGS: Barry, can you tell me, is she the lady who is deceased?

EXHIBIT B

TO STATE OF ALASKA'S RESPONSE TO LILLY'S MOTION IN LIMINE TO EXCLUDE TESTIMONY AND CALL NOTES OF NON-ALASKA BASED SALES REPRESENTATIVES

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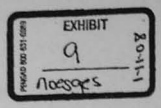

LillyUSA
Sales Good Promotional Practice
Definition of a Sales Call and Call Notes
Eli Lilly and Company
02-001

Objective: To provide a policy for defining a sales call between sales personnel and a Healthcare Professional.

Scope: This GPP applies to all sales personnel and sales support personnel in LillyUSA and all sales activities that take place in the United States or with US Healthcare Professionals.

Policy Statement: It is the policy of LillyUSA that all sales personnel appropriately document sales calls with Healthcare Professionals in the call tracking system.

Definitions:

Healthcare Professional: any physician, physician's assistant, nurse, nurse practitioner, diabetes nurse educator, clinical psychologists, clinical investigator, pharmacist, Pharmacy and Therapeutics Committee ("P&T") member, social worker, case worker, dietitian, office staff, or any individual involved in prescribing, P&T, access, formulary, purchasing and/or reimbursement decisions.

Sales Call: A "face-to-face" discussion about Lilly product(s) between a Healthcare Professional and a Lilly sales representative.

Call Note: A business record documented within a call system that accurately reflects all aspects of a sales call.

Information and Procedures:

- A sales call is a "face-to-face" discussion about Lilly product(s) between a Healthcare Professional and a Lilly sales representative.

- The goal of a sales call is to appropriately influence a Healthcare Professional using the approved Lilly product information to allow him/her to choose the best therapy for his/her patient(s) and ultimately to increase sales of Lilly products.

A "call" does **NOT include**:

- Dropping of material(s) and/or Lilly samples at the Healthcare Professional's office (e.g. leave behinds, patient brochures) without having a discussion with the Healthcare Professional.
- Speaking only with office staff, nurse or receptionist in the office that does not

have prescribing authority and is not an identified key non-prescribing customer by the Operations Team.
- o Phone call with a doctor or other office staff
- o Social interaction in which a specific Lilly product is not discussed
- o Written correspondence with a Healthcare Professional. (See GPP 02-003, Promotional Materials)

• For each sales call and/or sample drop, the sales representative must accurately document the interaction in the Structured Call Note (SCN) system in Premier. If applicable, unsolicited questions or medical letter requests must also be documented within the SCN system according to policy, GPP 02-004 Unsolicited Questions on Off-Label Information or Unapproved Products. In order to comply with company Red Book policies on document retention, sales representatives should avoid creating any other documentation about sales interactions outside of the SCN system (such as personal logs). The SCN system has automatic retention and retrieval capabilities that meet company document retention policies. However, if it is absolutely necessary to create any other documentation, the sales representative is personally accountable for complying with company document retention policies and must submit these documents to corporate upon request.

For additional information:
- Lilly Red Book
- Unsolicited Questions on Off-Label Information or Unapproved Products
- DVD Training on Structured Call Notes

Owner and Contact Information: Director of Sales Compliance

Effective Date: 6/1/04

Version: 2

Note: If you are using a printed copy of this document, check that the version number is consistent with the current version number in Knowledge Management on-line.

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IN THE SUPERIOR COURT FOR THE STATE OF
ALASKA THIRD JUDICIAL DISTRICT
AT ANCHORAGE

State of Alaska v. Eli Lilly and Company
Case No. 3AN-06-05630 CI

CONFIDENTIAL
AND FILED UNDER SEAL

See Judge Rindner's 6/13/08 order
page 18, #11
documents unsealed Exode 8/11/08

Pages 6179A-6271

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FILED
STATE OF ALASKA
THIRD DISTRICT

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

BY DEPUTY CLERK

STATE OF ALASKA,

Plaintiff,

vs.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-5630 CIV

NOTICE OF FILING UNDER SEAL

On this date the State of Alaska is filing a pleading titled "Plaintiff's Response to Defendant's Motion to Exclude References to Recent Regulatory Communications and Developments." Because one or more exhibits filed with this pleading may be confidential documents under the Court's April 6, 2007 oral ruling, the State of Alaska is submitting this pleading and the attached exhibits under seal.

DATED this 14 day of February, 2008.

See Judge Rindner's order of 6/13/08, page 18, #11
documents unsealed
Lucinda 8/11/08

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IN THE SUPERIOR COURT FOR THE STATE OF
ALASKA THIRD JUDICIAL DISTRICT
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State of Alaska v. Eli Lilly and Company
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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Case No. 3AN-06-05630 CI
	)	
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	
	)	

PLAINTIFF'S RESPONSE TO DEFENDANT'S MOTION IN LIMINE TO EXCLUDE REFERENCES TO RECENT REGULATORY COMMUNICATIONS AND DEVELOPMENTS

Defendant Eli Lilly and Company ("Lilly") has moved to exclude from the trial of this case any evidence relating to communications to or from the United States Food and Drug Administration ("FDA") or other regulatory communications or developments concerning Zyprexa labeling occurring after March 1, 2004.

I. FACTS

In its Motion in Limine to Exclude References to Foreign Regulatory Action, Lilly asserts that "[t]he question of liability in this Alaska case, where the relevant events

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occurred in the United States, turns solely upon United States regulatory action."[1] Inexplicably, in this motion Lilly seeks the exclusion of just such evidence.

When the State filed its complaint in this action in March 2006, and when it filed its brief concerning the proof it would offer in March 2007, it did so without the benefit of discovery regarding Lilly's ongoing conduct in violation of Alaska state law. Once the State became aware of correspondence from the U.S. Food and Drug Administration in late March 2007 flatly stating that the Zyprexa labeling did not adequately warn doctors of the drug's risks,[2] it sought discovery related to that correspondence and issues discussed therein. Lilly resisted that discovery, refusing to provide any response and requiring the State to file a motion to compel which was granted by the Discovery Master in September 2007. The State subsequently received responses to its discovery requests and in November 2007 issued a 30(b)(6) deposition notice to Lilly regarding a change to Zyprexa's label in October 2007 which stemmed from the FDA's criticism of the label in March. It was not until after this deposition that the State had most, yet still not all, discovery related to this particular issue. That evidence, including the FDA's March 2007 letter and further communications between FDA and Lilly between March and October 2007 indicates that even after Zyprexa's September 2003 label change, Lilly had not fully and adequately disclosed the full extent of Zyprexa's risks and further

[1] Def. Mot. in Limine to Exclude References to Foreign Regulatory Action, 4. The State does not agree with this assertion.

[2] Exhibit A, March 28, 2007 letter of FDA to Lilly.

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demonstrates continuing violations of the Alaska Unfair Trade Practices and Consumer Protection Act.

Just as it did in initially resisting any discovery related to the March 2007 FDA letter, Lilly attempts in the present motion to paint that letter as related to another product altogether, Symbyax. However, Symbyax is a combination of olanzapine (Zyprexa) and fluoxetine (Prozac), another Lilly drug. In the March 2007 letter, FDA specifically noted that "the labeling is deficient with regard to information about weight gain, hyperglycemia and hyperlipidemia that is associated with olanzapine use, whether taken alone or in combination with fluoxetine." It further stated:

> Our overall goal is to improve labeling with regard to these findings so that clinicians will be better informed on what the risks are for their patients. They cannot make reasonable treatment decisions until they have such information. We do not feel that the current labeling for either Symbyax or Zyprexa provides sufficient information on these risks, and we fully intend to insure that these labels are enhanced with the best available information to characterize these risks.[3]

The end result of FDA's communication with Lilly in the following months was its demand for an interim update to Zyprexa's label in order "to protect the public health"[4] which more accurately reflects the true nature of Zyprexa's risks.[5] It also belies Lilly's repeated misrepresentations over the course of years that the rates of diabetes between the

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3 *Id.* at 2.

4 Exhibit B (Exhibit 8 to Deposition of Robin Pitts-Wojcieszek, December 11, 2007)

5 Exhibit C, October 5, 2007 "Dear Health Care Professional" letter.

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various atypical antipsychotics were "comparable." The new October 2007 label states, ". . . the association between atypical antipsychotics and increases in blood glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics."[6]

This evidence is relevant and admissible on the issues of Zyprexa's defect, i.e., the lack of an adequate warning, the feasibility of certain safety precautions, notice of the extent of Zyprexa's risks, the falsity of Lilly's claim of "comparable rates" of diabetes and as impeachment evidence.

II. ARGUMENT

Lilly presents three arguments in support of the exclusion of any evidence regarding regulatory communications or developments after March 2004. First, Lilly argues the evidence is irrelevant. Second, Lilly argues that the time has lapsed for the State to supplement its expert reports and thus its experts cannot testify regarding any post-2004 regulatory developments. Finally, Lilly argues that evidence of changes to Zyprexa's label occurring after the State's complaint was filed would be subsequent remedial measures barred by Rule 407 of the Alaska Rules of Evidence. These arguments are addressed in this order below.

"Relevant evidence" means evidence having any tendency to make, the existence of any fact that is of consequence to the determination of the action more probable or less

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[6] *Id.* at 1, 3.

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probable than it would be without the evidence.[7] The State's burdens of proof in this case require it show, among other things, that Lilly marketed Zyprexa without adequate warnings of the risks it posed and that Lilly had notice of the risks presented by Zyprexa.[8] In determining the adequacy of warnings involving Zyprexa, the jury will be asked to consider whether any such warning clearly indicated the scope of the risk or danger, reasonably communicated the extent or seriousness of harm resulting from the risk, and whether the warning was conveyed in such a manner as to put a reasonable physician on notice of any scientifically knowable risks.[9] Further, the State must demonstrate that Lilly committed unfair or deceptive acts.[10] The evidence embodied in the regulatory communications and developments of 2007 is probative on all of these issues.

The FDA's March 2007 letter, the communications between the agency and Lilly through October 2007 and the new label are evidence of the inadequacy of Zyprexa's label, and evidence of notice to Lilly of that fact. Further, this line of evidence demonstrates that Lilly was in possession of studies and data regarding Zyprexa's risks that were not disclosed in Zyprexa's package insert or label, studies which it had been in

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7 Alaska R. Evid. 401.

8 *Shanks v. Upjohn Co.*, 835 P.2d 1189, 1199-1200 (Alaska 1992).

9 *Shanks*, 835 P.2d at 1200.

10 *Kenai Chrysler Center, Inc. v. Denison*, 167 P.3d 1240, 1255 (Alaska 2007); *State v. O'Neill Investigations, Inc.*, 609 P.2d 520, 534-35 (Alaska 1980).

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possession of for years.[11] It is also evidence that clearly refutes Lilly's "comparable rates" claims which are part of the basis of the State's UTPCPA allegations. Lilly continued to claim that diabetes occurred at "comparable rates" across all atypical antipsychotics, even after the publication of the *Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes* ("Consensus Statement") in February 2004.[12] The October 2007 label change for Zyprexa directly refutes the "comparable rates" claim and mirrors in numerous ways the findings and recommendations of the Consensus Statement. Finally, this evidence will serve to impeach testimony and other evidence offered by Lilly in contesting the State's allegations and asserting its own defenses. This last point provides an appropriate point of transition to Lilly's second basis for exclusion of this evidence.

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11 Exhibit D, Deposition of Robin Pitts Wojcieszek, December 11, 2007, 14-19.

12 Exhibit E, Zyprexa MDL Plaintiffs' Exhibit 2368 (*Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes*). In November 2003, the American Diabetes Association, the American Psychiatric Association, the American College of Clinical Endocrinologists, and the North American Association for the Study of Obesity convened a consensus development conference on the subject of antipsychotic drugs and diabetes. An eight member panel heard presentations from fourteen experts drawn from the fields of psychiatry, obesity and diabetes. Presentations were also made by representatives of the FDA and the atypical antipsychotic drug manufacturers. The panel also reviewed most of the known peer-reviewed English language scientific articles published in this area. After considering all of that scientific evidence, the consensus panel issued a statement refuting Lilly's "comparable rates" message. Of the six atypical antipsychotics discussed in the consensus statement, only Clozapine and Olanzapine were found to increase the risk for diabetes.

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While Lilly argues that the State has had ample opportunity to update its expert reports to reflect opinions regarding the recent regulatory communications and developments, the fact is that Lilly did not make its Rule 30(b)(6) witness available for the State to depose until December 11, almost a full month after the deadline for retained expert reports. More importantly, however, the facts underlying and giving rise to the recent regulatory communications and developments do not require "scientific, technical, or other specialized knowledge" for evaluation by the jury. There will be testimony by Lilly witnesses and a 30(b)(6) designee, which will provide evidence on the 2007 communications with FDA. That factual testimony, coupled with other testimony of both fact and expert witnesses about the general scientific issues and Lilly's conduct prior to 2007 is more than sufficient for the jury to draw appropriate conclusions in this case.

Finally, Lilly asserts that evidence of the October 2007 label change should be excluded as a subsequent remedial measure. Alaska Rule of Evidence 407 provides:

> When, after an event, measures are taken which, if taken previously, would have made the event less likely to occur, evidence of the subsequent measures is not admissible to prove negligence or culpable conduct in connection with the event. This rule does not require the exclusion of evidence of subsequent measures when offered for another purpose, such as impeachment or, if controverted, proving ownership, control, feasibility of precautionary measures, or defective condition in a products liability action.[13]

[13] Alaska R. Evid. 407.

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Applying the rule to the evidence at issue here demonstrates that it should not be excluded for several reasons.

First, the October 2007 label change is not even a "subsequent remedial measure." The policy behind Rule 407 was to avoid deterring defendants from making improvements or repairs after an injury occurred. However, courts have recognized that the rule should not apply when the defendant does not voluntarily undertake the improvements or repairs, but instead only does so because of governmental or regulatory requirements.[14] Lilly did not voluntarily change its label in October 2007. In the months after FDA's March 2007 letter it repeatedly told the agency it did not believe the label should be changed. Lilly only changed the label because in August 2007 FDA demanded the change in order to protect the public health.[15]

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[14] *See, e.g., In re Aircrash in Bali, Indonesia*, 871 F.2d 812, 816-17 (9th Cir. 1989) (holding that FAA investigation report on defendant's safety record and procedures was not a subsequent remedial measure because the defendant was required by federal regulations to participate in the FAA investigation); *Herndon v. Seven Bar Flying Serv., Inc.*, 716 F.2d 1322, 1331 (10th Cir. 1983) ("Where a superior authority requires a tort feasor to make post-accident repairs, the policy of encouraging voluntary repairs which underlies Rule 407 has no force – a tort feasor cannot be discouraged from voluntarily making repairs if he *must* make repairs in any case.").

[15] Exhibit B; Exhibit C, 191-92:

"Q: Why did Lilly decide to change its label in October of 2007?

A: We decided to change our label because we received a request from FDA on August 28. We were in the process of including more information around these particular metabolic issues at the time, and given that we are in a regulated industry and FDA's requesting us to make labeling changes, we complied with that request."

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Second, Lilly has conveniently overlooked a fundamental difference in Alaska Rule 407 and the analogous federal rule. While the federal rule explicitly prevents the use of any subsequent measure in the context of product liability suits absent certain exceptions, the Alaska rule does not.[16] As noted above, Alaska Rule 407 specifically provides an exception for proving "defective condition in a products liability action." In *Caterpillar Tractor Company v. Beck*, the Supreme Court of Alaska specifically recognized that Alaska's version of Rule 407 "provides that in a products liability action evidence of subsequent measures is admissible toward the feasibility of alternative designs as well as defective condition."[17] The court went on to note that:

> Even in negligence actions, where the rule of exclusion is most frequently applied, evidence of subsequent measures or accidents is generally admissible to impeach or prove that the product was capable of causing injury. Thus such evidence is similarly admissible toward those issues in strict liability actions.[18]

The evidence of recent regulatory developments and the October 2007 label change should likewise be admissible in this action.

For the reasons stated above, the Court should deny Defendant's Motion in Limine.

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16 *See* Fed. R. Evid. 407; Alaska R. Evid. 407.

17 *Caterpillar Tractor Company v. Beck*, 624 P.2d 790, 793-94 (Alaska 1981).

18 *Id.* at 793 n.8.

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Respectfully submitted this 14 day of February, 2008.

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Certificate of Service

I hereby certify that true and correct copies of **Plaintiff's Response to Defendant's Motion in Limine to Exclude References to Recent Regulatory Communications and Developments and (Proposed) Order** were served by messenger on:

Brewster H. Jamieson
Lane Powell LLC
301 W. Northern Lights Blvd., Ste. 301
Anchorage, Alaska 99503-2648

Barry Boise, via email
(boiseb@pepperlaw.com)
Pepper Hamilton

By Peggy S Crowe
Date 2/14/08

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EXHIBIT A
TO STATE OF ALASKA'S RESPONSE TO LILLY'S MOTION IN LIMINE REGARDING RECENT REGULATORY COMMUNICATIONS AND DEVELOPMENTS

006189

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-520/S-012

Eli Lilly & Company
Attention: Robin Pitts Wojcieszek, R.Ph.
Associate Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Wojcieszek:

Please refer to your supplemental new drug application dated September 28, 2006, received September 29, 2006 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbyax (olanzapine/fluoxetine) 3 mg/25 mg, 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50 mg (mg equivalent olanzapine/mg equivalent fluoxetine) capsules.

We acknowledge receipt of your amendments dated November 8, 28, 2006, December 11, 14, 2006, and February 5, 20, 2007.

This supplemental new drug application provides for the use of Symbyax (olanzapine/fluoxetine) capsules for Treatment Resistant Depression (TRD).

We completed our review of this application, and it is approvable. Before the application may be approved, however, you must address the following issues:

Updated Information on Risks of Weight Gain, Hyperglycemia, and Hyperlipidemia

A primary concern with this application and the primary basis for our not taking a final action is our view that we lack important safety information needed to adequately update the labeling with all relevant risk information. In particular, we are concerned that the labeling is deficient with regard to information about weight gain, hyperglycemia, and hyperlipidemia that is associated with olanzapine use, whether taken alone or in combination with fluoxetine. You must fully address these concerns before we will be able to take a final action on this application.

Defining what your response will need to be to fully address these concerns will likely involve an interactive process with us over a period of several weeks, because we, first of all, need to fully understand the universe of relevant olanzapine and olanzapine/fluoxetine combination (OFC) studies and their characteristics. Once we better understand this set of studies and what data pertinent to our concerns were collected, we will be in a better position to provide detailed advice on what studies to pool, what data to provide, and what additional analyses to conduct. In characterizing these trials, it will be important to provide details on what data were collected (e.g., plasma glucose, HbA1c, total cholesterol, HDL, LDL, triglyceride, and urine glucose), under what conditions (e.g., fasting vs non-

MAR 2 8 2007
G. Brophy

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fasting), the demographic characteristics of the subjects (e.g., pediatric vs adult), and at what intervals. Once we have this information, we will work with you to define what studies to pool, and what data to provide to us and in what format.

Regarding data displays, an overall strategy will be to subgroup patients on the basis of their status at baseline so that clinicians can better understand the risks associated with treatment of patients falling into different risk categories. For example, we note that your proposed Symbyax label includes information only on proportions of patients who are relatively normal at baseline with regard to random blood glucose (< 140 mg/dL), i.e., 2.9% of such patients receiving OFC had on-treatment levels ≥ 200 mg/dL compared to 0.3% of placebo-treated patients. However, we note that 46% of patients who were borderline to high at baseline (140 to 200) had such on-treatment levels compared to only 5% of placebo-treated patients. This latter finding was based on a small number of patients in the OFC program, and for this reason, we would like to see such data for the entire olanzapine program. In addition, we were troubled that this important finding was not included in your proposed label. We will want you to provide similar information based on subgroupings of patients on the basis of weight and BMI (for weight change), and lipid findings for the lipid data. We will want you to provide data both on proportions of patients meeting certain on-treatment criteria and also for mean change from baseline.

If you feel you have already aggregated and submitted data to address these concerns, then we ask that you direct us to precisely which submissions these are. If, on the other hand, you have aggregated the appropriate data for your own internal purposes but not submitted them, we ask you to submit them. Your recent February 20, 2007 response to our January 12, 2007 letter regarding the New York Times story has not been particularly helpful in addressing these concerns.

Our overall goal is to improve labeling with regard to these findings so that clinicians will be better informed on what the risks are for their patients. They cannot make reasonable treatment decisions until they have such information. We do not feel that current labeling for either Symbyax or Zyprexa, provides sufficient information on these risks, and we fully intend to insure that these labels are enhanced with the best available information to characterize these risks.

Post Marketing Commitments

Long-Term Efficacy Studies

Since TRD is a chronic illness, you are required to assess the longer-term effectiveness and safety of Symbyax in TRD. Accordingly, we ask for your commitment to submit, as a Postmarketing commitment, the results of this study to evaluate Symbyax's ability to reduce the risk of relapse in acutely remitted patients with TRD. We ask that you commit to submitting these results no later than 3 years after the date of approval of this supplemental application.

Labeling

Please submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling text for the package insert.

In addition, all previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

MAR 2 8 2007

G. Brophy

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Foreign Regulatory Update/Labeling

We require a review of the status of all Symbyax actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If Symbyax has been approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for Symbyax along with English translations when needed.

Request for Safety Update and World Literature Update

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Prior to an approval action, we require an updated report on the world's archival literature pertaining to the safety of Symbyax. Please provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. This report should include only literature not covered in your previous submissions. We will need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Symbyax. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of

MAR 2 6 2007
G. Brophy

articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Promotional Materials

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Psychiatry Products to discuss what further steps need to be taken before the application may be approved.

If you have any questions, call LCDR Renmeet Grewal, Pharm.D., Regulatory Project Manager, at (301) 796-1080.

Sincerely,

(See appended electronic signature page)

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

MAR 2 8 2007
G. Brophy

]

This version of labeling is based up on the version submitted with the application. We have used track changes to indicate our additions and deletions. We have added bracketed comments to explain our actions where needed.]

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Symbyax safely and effectively. See full prescribing information for Symbyax.

SYMBYAX® (olanzapine and fluoxetine HCl capsules) for oral administration
Initial U.S. Approval: 2003

WARNING

See full prescribing information for complete boxed warning.

SUICIDALITY IN CHILDREN AND ADOLESCENTS:

- Increased risk of suicidal thinking and behavior in children and adolescents taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Not approved for use in children and adolescents.

INCREASED MORTALITY IN ELDERLY PATIENTS:

- Increased mortality in elderly patients with dementia-related psychosis compared to placebo. Not approved for the treatment of patients with dementia-related psychosis.

~~SUICIDALITY IN CHILDREN AND ADOLESCENTS:~~

~~- Increased risk of suicidal thinking and behavior in children and adolescents taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Not approved for use in children and adolescents.~~

RECENT MAJOR CHANGES

~~Warnings and Precautions, Mortality, in patients with dementia-related psychosis (5.1)~~	~~10/2005~~
Contraindications, Pimozide (4)	3/2006
Warnings and Precautions, Hepatobiliary events (5.14)	4/2006
Warnings and Precautions, Serotonin Syndrome (5.8)	8/2006
~~Warnings and Precautions, Weight Gain~~	
Warnings and Precautions, Risk of Glucose Dysregulation	
Warnings and Precautions, Hypercholesterolemia	

INDICATIONS AND USAGE

SYMBYAX combines olanzapine, a psychotropic agent belonging to the thienobenzodiazepine class, and fluoxetine, a selective serotonin reuptake inhibitor, indicated for treatment of:

- Depressive episodes associated with bipolar disorder (1.1)
- Treatment Resistant Depression (major depressive disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode) (1.2)

DOSAGE AND ADMINISTRATION

- Once daily in the evening, generally beginning with 6 mg/25 mg (2)
- Exercise dose cautiously in patients predisposed to hypotensive reactions, hepatic impairment, or with potential for slowed metabolism (2.3)
- Discontinue gradually (2.4)
- The safety of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical trials.

DOSAGE FORMS AND STRENGTHS

- Capsules: 3 mg/25 mg, 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50 mg (mg equivalent olanzapine/mg equivalent fluoxetine) (3)

CONTRAINDICATIONS

- Do not use with an MAOI or within 14 days of discontinuing an MAOI. At least 5 weeks should be allowed after stopping SYMBYAX before starting treatment with an MAOI (4, 7.13)
- Do not use with Pimozide (4, 7.15)
- Do not use with Thioridazine. Do not use Thioridazine within 5 weeks of discontinuing SYMBYAX (4, 7.18)

WARNINGS AND PRECAUTIONS

- Patients should be monitored for clinical worsening and suicidal thinking and behavior (5.2)
- Cerebrovascular adverse events including fatalities were reported more commonly with olanzapine than placebo in trials of elderly patients with dementia-related psychosis (5.3)
- Neuroleptic Malignant Syndrome has been reported with atypical antipsychotics (5.4)

[See Approvable Letter for information requested for hyperglycemia/diabetes.]

- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics, including olanzapine alone as well as olanzapine taken concomitantly with fluoxetine. Diabetic patients should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Monitor all patients for symptoms of hyperglycemia. (5.5)
- ~~Hypercholesterolemia and hypertriglyceridemia were seen. See Approvable Letter.~~
- ~~Clinically significant weight gain may occur.~~
- Serotonin Syndrome may occur with SYMBYAX (5.6)
- Discontinue upon appearance of rash or allergic phenomena (5.7)
- Screen for bipolar disorder and monitor for mania/hypomania (5.8)
- Tardive Dyskinesia may develop acutely or chronically (5.9)
- Orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some patients, syncope may occur, especially during initial dose titration. Use caution in patients with cardiovascular disease, cerebrovascular disease, and those conditions that could affect hemodynamic responses (5.10)
- Use cautiously in patients at risk for aspiration pneumonia due to esophageal dysmotility (5.11)
- Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold (5.12)
- ~~Clinically significant weight gain may occur (5.13)~~
- Asymptomatic elevations of hepatic transaminases and alkaline phosphatase have been observed with olanzapine. Periodic assessment recommended in patients with hepatic disease (5.14)
- May increase the risk of bleeding. Use with NSAIDs or drugs that affect coagulation may potentiate the risk of gastrointestinal or other bleeding (5.15)
- Hyponatremia (some cases with serum sodium lower than 110 mmol/L) possibly associated with the syndrome of inappropriate antidiuretic hormone (SIADH) have been reported with fluoxetine (5.16)
- Has potential to impair judgment, thinking, and motor skills (5.17)
- May disrupt temperature regulation (5.18)
- Due to anticholinergic activity, use with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus or related conditions (5.19)
- Use a lower dose in patients with cirrhosis (5.19)
- May elevate prolactin levels (5.20)
- Use caution when prescribing with other products containing olanzapine, and/or fluoxetine as active ingredients (i.e., Zyprexa, Prozac, Sarafem) (5.21)
- Fluoxetine has a long elimination half-life (5.22)
- Monitor when discontinuing treatment since discontinuation symptoms may occur (5.23)

ADVERSE REACTIONS

Most common adverse events (≥5% and at least twice that for placebo) are disturbance in attention, dry mouth, fatigue, hypersomnia, increased appetite, peripheral edema, sedation, somnolence, tremor, vision blurred, and weight increased (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lilly at 1-800-545-5979 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Antihypertensives – enhanced antihypertensive effect (7.1)
- Anti-Parkinsonian – may antagonize levodopa/dopamine agonists (7.2)

MAR 2 6 2007
G. Brophy

- Benzodiazepines – may potentiate orthostatic hypotension and sedation (7.3)
- Carbamazepine – potential for elevated carbamazepine levels (7.5)
- Clozapine – may elevate Clozapine levels (7.6).
- CNS Acting Drugs – caution should be used when taken in combination with other centrally acting drugs and alcohol (7.7)
- Ethanol – may potentiate sedation and orthostatic hypotension (7.9)
- Fluvoxamine – may double olanzapine levels (7.10)
- Haloperidol – elevated haloperidol levels have been observed (7.11)
- Lithium – monitor lithium levels (7.12)
- Phenytoin – potential for elevated phenytoin levels (7.14)
- Serotonergic drugs – potential for Serotonin Syndrome (5.6, 7.16, 7.20)
- Tricyclic antidepressants (TCAs) – monitor TCA levels (7.17)
- Warfarin – increase monitoring with SYMBYAX dose change (7.23)
- Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.) may potentiate the risk of bleeding (7.24)
- Fluoxetine is an inhibitor of CYP450 2D6 enzyme pathway (7.25)
- Drugs highly bound to plasma protein, may cause shift in plasma concentrations (7.29)

USE IN SPECIFIC POPULATIONS

- Pregnancy: SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1)
- Nursing mothers: breast feeding is not recommended (8.3)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling.

Revised: (9/2006)

(BNL561JAMP)

MAR 2 8 2007
G. Brophy

FULL PRESCRIBING INFORMATION: CONTENTS*

[Section reference numbers must be re-ordered to reflect changes both here and in the body of the document.]

WARNING — INCREASED MORTALITY IN ELDERLY PATIENTS and SUICIDALITY IN CHILDREN AND ADOLESCENTS
1 INDICATIONS AND USAGE
1.1 Bipolar Depression
1.2 Treatment Resistant Depression
2 DOSAGE AND ADMINISTRATION
2.1 Bipolar Depression
2.2 Treatment Resistant Depression
2.3 Special Populations
2.4 Discontinuation of Treatment with SYMBYAX
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
5.2 Clinical Worsening and Suicide Risk
5.3 Cerebrovascular Adverse Events (CVAE), Including Stroke, in Elderly Patients with Dementia-Related Psychosis
5.4 Neuroleptic Malignant Syndrome (NMS)
5.5 Hyperglycemia and Diabetes Mellitus
Hypothyroidism
Weight Gain
5.6 Serotonin Syndrome
5.7 Allergic Events and Rash
5.8 Screening Patients for Bipolar Disorder and Monitor for Mania/Hypomania
5.9 Tardive Dyskinesia
5.10 Orthostatic Hypotension
5.11 Dysphagia
5.12 Seizures
5.13 Weight Gain
5.14 Transaminase Elevations
5.15 Abnormal Bleeding
5.16 Hyponatremia
5.17 Cognitive and Motor Impairment
5.18 Body Temperature Regulation
5.19 Use in Patients with Concomitant Illness
5.20 Hyperprolactinemia
5.21 Concomitant Use of Olanzapine and Fluoxetine Products
5.22 Long Half-Life of Fluoxetine
5.23 Discontinuation of Treatment with SYMBYAX
5.24 Laboratory Tests
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
7.1 Antihypertensive Agents
7.2 Anti-Parkinsonian Agents
7.3 Benzodiazepines
7.4 Biperiden
7.5 Carbamazepine
7.6 Clozapine
7.7 CNS Acting Drugs
7.8 Electroconvulsive therapy (ECT)
7.9 Ethanol
7.10 Fluvoxamine
7.11 Haloperidol
7.12 Lithium
7.13 Monoamine oxidase inhibitors
7.14 Phenytoin
7.15 Pimozide
7.16 Serotonergic drugs
7.17 Theophylline
7.18 Thioridazine
7.19 Tricyclic antidepressants (TCAs)
7.20 Triptans
7.21 Tryptophan
7.22 Valproate
7.23 Warfarin
7.24 Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.)
7.25 Drugs metabolized by CYP2D6
7.26 Drugs metabolized by CYP3A
7.27 Effect of olanzapine on drugs metabolized by other CYP enzymes
7.28 The effect of other drugs on olanzapine
7.29 Drugs highly bound to plasma proteins
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.3 Dependence
10 OVERDOSAGE
10.1 Management of Overdose
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Special Populations
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Bipolar Depression
14.2 Treatment Resistant Depression
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Information for Patients
17.2 Clinical Worsening and Suicide Risk
17.3 Serotonin Syndrome
17.4 FDA approved Medication Guide

*Sections or subsections omitted from the full prescribing information are not listed.

MAR 9 [illegible]
G. Brophy

4
FULL PRESCRIBING INFORMATION

WARNING

Suicidality in Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SYMBYAX or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SYMBYAX is not approved for use in pediatric patients. *[See Warnings and Precautions (5.2) and Use in Specific Populations (8.4)].*

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials. *[See Warnings and Precautions (5.2)].*

Increased Mortality in Elderly Patients — Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infections (e.g., pneumonia) in nature. SYMBYAX (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)].*

~~Suicidality in Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SYMBYAX or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SYMBYAX is not approved for use in pediatric patients. *[See Warnings and Precautions (5.2) and Use in Specific Populations (8.4)].*~~

~~Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials. *[See Warnings and Precautions (5.2)].*~~

1 INDICATIONS AND USAGE

1.1 Bipolar Depression

SYMBYAX is indicated for the treatment of depressive episodes associated with bipolar disorder.

Unlike with unipolar depression, there are no established guidelines for the length of time patients with bipolar disorder experiencing a major depressive episode should be treated with agents containing antidepressant drugs.

The effectiveness of SYMBYAX for maintaining antidepressant response in this patient population beyond 8 weeks has not been established in controlled clinical studies. Physicians who elect to use SYMBYAX for extended periods should periodically reevaluate the benefits and long-term risks of the drug for the individual patient.

1.2 Treatment Resistant Depression

SYMBYAX is indicated for treatment resistant depression (major depressive disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode) *[see Clinical Studies (14.2)]*.

The effectiveness of SYMBYAX for maintaining antidepressant response in this patient population beyond 8 weeks has not been established in controlled clinical studies. Physicians who elect to use SYMBYAX for extended periods should periodically reevaluate the benefits and long-term risks of the drug for the individual patient.

MAR 2 8 2007
G. Brophy

5

2 DOSAGE AND ADMINISTRATION

2.1 Bipolar Depression

SYMBYAX should be administered once daily in the evening, generally beginning with the 6-mg/25-mg capsule. While food has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of SYMBYAX has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with SYMBYAX in a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg *[see Clinical Studies (14)]*.

The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies.

2.2 Treatment Resistant Depression

SYMBYAX should be administered once daily in the evening, generally beginning with the 6-mg/25-mg capsule. While food has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of SYMBYAX has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with SYMBYAX in a dose range of olanzapine 6 to 18 mg and fluoxetine 25 to 50 mg *[see Clinical Studies (14)]*. The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies.

2.3 Special Populations

The starting dose of SYMBYAX 3 mg/25 - 6 mg/25 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of SYMBYAX (female gender, geriatric age, nonsmoking status) or those patients who may be pharmacodynamically sensitive to olanzapine. When indicated, dose escalation should be performed with caution in these patients. SYMBYAX has not been systematically studied in patients over 65 years of age or in patients <18 years of age *[see Warnings and Precautions (5.19), Use in Specific Populations (8.4 and 8.5), and Clinical Pharmacology (12.3)]*.

2.4 Discontinuation of Treatment with SYMBYAX

Symptoms associated with discontinuation of fluoxetine, a component of SYMBYAX, and other SSRIs and SNRIs, have been reported *[see Warnings and Precautions (5.23)]*.

3 DOSAGE FORM AND STRENGTHS

Capsules (mg equivalent olanzapine/mg equivalent fluoxetine):

- 3 mg/25 mg
- 6 mg/25 mg
- 6 mg/50 mg
- 12 mg/25 mg
- 12 mg/50 mg

4 CONTRAINDICATIONS

The use of SYMBYAX is contraindicated with the following:

- Monoamine Oxidase Inhibitors (MAOI) — *[see Drug Interactions (7.13)]*
- Pimozide — *[see Drug Interactions (7.15)]*
- Thioridazine — *[see Drug Interactions (7.18)]*

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SYMBYAX is not approved for the treatment of patients with dementia-related psychosis *(see Box Warning)*.

In olanzapine placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

5.2 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that

MAR 2 8 2007
C. Brophy

antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in any of these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms *(see Warnings and Precautions (5.23) and Dosage and Administration (2.4)*, for a description of the risks of discontinuation of SYMBYAX).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for SYMBYAX should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

It should be noted that SYMBYAX is not approved for use in treating any indications in the pediatric population.

5.3 **Cerebrovascular Adverse Events (CVAE), Including Stroke, in Elderly Patients with Dementia-Related Psychosis**

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine and SYMBYAX are not approved for the treatment of patients with dementia-related psychosis.

5.4 **Neuroleptic Malignant Syndrome (NMS)**

A potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or

MAR 2, 8 2007
S. Brophy

inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If after recovering from NMS, a patient requires treatment with an antipsychotic, the patient should be carefully monitored, since recurrences of NMS have been reported.

[As noted above, we have requested additional information on treating patients with hyperglycemia in the Approvable Letter. Section 5.5 will be modified when we have reviewed the requested information. We have also grouped hyperglycemia, hyperlipidemia, and weight gain together (see Full Prescribing Contents section and order the appropriate sections below to correspond to those changes.)]

5.5 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

5.6 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome may occur with SYMBYAX, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of SYMBYAX with MAOIs intended to treat depression is contraindicated *[see Contraindications (4) and Drug Interactions (7.13)]*.

If concomitant treatment of SYMBYAX with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions (7.19)]*.

The concomitant use of SYMBYAX with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions (7.20)]*.

5.7 Allergic Events and Rash

In SYMBYAX premarketing controlled clinical studies, the overall incidence of rash or allergic events in SYMBYAX-treated patients [4.6% (26/571)] was similar to that of placebo [5.2% (25/477)]. The majority of the cases of rash and/or urticaria were mild; however, three patients discontinued (one due to rash, which was moderate in severity and two due to allergic events, one of which included face edema).

In fluoxetine US clinical studies, 7% of 10,782 fluoxetine-treated patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical studies, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In fluoxetine premarketing clinical studies, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of fluoxetine, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possible allergic phenomena for which an alternative etiology cannot be identified, SYMBYAX should be discontinued.

5.8 Screening Patients for Bipolar Disorder and Monitor for Mania/Hypomania

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described for clinical worsening and suicide risk represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SYMBYAX is approved for use in treating bipolar depression.

In the two controlled bipolar depression studies there was no statistically significant difference in the incidence of manic events (manic reaction or manic depressive reaction) between SYMBYAX- and placebo-treated patients. In one of the studies, the incidence of manic events was (7% [3/43]) in SYMBYAX-treated patients compared to (3% [5/184]) in placebo-treated patients. In the other study, the incidence of manic events was (2% [1/43]) in SYMBYAX-treated patients compared to (8% [15/193]) in placebo-treated patients. This limited controlled trial experience of SYMBYAX in the treatment of bipolar depression makes it difficult to interpret these findings until additional data is obtained. Because of this and the cyclical nature of bipolar disorder, patients should be monitored closely for the development of symptoms of mania/hypomania during treatment with SYMBYAX.

5.9 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

The incidence of dyskinetic movement in SYMBYAX-treated patients was infrequent. The mean score on the Abnormal Involuntary Movement Scale (AIMS) in the SYMBYAX-controlled database across clinical studies involving SYMBYAX-treated patients decreased from baseline. Nonetheless, SYMBYAX should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on SYMBYAX, drug discontinuation should be considered. However, some patients may require treatment with SYMBYAX despite the presence of the syndrome. The need for continued treatment should be reassessed periodically.

5.10 Orthostatic Hypotension

SYMBYAX may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some patients, syncope, especially during the initial dose-titration period.

In the SYMBYAX-controlled clinical trials across all indications, there were no significant differences between SYMBYAX-treated patients and olanzapine, fluoxetine or placebo-treated patients in exposure adjusted rates of orthostatic systolic blood pressure

MAR 2 8 2007
G. Brophy
006201

decreases of at least 30 mm Hg. Orthostatic systolic blood pressure decreases of at least 30 mm Hg occurred in 4.0% (28/705), 2.3% (19/831), 4.5% (18/399), and 1.8% (8/442) of the SYMBYAX, olanzapine, fluoxetine, and placebo groups, respectively. In this group of studies, the incidence of syncope-related adverse events (i.e., syncope and/or loss of consciousness) in SYMBYAX-treated patients was 0.4% (3/771) compared to placebo 0.2% (1/477).

In a clinical pharmacology study of SYMBYAX, three healthy subjects were discontinued from the trial after experiencing severe, but self-limited, hypotension and bradycardia that occurred 2 to 9 hours following a single 12-mg/50-mg dose of SYMBYAX. Reactions consisting of this combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in at least three other healthy subjects treated with various formulations of olanzapine (one oral, two intramuscular). In controlled clinical studies, the incidence of patients with a ≥20 bpm decrease in orthostatic pulse concomitantly with a ≥20 mm Hg decrease in orthostatic systolic blood pressure was 0.3% (2/706) in the SYMBYAX group, 0.2% (1/445) in the placebo group, 0.7% (6/837) in the olanzapine group, and 0% (0/404) in the fluoxetine group.

SYMBYAX should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

5.11 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.12 Seizures

Seizures occurred in 0.2% (4/2547) of SYMBYAX-treated patients during open-label clinical studies. No seizures occurred in the controlled SYMBYAX studies. Seizures have also been reported with both olanzapine and fluoxetine monotherapy. SYMBYAX should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of ≥65 years of age.

[As noted, we will want the Weight Section revised with new requested information and moved to be adjacent to the hyperglycemia and hyperlipidemia sections.]

5.13 Weight Gain

In clinical studies, the mean weight increase for SYMBYAX-treated patients after 8 weeks of treatment was statistically significantly greater than placebo-treated (4.3 kg vs -0.5 kg) and fluoxetine-treated (4.3 kg vs -0.2 kg) patients, but was not statistically significantly different from olanzapine-treated patients (4.3 kg vs 4.1 kg). Thirty-five percent of SYMBYAX-treated patients met criterion for having gained >7% of their baseline weight. This was statistically significantly greater than placebo-treated (3%) and fluoxetine-treated patients (3%) but was not statistically significantly different than olanzapine-treated patients (31%).

5.14 Transaminase Elevations

As with olanzapine, asymptomatic elevations of hepatic transaminases [ALT (SGPT), AST (SGOT), and GGT] and alkaline phosphatase have been observed with SYMBYAX. In the SYMBYAX-controlled database, ALT (SGPT) elevations (normal baseline and ≥3 times the upper limit of the normal range post-baseline) were observed in 3.4% (20/586) of patients exposed to SYMBYAX compared with none of the 342 placebo patients and 3.5% (23/665) of olanzapine-treated patients. The difference between SYMBYAX and placebo was statistically significant. Of the SYMBYAX patients who started normal at baseline and had increases in ALT ≥5 times the upper limit of normal range, none experienced jaundice and four had transient elevations >200 IU/L. ~~In the premarketing SYMBYAX controlled database, ALT (SGPT) elevations (≥3 times the upper limit of the normal range) was observed in 6.3% (31/495) of patients exposed to SYMBYAX compared with 0.55% (3/384) of the placebo patients and 4.5% (25/560) of olanzapine-treated patients. [see Adverse Reactions (6.1)].~~

In olanzapine placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared with 0% (0/115) of the placebo patients. None of these patients experienced jaundice. In 2 of these patients, liver enzymes decreased toward normal despite continued treatment, and in 2 others, enzymes decreased upon discontinuation of olanzapine. In the remaining 2 patients, 1, seropositive for hepatitis C, had persistent enzyme elevations for 4 months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger olanzapine premarketing database of about 2400 patients with baseline SGPT ≤90 IU/L, the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued. Among all 2500 patients in olanzapine clinical studies, approximately 1% (23/2500) discontinued treatment due to transaminase increases.

MAR 2 8 2007

G. Brophy

10

Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period.

Caution should be exercised in patients with signs and symptoms of hepatic impairment. In patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant hepatic disease *[see Warnings and Precautions (5.24)]*.

5.15 Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding *[see Drug Interactions (7.23, 7.24)]*. Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of SYMBYAX with NSAIDs, aspirin, or other drugs that affect coagulation.

5.16 Hyponatremia

Hyponatremia has been observed in SYMBYAX premarketing clinical studies. In controlled trials, no SYMBYAX-treated patients had a treatment-emergent serum sodium below 129 mmol/L; however, a lowering of serum sodium below the reference range occurred at an incidence of 1.6% (11/693) of SYMBYAX-treated patients compared with 0.5% (2/380) of placebo patients. This difference was not statistically significant. In open label studies, 0.0% (1/2376) of these SYMBYAX-treated patients had a treatment-emergent serum sodium below 129 mmol/L.

Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported with fluoxetine. The hyponatremia appeared to be reversible when fluoxetine was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In two 6-week controlled studies in patients ≥60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

5.17 Cognitive and Motor Impairment

Sedation-related adverse events were commonly reported with SYMBYAX treatment occurring at an incidence of 26.6% in SYMBYAX-treated patients compared with 10.9% in placebo-treated patients. Sedation-related adverse events (sedation, somnolence, hypersomnia, and lethargy) led to discontinuation in 2% (15/771) of patients in the controlled clinical studies. As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them adversely.

5.18 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic drugs. Appropriate care is advised when prescribing SYMBYAX for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

5.19 Use in Patients with Concomitant Illness

Clinical experience with SYMBYAX in patients with concomitant systemic illnesses is limited *[see Clinical Pharmacology (12.4)]*. The following precautions for the individual components may be applicable to SYMBYAX.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical studies, SYMBYAX was associated with constipation, dry mouth, and tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events were not often the basis for study discontinuations; SYMBYAX should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, a history of paralytic ileus, or related conditions.

In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse events were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse events was significantly greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

MAR 2 8 2007
G. Brophy
006203

11
If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised *[see Box Warning and Warnings and Precautions (5.1)]*.

As with other CNS-active drugs, SYMBYAX should be used with caution in elderly patients with dementia. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised *[see Box Warning and Warnings and Precautions(5.1)]*.

SYMBYAX has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the premarket testing.

Caution is advised when using SYMBYAX in cardiac patients and in patients with diseases or conditions that could affect hemodynamic responses *[see Warnings and Precautions (5.10)]*.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower dose of the fluoxetine-component of SYMBYAX should be used in patients with cirrhosis. Caution is advised when using SYMBYAX in patients with diseases or conditions that could affect its metabolism *[see Clinical Pharmacology (12.4) and Dosage and Administration (2.3)]*.

Olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not routinely required *[see Clinical Pharmacology (12.4)]*.

5.20 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, SYMBYAX elevates prolactin levels, and a modest elevation persists during administration; however, possibly associated clinical manifestations (e.g., galactorrhea and breast enlargement) were infrequently observed.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds that increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. However, neither clinical studies nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

5.21 Concomitant Use of Olanzapine and Fluoxetine Products

SYMBYAX contains the same active ingredients that are in Zyprexa and Zyprexa Zydis (olanzapine) and in Prozac, Prozac Weekly, and Sarafem (fluoxetine HCl). Caution should be exercised when prescribing these medications concomitantly with SYMBYAX *[see Overdosage (10)]*.

5.22 Long Half-Life of Fluoxetine

Because of the long elimination half-lives of fluoxetine and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment *[see Clinical Pharmacology (12.3)]*.

5.23 Discontinuation of Treatment with SYMBYAX

During marketing of fluoxetine, a component of SYMBYAX, and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with fluoxetine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy, which may minimize the risk of discontinuation symptoms with this drug *[see Dosage and Administration (2.4)]*.

5.24 Laboratory Tests

Periodic assessment of transaminases is recommended in patients with significant hepatic disease *[see Warnings and Precautions, 5.14)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

MAR 2 8 2007

G. Brophy

12

The information below is derived from a clinical study database for SYMBYAX consisting of 2547 patients with treatment resistant depression, bipolar depression, major depressive disorder with psychosis, or sexual dysfunction with approximately 1085 patient-years of exposure. The conditions and duration of treatment with SYMBYAX varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or long-term exposure.

Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories.

In the tables and tabulations that follow, MedDRA or COSTART Dictionary terminology has been used to classify reported adverse events. The data in the tables represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is possible that events reported during therapy were not necessarily related to drug exposure.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing clinician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Incidence in Controlled Clinical Studies

The following findings are based on the short-term, controlled studies including bipolar depression and treatment resistant depression.

Adverse events associated with discontinuation of treatment — Overall, 11.3% of the 771 patients in the SYMBYAX group discontinued due to adverse events compared with 4.4% of the 477 patients for placebo. Adverse events leading to discontinuation associated with the use of SYMBYAX (incidence of at least 1% for SYMBYAX and greater than that for placebo) using MedDRA Dictionary coding were weight increased (2%) and sedation (1%) versus placebo patients which had 0% incidence of weight increased and sedation.

Commonly observed adverse events in controlled clinical studies — The most commonly observed adverse events associated with the use of SYMBYAX (incidence ≥5% and at least twice that for placebo in the SYMBYAX-controlled database) using MedDRA Dictionary coding were: disturbance in attention, dry mouth, fatigue, hypersomnia, increased appetite, peripheral edema, sedation, somnolence, tremor, vision blurred and weight increased. Adverse events reported in clinical trials of olanzapine/fluoxetine in combination are generally consistent with treatment-emergent adverse events during olanzapine or fluoxetine monotherapy.

Adverse events occurring at an incidence of 2% or more in short-term controlled clinical studies — Table 1 enumerates the treatment-emergent adverse events associated with the use of SYMBYAX (incidence of at least 2% for SYMBYAX and twice or more than for placebo). The SYMBYAX-controlled column includes patients with various diagnoses while the placebo column includes only patients with bipolar depression and major depression with psychotic features.

Table 1: Treatment-Emergent Adverse Events: Incidence in Controlled Clinical Studies

System Organ Class	Adverse Event	Percentage of Patients Reporting Event	
		SYMBYAX-Controlled (N=771)	Placebo (N=477)
Eye disorders	Vision blurred	5	2
Gastrointestinal disorders	Dry mouth	15	6
	Flatulence	3	1
	Abdominal distension	2	0
General disorders and administration site conditions	Fatigue	12	2
	Edema peripheral	9	0
	Edema	3	0
	Asthenia	3	1
	Pain	2	1

MAR 2 6 2007
G. Brophy

13

	Pyrexia	2	1
Infections and infestations	Sinusitis	2	1
Investigations	Weight increased	25	3
Metabolism and nutrition disorders	Increased appetite	20	4
Musculoskeletal and connective tissue disorders	Arthralgia	4	1
	Pain in extremity	3	1
	Musculoskeletal stiffness	2	1
Nervous system disorders	Somnolence	14	6
	Tremor	9	3
	Sedation	8	4
	Hypersomnia	5	1
	Disturbance in attention	5	1
	Lethargy	3	1
Psychiatric disorders	Restlessness	4	1
	Thinking abnormal	2	1
	Nervousness	2	1
Reproductive system and breast disorders	Erectile dysfunction	2	1

Additional Findings Observed in Clinical Studies

Effect on cardiac repolarization — The mean increase in QT$_c$ interval for SYMBYAX-treated patients (4.4 msec) in clinical studies was significantly greater than that for placebo-treated (-0.8 msec), olanzapine-treated (-0.3 msec) patients, and fluoxetine-treated (1.7 msec) patients. There were no significant differences between patients treated with SYMBYAX, placebo, olanzapine, or fluoxetine in the incidence of QT$_c$ outliers (>500 msec).

[As discussed above, we intend to move and group together data relevant to treatment-emergent hyperglycemia, hyperlipidemia, and weight gain to Warnings/Precautions. In addition, the information in these sections will need to be revised to include new information based on requested new data searches and analyses.]

Laboratory changes — In SYMBYAX clinical studies, (including treatment resistant depression, bipolar depression, major depressive disorder with psychosis, or sexual dysfunction) SYMBYAX was associated with statistically significantly greater frequencies for the following treatment-emergent findings in laboratory analytes (normal at baseline to abnormal at any time during the trial) compared to placebo: elevated random blood glucose levels of ≥200 mg/dL in patients with levels of <140 mg/dL at baseline (2.9% vs. 0.3%); elevated random cholesterol ≥240 mg/dL in patients with levels of <200 mg/dL at baseline (9.7% vs. 1.9%); elevated prolactin (27.6% vs. 4.8%); elevated urea nitrogen (2.8% vs. 0.8%); elevated uric acid (2.9% vs. 0.3%); low albumin (2.7% vs. 0.3%); low bicarbonate (14.1% vs. 8.8%); low hemoglobin (2.6% vs. 0%); low inorganic phosphorus (1.9% vs. 0.3%); low lymphocytes (1.9% vs. 0%); and low total bilirubin (15.3% vs. 3.9%).

In olanzapine clinical studies among olanzapine-treated patients with random triglyceride levels of <150 mg/dL at baseline (N=659), 0.5% of patients experienced triglyceride levels of ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=1185) had a mean increase of 20 mg/dL in triglycerides from a mean baseline value of 175 mg/dL.

Sexual dysfunction — In the pool of controlled SYMBYAX studies in patients with bipolar depression, there were higher rates of the treatment-emergent adverse events decreased libido, anorgasmia, impotence and abnormal ejaculation in the SYMBYAX group than in the placebo group. One case of decreased libido led to discontinuation in the SYMBYAX group. In the controlled studies that contained a fluoxetine arm, the rates of decreased libido and abnormal ejaculation in the SYMBYAX group were less than the rates in the fluoxetine group. None of the differences were statistically significant.

Sexual dysfunction, including priapism, has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Vital signs — Tachycardia, bradycardia, and orthostatic hypotension have occurred in SYMBYAX-treated patients *[see Warnings and Precautions (5.10)]*. The mean standing pulse rate of SYMBYAX-treated patients was reduced by 0.7 beats/min.

MAR 28 2007
G. Brophy

14

Other Events Observed in Clinical Studies

Following is a list of treatment-emergent adverse events reported by patients treated with SYMBYAX in clinical trials. This listing is not intended to include events (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo.

Events are classified by body system using the following definitions: frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; and rare events are those occurring in fewer than 1/1000 patients.

[Provide your justification for modifying the listings of events below from currently approved labeling.]

Body as a Whole — *Frequent:* chills, neck rigidity, photosensitivity reaction.

Cardiovascular System — *Frequent:* vasodilatation; *Infrequent:* QT-interval prolonged.

Digestive System — *Frequent:* diarrhea; *Infrequent:* gastritis, gastroenteritis, nausea and vomiting, peptic ulcer; *Rare:* gastrointestinal hemorrhage, intestinal obstruction, liver fatty deposit, pancreatitis.

Hemic and Lymphatic System — *Frequent:* ecchymosis; *Infrequent:* anemia; *Rare:* leukopenia, purpura.

Metabolic and Nutritional — *Frequent:* generalized edema, weight loss; *Infrequent:* glycosuria, obesity; *Rare:* bilirubinemia, creatinine increased, gout.

Musculoskeletal System — *Rare:* osteoporosis.

Nervous System — *Frequent:* amnesia; *Infrequent:* ataxia, buccoglossal syndrome, cogwheel rigidity, dysarthria, emotional lability, euphoria, extrapyramidal syndrome, hypokinesia, movement disorder, myoclonus; *Rare:* dystonia, hyperkinesia, libido increased, withdrawal syndrome.

Respiratory System — *Infrequent:* epistaxis, yawn; *Rare:* laryngismus.

Skin and Appendages — *Infrequent:* alopecia, dry skin, pruritis; *Rare:* exfoliative dermatitis.

Special Senses — *Frequent:* taste perversion; *Infrequent:* abnormality of accommodation, dry eyes.

Urogenital System — *Frequent:* breast pain, menorrhagia[1], urinary frequency, urinary incontinence; *Infrequent:* amenorrhea[1], female lactation[1], hypomenorrhea[1], metrorrhagia[1], urinary retention, urinary urgency, urination impaired; *Rare:* breast engorgement[1].

[1] Adjusted for gender.

Other Events Observed with Olanzapine or Fluoxetine Monotherapy

The following adverse events were not observed in SYMBYAX-treated patients during premarketing clinical studies but have been reported with olanzapine or fluoxetine monotherapy: aplastic anemia, cholestatic jaundice, diabetic coma, dyskinesia, eosinophilic pneumonia, erythema multiforme, jaundice, rhabdomyolysis, serotonin syndrome, vasculitis, venous thromboembolic events (including pulmonary embolism and deep venous thrombosis), violent behaviors. Random triglyceride levels of ≥1000 mg/dL have been rarely reported.

7 DRUG INTERACTIONS

The risks of using SYMBYAX in combination with other drugs have not been extensively evaluated in systematic studies. The drug-drug interactions of the individual components are applicable to SYMBYAX. As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility. Caution is advised if the concomitant administration of SYMBYAX and other CNS-active drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status *[see Clinical Pharmacology (12.3)]*.

7.1 Antihypertensive agents

Because of the potential for olanzapine to induce hypotension, SYMBYAX may enhance the effects of certain antihypertensive agents *[see Warnings and Precautions (5.10)]*.

7.2 Anti-Parkinsonians

The olanzapine component of SYMBYAX may antagonize the effects of levodopa and dopamine agonists.

7.3 Benzodiazepines

Multiple doses of olanzapine did not influence the pharmacokinetics of diazepam and its active metabolite N-desmethyldiazepam. However, the coadministration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine.

MAR 2 6 2007
G. Brophy

15

When concurrently administered with fluoxetine, the half-life of diazepam may be prolonged in some patients *[see Clinical Pharmacology (7.29, 12.3)]*. Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

7.4 Biperiden

Multiple doses of olanzapine did not influence the pharmacokinetics of biperiden.

7.5 Carbamazepine

Carbamazepine therapy (200 mg BID) causes an approximate 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Patients on stable doses of carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

7.6 Clozapine

Elevation of blood levels of clozapine has been observed in patients receiving concomitant fluoxetine.

7.7 CNS Acting Drugs

Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs.

7.8 Electroconvulsive therapy (ECT)

There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment *[see Warnings and Precautions (5.12)]*.

7.9 Ethanol

Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The coadministration of ethanol with SYMBYAX may potentiate sedation and orthostatic hypotension.

7.10 Fluvoxamine

Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine C_{max} following fluvoxamine administration of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of the olanzapine component of SYMBYAX should be considered in patients receiving concomitant treatment with fluvoxamine.

7.11 Haloperidol

Elevation of blood levels of haloperidol has been observed in patients receiving concomitant fluoxetine.

7.12 Lithium

Multiple doses of olanzapine did not influence the pharmacokinetics of lithium.

There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored in patients taking SYMBYAX concomitantly with lithium.

7.13 Monoamine oxidase inhibitors

SYMBYAX should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. There have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with an MAOI, and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses *[see Clinical Pharmacology (12.3)]* should be allowed after stopping SYMBYAX before starting an MAOI. *[See Contraindications (4)]*.

7.14 Phenytoin

Patients on stable doses of phenytoin have developed elevated plasma levels of phenytoin with clinical phenytoin toxicity following initiation of concomitant fluoxetine.

7.15 Pimozide

Concomitant use of fluoxetine and pimozide is contraindicated. Clinical studies of pimozide with other antidepressants demonstrate an increase in drug interaction or QT_c prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QT_c prolongation warrants restricting the concurrent use of pimozide and fluoxetine. *[See Contraindications (4)]*.

MAR 3 8 2007
G. Brophy

006208

7.16 Serotonergic Drugs

Based on the mechanism of action of SYMBYAX and the potential for serotonin syndrome, caution is advised when SYMBYAX is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort *[see Warnings and Precautions (5.6)]*. The concomitant use of SYMBYAX with other SSRIs, SNRIs or tryptophan is not recommended *[see Drug Interactions (7.21)]*.

7.17 Theophylline

Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

7.18 Thioridazine

Thioridazine should not be administered with SYMBYAX or administered within a minimum of 5 weeks after discontinuation of SYMBYAX.

In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max}, and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs that inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine *[see Contraindications (4)]*.

Thioridazine administration produces a dose-related prolongation of the QT, interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism *[see Contraindications (4)]*.

7.19 Tricyclic antidepressants (TCAs)

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

In two fluoxetine studies, previously stable plasma levels of imipramine and desipramine have increased >2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when SYMBYAX is coadministered or has been recently discontinued *[see Drug Interactions (7.23) and Clinical Pharmacology (12.3)]*.

7.20 Triptans

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of SYMBYAX with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Warnings and Precautions (5.6)]*.

7.21 Tryptophan

Five patients receiving fluoxetine in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress. Concomitant use with tryptophan is not recommended.

7.22 Valproate

In vitro studies using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. Thus, a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

7.23 Warfarin

Warfarin (20-mg single dose) did not affect olanzapine pharmacokinetics. Single doses of olanzapine did not affect the pharmacokinetics of warfarin.

Altered anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin *[see Warnings and Precautions (5.15)]*. Patients receiving warfarin therapy should receive careful coagulation monitoring when SYMBYAX is initiated or stopped.

7.24 Drugs that Interfere with Hemostasis (NSAIDs, aspirin, warfarin, etc.)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding *[see Warnings and Precautions (5.15)]*. Thus, patients should be cautioned about the use of such drugs concurrently with SYMBYAX.

7.25 Drugs metabolized by CYP2D6

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP2D6. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by this enzyme.

MAR 2 8 2007
G. Brophy

17

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6. Such individuals have been referred to as poor metabolizers of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most antidepressants, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite, the sum of the plasma concentrations of the 4 enantiomers is comparable between poor and extensive metabolizers *[see Clinical Pharmacology (12.3)]*.

Fluoxetine, like other agents that are metabolized by CYP2D6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble poor metabolizers. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous five weeks. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for a decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (including but not limited to, flecainide, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated thioridazine plasma levels, thioridazine should not be administered with fluoxetine or within a minimum of five weeks after fluoxetine has been discontinued *[see Contraindications, (4) and Drug Interactions (7.18)]*.

7.26 Drugs metabolized by CYP3A

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

In an in vivo interaction study involving the coadministration of fluoxetine with single doses of terfenadine (a CYP3A substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A activity is not likely to be of clinical significance.

7.27 Effect of olanzapine on drugs metabolized by other CYP enzymes

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, and CYP2C19. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

7.28 The effect of other drugs on olanzapine

Fluoxetine, an inhibitor of CYP2D6, decreases olanzapine clearance a small amount *[see Clinical Pharmacology (12.3)]*. Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Fluvoxamine, an inhibitor of CYP1A2, decreases olanzapine clearance *[see Drug Interactions (7.10)]*. The effect of CYP1A2 inhibitors, such as fluvoxamine and some fluoroquinolone antibiotics, on SYMBYAX has not been evaluated. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

7.29 Drugs tightly bound to plasma protein

The in vitro binding of SYMBYAX to human plasma proteins is similar to the individual components. The interaction between SYMBYAX and other highly protein-bound drugs has not been fully evaluated. Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects — Pregnancy Category C

[We have removed inaccurate and redundant information in the following section.]

~~SYMBYAX — SYMBYAX has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in rats when given in doses of olanzapine and fluoxetine in combination at 2 and 1 times the human dose, respectively. There are no adequate and well-controlled studies in pregnant women. SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.~~ Embryo fetal development studies were conducted in rats and rabbits with olanzapine and fluoxetine in low-dose and high-dose combinations. In rats, the doses were: 2 and 4 mg/kg/day (low-dose) [1 and 0.5 times the MRHD on a mg/m^2 basis, respectively], and 4 and 8 mg/kg/day (high-dose) [2 and 1 times the MRHD on a mg/m^2 basis, respectively]. In rabbits, the doses were 4 and 4 mg/kg/day (low-dose) [4 and 1 times the MRHD on a mg/m^2 basis, respectively], and 8 and 8 mg/kg/day (high-dose) [9 and 2 times the MRHD on a mg/m^2 basis, respectively]. In these studies, olanzapine and fluoxetine were

MAR 2 6 2007
G. Brophy

18

also administered alone at the high-doses (4 and 8 mg/kg/day, respectively, in the rat; 8 and 8 mg/kg/day, respectively, in the rabbit). In the rabbit, there was no evidence of teratogenicity; however, the high-dose combination produced decreases in fetal weights and retarded skeletal ossification in conjunction with maternal toxicity. Similarly, in the rat there was no evidence of teratogenicity; however, a decrease in fetal weight was observed with the high-dose combination.

In a pre- and postnatal study conducted in rats, olanzapine and fluoxetine were administered during pregnancy and throughout lactation in combination (low-dose: 2 and 4 mg/kg/day [1 and 0.5 times the MRHD on a mg/m^2 basis], respectively, high-dose: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m^2 basis], respectively, and alone: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m^2 basis], respectively). Administration of the high-dose combination resulted in a marked elevation in offspring mortality and growth retardation in comparison to the same doses of olanzapine and fluoxetine administered alone. These effects were not observed with the low-dose combination; however, there were a few cases of testicular degeneration and atrophy, depletion of epididymal sperm and infertility in the male progeny. The effects of the high-dose combination on postnatal endpoints could not be assessed due to high progeny mortality.

There are no adequate and well-controlled studies with SYMBYAX in pregnant women.

SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Olanzapine — In reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the MRHD on a mg/m^2 basis, respectively), no evidence of teratogenicity was observed. In a rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD on a mg/m^2 basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the MRHD on a mg/m^2 basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled clinical studies with olanzapine in pregnant women. Seven pregnancies were observed during premarketing clinical studies with olanzapine, including two resulting in normal births, one resulting in neonatal death due to a cardiovascular defect, three therapeutic abortions, and one spontaneous abortion.

Fluoxetine — In embryo fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times the MRHD on a mg/m^2 basis, respectively) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis).

Treatment of Pregnant Women During the Third Trimester — Neonates exposed to fluoxetine, a component of ~~SYMBYAX~~SYMBYAX, and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Contraindications (4) and Drug Interactions (7.16)]*. When treating pregnant women with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering fluoxetine in the third trimester.

8.2 Labor and Delivery

SYMBYAX — The effect of SYMBYAX on labor and delivery in humans is unknown. Parturition in rats was not affected by SYMBYAX. SYMBYAX should be used during labor and delivery only if the potential benefit justifies the potential risk.

Olanzapine — The effect of olanzapine on labor and delivery in humans is unknown. Parturition in rats was not affected by olanzapine.

Fluoxetine — The effect of fluoxetine on labor and delivery in humans is unknown. Fluoxetine crosses the placenta; therefore, there is a possibility that fluoxetine may have adverse effects on the newborn.

8.3 Nursing Mothers

SYMBYAX — There are no adequate and well-controlled studies with SYMBYAX in nursing mothers or infants. Studies evaluating the individual components of SYMBYAX (olanzapine and fluoxetine) in nursing mothers are described below. It is not known whether SYMBYAX is excreted in human milk and because of the potential for serious adverse reactions in nursing infants

MAR 2 C 2007
G. Brophy

006211

from SYMBYAX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is recommended that women not breast-feed when receiving SYMBYAX.

Olanzapine — In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving olanzapine should not breast-feed.

Fluoxetine — Fluoxetine is excreted in human breast milk. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on fluoxetine developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the 2nd day of feeding.

8.4 Pediatric Use

SYMBYAX — Safety and effectiveness in the pediatric population have not been established *[see Box Warning and Warnings and Precautions (5.3)]*. Anyone considering the use of SYMBYAX in a child or adolescent must balance the potential risks with the clinical need.

Fluoxetine — Significant toxicity, including myotoxicity, long-term neurobehavioral and reproductive toxicity, and impaired bone development, has been observed following exposure of juvenile animals to fluoxetine. Some of these effects occurred at clinically relevant exposures.

In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from weaning (Postnatal Day 21) through adulthood (Day 90), male and female sexual development was delayed at all doses, and growth (body weight gain, femur length) was decreased during the dosing period in animals receiving the highest dose. At the end of the treatment period, serum levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and hypospermia) was observed at the high dose. When animals were evaluated after a recovery period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased reactivity at all doses and learning deficit at the high dose) and reproductive functional impairment (decreased mating at all doses and impaired fertility at the high dose) were seen; in addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were found in the high dose group, indicating that the reproductive organ effects seen at the end of treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dose in this study were approximately 0.1-0.2, 1-2, and 5-10 times, respectively, the average exposure in pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat exposures to the major metabolite, norfluoxetine, were approximately 0.3-0.8, 1-8, and 3-20 times, respectively, pediatric exposure at the MRD.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg, intraperitoneal) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These doses did not affect overall growth (body weight gain or femoral length). The doses administered to juvenile mice in this study are approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area (mg/m^2) basis.

In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric MRD on a mg/m^2 basis. Because of the early dosing period in this study, the significance of these findings to the approved pediatric use in humans is uncertain.

8.5 Geriatric Use

SYMBYAX — Clinical studies of SYMBYAX did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Dosage and Administration (2.1)]*.

Olanzapine — Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263 patients) were ≥65 years of age. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared with younger patients. Studies in patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared with younger patients with schizophrenia. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the

MAR 2 8 2007
G. Brophy

20

treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised [see *Box Warning, Warnings and Precautions* (5.19) and *Dosage and Administration* (2.3)].

As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient.

Fluoxetine — US fluoxetine clinical studies (10,782 patients) included 687 patients ≥65 years of age and 93 patients ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients.

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

SYMBYAX, as with fluoxetine and olanzapine, has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical studies did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of SYMBYAX (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

In studies in rats and rhesus monkeys designed to assess abuse and dependence potential, olanzapine alone was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence at oral doses up to 15 (rat) and 8 (monkey) times the MRHD (20 mg) on a mg/m^2 basis.

10 OVERDOSAGE

SYMBYAX — During premarketing clinical studies of the olanzapine/fluoxetine combination, overdose of both fluoxetine and olanzapine were reported in five study subjects. Four of the five subjects experienced loss of consciousness (3) or coma (1). No fatalities occurred.

Adverse events involving overdose of fluoxetine and olanzapine in combination, and SYMBYAX, have been reported spontaneously to Eli Lilly and Company. An overdose of combination therapy is defined as confirmed or suspected ingestion of a dose of >20 mg olanzapine in combination with a dose of >80 mg fluoxetine. Adverse events associated with these reports included somnolence (sedation), impaired consciousness (coma), impaired neurologic function (ataxia, confusion, convulsions, dysarthria), arrhythmias, lethargy, essential tremor, agitation, acute psychosis, hypotension, hypertension, and aggression. Fatalities have been confounded by exposure to additional substances including alcohol, thioridazine, oxycodone, and propoxyphene.

Olanzapine — In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia as well as a patient that experienced sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

Fluoxetine — Worldwide exposure to fluoxetine is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdose, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdose were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died. 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients

MAR 2 6 2007
G. Brophy

21

had an unknown outcome. One of the 6 fatalities was a 9-year-old boy who had a history of OCD, Tourette's Syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams, which was non-lethal.

Other important adverse events reported with fluoxetine overdose (single or multiple drugs) included coma, delirium, ECG abnormalities (such as QT-interval prolongation and ventricular tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like events, pyrexia, stupor, and syncope.

10.1 Management of Overdose

In managing overdose, the possibility of multiple drug involvement should be considered. In case of acute overdose, establish and maintain an airway and ensure adequate ventilation, which may include intubation. Induction of emesis is not recommended as the possibility of obtundation, seizures, or dystonic reactions of the head and neck following overdose may create a risk for aspiration. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

A specific precaution involves patients who are taking or have recently taken SYMBYAX and may have ingested excessive quantities of a TCA (tricyclic antidepressant). In such cases, accumulation of the parent TCA and/or an active metabolite may increase the possibility of serious sequelae and extend the time needed for close medical observation.

Due to the large volume of distribution of olanzapine and fluoxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidote for either fluoxetine or olanzapine overdose is known. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Do not use epinephrine, dopamine, or other sympathomimetics with β-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.

The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*.

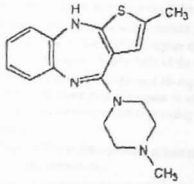
11 DESCRIPTION

SYMBYAX® (olanzapine and fluoxetine HCl capsules) combines 2 psychotropic agents, olanzapine (the active ingredient in Zyprexa®, and Zyprexa Zydis®) and fluoxetine hydrochloride (the active ingredient in Prozac®, Prozac Weekly™, and Sarafem®).

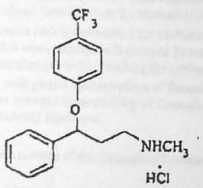
Olanzapine belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44.

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI). The chemical designation is (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride. The molecular formula is $C_{17}H_{18}F_3NO{\cdot}HCl$, which corresponds to a molecular weight of 345.79.

The chemical structures are:



Olanzapine



fluoxetine hydrochloride

Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

MAR 2 6 2007
G. Brophy

22

Each capsule also contains pregelatinized starch, gelatin, dimethicone, titanium dioxide, sodium lauryl sulfate, edible black ink, red iron oxide, yellow iron oxide, and/or black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Although the exact mechanism of SYMBYAX is unknown, it has been proposed that the activation of 3 monoaminergic neural systems (serotonin, norepinephrine, and dopamine) is responsible for its enhanced antidepressant effect. This is supported by animal studies in which the olanzapine/fluoxetine combination has been shown to produce synergistic increases in norepinephrine and dopamine release in the prefrontal cortex compared with either component alone, as well as increases in serotonin.

12.2 Pharmacodynamics

Olanzapine is a psychotropic agent with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$ (K_i=4 and 11 nM, respectively), dopamine D_{1-4} (K_i=11 to 31 nM), muscarinic M_{1-5} (K_i=1.9 to 25 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors (K_i=19 nM). Olanzapine binds weakly to $GABA_A$, BZD, and β-adrenergic receptors (K_i>10 μM). Fluoxetine is an inhibitor of the serotonin transporter and is a weak inhibitor of the norepinephrine and dopamine transporters.

Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic effects. The antagonism of histamine H_1 receptors by olanzapine may explain the somnolence observed with this drug. The antagonism of α_1-adrenergic receptors by olanzapine may explain the orthostatic hypotension observed with this drug. Fluoxetine has relatively low affinity for muscarinic, α_1-adrenergic, and histamine H_1 receptors.

12.3 Pharmacokinetics

SYMBYAX — Fluoxetine (administered as a 60-mg single dose or 60 mg daily for 8 days) caused a small increase in the mean maximum concentration of olanzapine (16%) following a 5-mg dose, an increase in the mean area under the curve (17%) and a small decrease in mean apparent clearance of olanzapine (16%). In another study, a similar decrease in apparent clearance of olanzapine of 14% was observed following olanzapine doses of 6 or 12 mg with concomitant fluoxetine doses of 25 mg or more. The decrease in clearance reflects an increase in bioavailability. The terminal half-life is not affected, and therefore the time to reach steady state should not be altered. The overall steady-state plasma concentrations of olanzapine and fluoxetine when given as the combination in the therapeutic dose ranges were comparable with those typically attained with each of the monotherapies. The small change in olanzapine clearance, observed in both studies, likely reflects the inhibition of a minor metabolic pathway for olanzapine via CYP2D6 by fluoxetine, a potent CYP2D6 inhibitor, and was not deemed clinically significant. Therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination.

Absorption and Bioavailability

SYMBYAX — Following a single oral 12-mg/50-mg dose of SYMBYAX, peak plasma concentrations of olanzapine and fluoxetine occur at approximately 4 and 6 hours, respectively. The effect of food on the absorption and bioavailability of SYMBYAX has not been evaluated. The bioavailability of olanzapine given as Zyprexa, and the bioavailability of fluoxetine given as Prozac were not affected by food. It is unlikely that there would be a significant food effect on the bioavailability of SYMBYAX.

Olanzapine — Olanzapine is well absorbed and reaches peak concentration approximately 6 hours following an oral dose. Food does not affect the rate or extent of olanzapine absorption when olanzapine is given as Zyprexa. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation.

Fluoxetine — Following a single oral 40-mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine given as Prozac, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant.

Distribution

SYMBYAX — The in vitro binding to human plasma proteins of the olanzapine/fluoxetine combination is similar to the binding of the individual components.

Olanzapine — Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1-acid glycoprotein.

Fluoxetine — Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated *[see Drug Interactions (7.2)]*.

MAR 2 8 2007

G. Brophy

23

Metabolism and Elimination

SYMBYAX — SYMBYAX therapy yielded steady-state concentrations of norfluoxetine similar to those seen with fluoxetine in the therapeutic dose range.

Olanzapine — Olanzapine displays linear pharmacokinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr). Administration of olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.4)]*.

Following a single oral dose of ^{14}C-labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and CYP450-mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYP1A2, CYP2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6-mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Fluoxetine — Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Fluoxetine is extensively metabolized in the liver to its only identified active metabolite, norfluoxetine, via the CYP2D6 pathway. A number of unidentified metabolites exist.

In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical Issues Related to Metabolism and Elimination

The complexity of the metabolism of fluoxetine has several consequences that may potentially affect the clinical use of SYMBYAX.

Variability in metabolism — A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme CYP2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants (TCAs). In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative nonsaturable pathways (non-CYP2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because the metabolism of fluoxetine, like that of a number of other compounds including TCAs and other selective serotonin antidepressants, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions *[see Drug Interactions (7.19 and 7.25)]*.

Accumulation and slow elimination — The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because the metabolism of fluoxetine is not proportional to dose. However, norfluoxetine appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine.

12.4 Special Populations

Geriatric — Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in geriatric patients. Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity.

In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly subjects (≥65 years of age) than in non-elderly subjects (≤65 years of age).

The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in these elderly patients.

Renal Impairment — The pharmacokinetics of SYMBYAX has not been studied in patients with renal impairment. However, olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not routinely required.

Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on olanzapine metabolite elimination has not been studied.

In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.

Hepatic Impairment — Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in patients with hepatic impairment. The lowest starting dose should be considered for patients with hepatic impairment *[see Warnings and Precautions (5.19) and Dosage and Administration (2.3)]*.

Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (N=6) with clinically significant cirrhosis (Childs-Pugh Classification A and B) revealed little effect on the pharmacokinetics of olanzapine.

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects.

Gender — Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status — Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely required.

Race — No SYMBYAX pharmacokinetic study was conducted to investigate the effects of race. Results from an olanzapine cross-study comparison between data obtained in Japan and data obtained in the US suggest that exposure to olanzapine may be about 2-fold greater in the Japanese when equivalent doses are administered. Olanzapine clinical study safety and efficacy data, however, did not suggest clinically significant differences among Caucasian patients, patients of African descent, and a 3rd pooled category including Asian and Hispanic patients. Dosage modifications for race, therefore, are not routinely required.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance of olanzapine in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. SYMBYAX dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of the olanzapine component *[see Dosage and Administration (2.3)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity, or fertility studies were conducted with SYMBYAX. The following data are based on findings in studies performed with the individual components.

MAR 2 6 2007
G. Brophy

25

Carcinogenesis

Olanzapine — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, and 30/20 mg/kg/day [equivalent to 0.8 to 5 times the maximum recommended human daily dose (MRHD) on a mg/m^2 basis] and 0.25, 2, and 8 mg/kg/day (equivalent to 0.06 to 2 times the MRHD on a mg/m^2 basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, and 4 mg/kg/day (males) and 0.25, 1, 4, and 8 mg/kg/day (females) (equivalent to 0.1 to 2 and 0.1 to 4 times the MRHD on a mg/m^2 basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in females dosed at 8 mg/kg/day (2 times the MRHD on a mg/m^2 basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2 to 5 times the MRHD on a mg/m^2 basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the MRHD on a mg/m^2 basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the finding of prolactin-mediated endocrine tumors in rodents is unknown *[see Warning and Precautions (5.20)]*.

Fluoxetine — The dietary administration of fluoxetine to rats and mice for two years at doses of up to 10 and 12 mg/kg/day, respectively (approximately 1.2 and 0.7 times, respectively, the MRHD on a mg/m^2 basis), produced no evidence of carcinogenicity.

Mutagenesis

Olanzapine — No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Fluoxetine — Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of Fertility

SYMBYAX — Fertility studies were not conducted with SYMBYAX. However, in a repeat-dose rat toxicology study of three months duration, ovary weight was decreased in females treated with the low-dose [2 and 4 mg/kg/day (1 and 0.5 times the MRHD on a mg/m^2 basis), respectively] and high-dose [4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m^2 basis), respectively] combinations of olanzapine and fluoxetine. Decreased ovary weight, and corpora lutea depletion and uterine atrophy were observed to a greater extent in the females receiving the high-dose combination than in females receiving either olanzapine or fluoxetine alone. In a 3-month repeat-dose dog toxicology study, reduced epididymal sperm and reduced testicular and prostate weights were observed with the high-dose combination of olanzapine and fluoxetine [5 and 5 mg/kg/day (9 and 2 times the MRHD on a mg/m^2 basis), respectively] and with olanzapine alone (5 mg/kg/day or 9 times the MRHD on a mg/m^2 basis).

Olanzapine — In a fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (1 and 1.5 times the MRHD on a mg/m^2 basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male-mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the MRHD on a mg/m^2 basis). Diestrous was prolonged and estrous was delayed at 1.1 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis); therefore, olanzapine may produce a delay in ovulation.

Fluoxetine — Two fertility studies conducted in adult rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m^2 basis) indicated that fluoxetine had no adverse effects on fertility *[see Use in Specific Populations (8.4)]*.

14 CLINICAL STUDIES

14.1 Bipolar Depression

The efficacy of SYMBYAX for the treatment of depressive episodes associated with bipolar disorder was established in 2 identically designed, 8-week, randomized, double-blind, controlled studies of patients who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for Bipolar I Disorder, Depressed utilizing flexible dosing of SYMBYAX (6/25, 6/50, or 12/50 mg/day), olanzapine (5 to 20 mg/day), and placebo. These studies included patients (≥18 years of age (n=788)) with or without psychotic symptoms and with or without a rapid cycling course.

MAR 2 8 2007
G. Brophy

26

The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 to 60. The primary outcome measure of these studies was the change from baseline to endpoint in the MADRS total score. In both studies, SYMBYAX was statistically significantly superior to both olanzapine monotherapy and placebo in reduction of the MADRS total score. The results of the studies are summarized below (Table 3).

Table 2: MADRS Total Score
Mean Change from Baseline to Endpoint

	Treatment Group	Baseline Mean	Change to Endpoint Mean[1]
Study 1	SYMBYAX (N=40)	30	-16*
	Olanzapine (N=153)	33	-12
	Placebo (N=181)	31	-10
Study 2	SYMBYAX (N=42)	32	-18*
	Olanzapine (N=169)	33	-14
	Placebo (N=174)	31	-9

[1] Negative number denotes improvement from baseline.
*Statistically significant compared to both olanzapine and placebo.

14.2 Treatment Resistant Depression

[We have revised the following section to more accurately reflect the data used to assess efficacy.]

The efficacy of SYMBYAX in treatment resistant depression was demonstrated with data from 3 clinical studies (n=579) (Table 3). Doses evaluated in these studies ranged from 6/25 to 12/50 mg for olanzapine and 2520/50-60 mg for fluoxetine.

Two identically designed An 8-week randomized, double-blind controlled studyies (Study 1 and 5) were conducted to evaluate the efficacy of SYMBYAX in patients (n = 300) who met DSM-IV criteria for major depressive disorder and did not respond to 2 antidepressants of adequate dose and duration in their current episode (N=605). Patients who were not responding to an antidepressant in their current episode entered an 8-week open-label fluoxetine lead-in; non-responders were randomized (1:1:1) to receive SYMBYAX, olanzapine, or fluoxetine, and were treated for 8 weeks. SYMBYAX was flexibly dosed between 6/50 mg, 12/50 mg, and 18/50 mg. Results from one (Study 1) of these 2 studiesthis study yielded statistically significant greater reduction (p<0.001) in mean total MADRS scores from baseline to endpoint for SYMBYAX (-14.6) versus fluoxetine (-9.0) and olanzapine (-7.7). A second study with the same treatment-resistant patient population (n=28), when analyzed with change in MADRS as the primary outcome measure, demonstrated statistically significantly greater reduction in MADRS scores for SYMBYAX versus fluoxetine and olanzapine. Additionally A third study, 3, similarly designed studies (Study 2, 3, and 4) of 8-12 weeks duration (n=28, 251, 369, respectively) demonstrated statistically significantly greater reduction in total MADRS scores for SYMBYAX versus fluoxetine (p=0.013, 0.021, 0.106) and or olanzapine alone (p=0.035, 0.003, 0.007) respectively, when analyzed for the same in a subpopulation of depressed patients (n=251) who met the definition of treatment resistance (patients who were had not responding responded to 2 antidepressants of adequate dose and duration, both during in the current episode).

An integrated analysis of the 5 studies yielded statistically significant greater reduction in mean total MADRS scores from baseline to endpoint in the defined population (p=0.015, p=0.007 versus fluoxetine and olanzapine, respectively) for SYMBYAX (-12.2) versus fluoxetine (-8.5) and olanzapine (-7.7).

Table 3: MADRS Total Score
Mean Change from Baseline to Endpoint in
Treatment Resistant Depression

MAR 2 6 2007

G. Brophy

27

	Treatment Group	Baseline Mean	Change to Endpoint Mean[1]
Study 1	SYMBYAX (N=97)	30.6	-14.6
	Fluoxetine (N=101)	30.1	-9.0**
	Olanzapine (N=102)	30.1	-7.7**
Study 2	SYMBYAX (N=10)	29.5	-17.6
	Fluoxetine (N=10)	32.8	-1.3**
	Olanzapine (N=8)	25.0	-2.8**
Study 3	SYMBYAX (N=163)	30.1	-12.3
	Fluoxetine (N=41)	31.1	-10.0**
	Olanzapine (N=43)	31.5	-8.8**
Study 4	SYMBYAX (N=91)	29.4	-9.0
	Fluoxetine (N=88)	28.9	-7.0**
	Olanzapine (N=90)	28.4	-5.1**
Study 5	SYMBYAX (N=101)	30.5	-10.8
	Fluoxetine (N=102)	29.7	-9.4**
	Olanzapine (N=95)	29.7	-10.1**
Integrated analysis of 5 studies	SYMBYAX (N=462)	29.9	-12.0
	Fluoxetine (N=342)	29.6	-8.5**
	Olanzapine (N=342)	29.6	-7.7**

[1] Negative number denotes improvement from baseline.

* SYMBYAX statistically significant ($p<0.05$) compared to fluoxetine and olanzapine.

** SYMBYAX demonstrated a greater reduction in total MADRS score, however did not reach statistical significance ($p<0.05$)

16 HOW SUPPLIED/STORAGE AND HANDLING

SYMBYAX capsules are supplied in 3/25-, 6/25-, 6/50-, 12/25-, and 12/50-mg (mg equivalent olanzapine/mg equivalent fluoxetine*) strengths.

SYMBYAX	CAPSULE STRENGTH				
	3 mg/25 mg	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
Color	Peach & Light Yellow	Mustard Yellow & Light Yellow	Mustard Yellow & Light Grey	Red & Light Yellow	Red & Light Grey
Capsule No.	PU3230	PU3231	PU3233	PU3232	PU3234
Identification	Lilly 3230 3/25	Lilly 3231 6/25	Lilly 3233 6/50	Lilly 3232 12/25	Lilly 3234 12/50
NDC Codes					
Bottles 30	0002-3230-30	0002-3231-30	0002-3233-30	0002-3232-30	0002-3234-30
Bottles 100		0002-3231-02	0002-3233-02	0002-3232-02	0002-3234-02
Bottles 1000		0002-3231-04	0002-3233-04	0002-3232-04	0002-3234-04
Blisters ID[†] 100		0002-3231-33	0002-3233-33	0002-3232-33	0002-3234-33

* Fluoxetine base equivalent

† IDENTI-DOSE®, Unit Dose Medication, Lilly.

MAR 2 6 2007

G. Brophy

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Keep tightly closed and protect from moisture.

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SYMBYAX and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for SYMBYAX. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SYMBYAX.

Patients should be cautioned about the concomitant use of SYMBYAX and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding *[see Warnings and Precautions (5.15)]*.

Patients should be advised to avoid alcohol while taking SYMBYAX.

As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them adversely.

Patients should be advised to inform their physician if they are taking Prozac®, Prozac Weekly™, Sarafem®, fluoxetine, Zyprexa®, or Zyprexa Zydis®. Patients should be advised to inform their physicians if they are taking or plan to take any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions. Patients should also be advised to inform their physicians if they plan to discontinue any medications they are taking while taking SYMBYAX, as stopping a medication may also impact the overall blood level of SYMBYAX.

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Patients, if taking SYMBYAX, should be advised not to breast-feed.

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol *[see Warnings and Precautions (5.10) and Drug Interactions (7)]*.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during SYMBYAX therapy.

Patients should be advised to notify their physician if they develop a rash or hives while taking SYMBYAX.

Patients should be advised to take SYMBYAX exactly as prescribed, and to continue taking SYMBYAX as prescribed even after their mood symptoms improve. Patients should be advised that they should not alter their dosing regimen, or stop taking SYMBYAX, without consulting their physician.

Patient information is printed at the end of this insert. Physicians should discuss this information with their patients and instruct them to read the Medication Guide before starting therapy with SYMBYAX and each time their prescription is refilled.

17.2 Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

17.3 Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of SYMBYAX and triptans, tramadol or other serotonergic agents.

17.4 FDA Approved Medication Guide

MAR 2 8 2007
G. Brophy

29

Medication Guide

About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your health care provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her health care provider

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your health care provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's health care provider between visits if needed.

3. You Should Watch for Certain Signs if Your Child is Taking an Antidepressant

Contact your child's health care provider *right away* if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

MAR 2 8 2007
G. Brophy
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- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her health care provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your health care provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine, and clomipramine (Anafranil®).

Your health care provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your health care provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your health care provider or pharmacist where to find more information.

Prozac® is a registered trademark of Eli Lilly and Company.
Zoloft® is a registered trademark of Pfizer Pharmaceuticals.
Anafranil® is a registered trademark of Mallinckrodt Inc.

This Medication Guide has been approved by the US Food and Drug Administration for all antidepressants.

Rx only

Literature revised September 8, 2006

Eli Lilly and Company
Indianapolis, IN 46285

www.SYMBYAX.com

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/s/

Thomas Laughren
3/28/2007 02:51:39 PM

EXHIBIT B
TO STATE OF ALASKA'S
RESPONSE TO LILLY'S MOTION IN
LIMINE REGARDING RECENT
REGULATORY COMMUNICATIONS
AND DEVELOPMENTS

MAR 2 6 2007
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EXHIBIT B
TO STATE OF ALASKA'S RESPONSE TO LILLY'S MOTION IN LIMINE REGARDING RECENT REGULATORY COMMUNICATIONS AND DEVELOPMENTS

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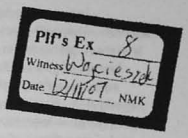
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-520 – Symbyax (olanzapine/fluoxetine combination)
NDA 20-592 – Zyprexa (olanzapine) tablets
NDA 21-086 – Zyprexa Zydis (olanzapine) orally disintegrating tablets
NDA 21-253 – Zyprexa IntraMuscular (olanzapine for injection)



Eli Lilly and Company
Attention: Robin Wojcieszek, R.Ph.
Associate Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Wojcieszek:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbyax (olanzapine/fluoxetine combination), Zyprexa (olanzapine) tablets, Zyprexa Zydis (olanzapine) orally disintegrating tablets, and Zyprexa IntraMuscular (olanzapine for injection).

We also refer to your April 25, 2007 submission, containing a briefing document that summarizes results on weight gain, lipids, glucose dysregulation, and metabolic syndrome.

We have reviewed the data you have submitted thus far as well as the available literature, and we would like to request that you make the labeling changes listed below pertaining to the effect of olanzapine and Symbyax on body weight, lipids, and glucose. We anticipate that additional labeling changes will be necessary when we have reviewed the results of the additional analyses that we have requested. Given that your completing these analyses and our review of them will take some time, we believe that it is in the best interest of the public health to make interim labeling changes now based on the data that we already have available.

We request that the following language regarding hyperglycemia be implemented in the WARNINGS subsection in place of the present language in labeling regarding this risk. In addition, we request the following language regarding weight gain and hyperlipidemia be added as new WARNINGS subsections: (strike through font denotes deletions to our labeling and double underline font denotes additions).

WARNINGS

~~Hyperglycemia and Diabetes Mellitus~~ — Hyperglycemia, ~~in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility~~ of an ~~increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus~~

~~in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.~~

~~Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.~~

Hyperglycemia

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. The relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Olanzapine (and clozapine) treatments have been associated with a greater potential to induce hyperglycemia than other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The exposure adjusted mean increase from baseline to the average of the two highest serum concentrations of serum glucose was 13.7 mg/dl.

In another clinical trial database, where olanzapine and fluoxetine were administered individually and in combination in separate arms of the trial, a significantly higher number of patients who were normoglycemic (non-fasting blood glucose < 140 mg/dl) before treatment became hyperglycemic (non-fasting blood glucose ≥ 200 mg/dl) at some point during the 6-12 weeks of treatment (olanzapine vs. placebo: 2.4% vs. 0.3% and olanzapine/fluoxetine combination vs. placebo: 2.9% vs. 0.3% placebo). Approximately one-third of patients on olanzapine (33.3%, n=27) and one-half of patients on the olanzapine/fluoxetine combination (45.7%, n=27) who had borderline increased serum blood glucose (non-fasting, between 140 and 200 mg/dl) at the beginning of the study progressed to high blood glucose (≥ 200 mg/dl) at some time during the 6-12 weeks olanzapine treatment.

Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus or having borderline increased blood glucose level (fasting 100 – 140 mg/dl, non-fasting 140 – 200 mg/dl). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes

mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

WARNINGS

Weight Gain

In placebo-controlled, 6-week studies, olanzapine-treated patients gained an average of 2.8 kg (6.2 lb), compared to an average 0.4 kg (0.9 lb) weight loss in placebo-treated patients; 29% of olanzapine-treated patients gained greater than 7% of their baseline weight, compared to 3% of placebo-treated patients. During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg (11.9 lb).

Table 1 includes data on weight gain with olanzapine pooled from 68 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 1. Weight Gain with Olanzapine Use

Amount Gained Kg (lb)	6 weeks (N=2,976) (%)	6 months (N=1536) (%)	12 months (N=778) (%)	24 months (N=422) (%)
<0	27	21	20	22
0-5 (0-11 lb)	57	34	25	22
5-10 (11-22 lb)	15	26	25	22
10-15 (22-33 lb)	2	12	16	18
≥15 (≥33 lb)	0	6	14	16

Adolescents — In pooled data from two placebo-controlled olanzapine monotherapy studies of adolescent patients with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), weight gain was reported as an adverse event in 29.6% of olanzapine-treated patients compared to 5.6% of placebo-treated patients. Olanzapine-treated patients gained an average of 3.9 kg, compared to an average of 0.2 kg in placebo-treated patients; 43.5% of olanzapine-treated patients gained greater than 7% of their baseline body weight, compared to 6.8% of placebo-treated patients. A categorization of patients by baseline on the basis of body mass index (BMI) revealed a similar mean increase in weight in the olanzapine-treated patients in each category. During long-term continuation therapy with olanzapine, 65% of olanzapine-treated patients met

the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.3 kg.

Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight.

WARNINGS

Hyperlipidemia

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. In clinical trials among olanzapine-treated patients with random triglyceride levels of ≤150 mg/dL at baseline (N=659), 0.5% of patients experienced triglyceride levels of ≥500 mg/dL some time during the trials. [Note to sponsor: Insert placebo data here.] In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in fasting triglycerides in patients taking olanzapine was 40.5 mg/dL.

Modest mean increases in total cholesterol and decreases in HDL cholesterol have also been seen with olanzapine use. In phase 1 of CATIE, the median increase in fasting total cholesterol was 9.4 mg/dL.

Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised.

We request that you make these labeling changes within 30 days of this letter. In addition, we are requesting that you issue a "Dear Healthcare Practitioner" letter conveying this new prescribing information pertaining to the metabolic effects of olanzapine and Symbyax. Please submit this "Dear Health Care Practitioner" letter to us for review prior to distributing it.

We request that you include as the last paragraph of the "Dear Healthcare Practitioner" letter the following language:

> The Medical Community can further our understanding of adverse events by reporting all cases to the Agency via the MedWatch program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, via the MedWatch website at www.fda.gov/medwatch, or by mail:
>
> MEDWATCH
> Food and Drug Administration
> 5515 Security Lane
> Suite 5100, HFD-001
> Rockville, MD 20852

If you have any questions, call Sonny Saini, Pharm.D., Safety Regulatory Project Manager, at 301-796-0532.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

State of Alaska v. Eli Lilly Co. Confidential - Subject to Protective Order
Exhibit B, Page 6 of 7
SOA Response to Lilly Motion in Limine Regarding Recent Regulatory Communications and Developments
Case No. 3AN-06-5630 CI
ZYAK-AG20030168

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
8/28/2007 12:36:53 PM

EXHIBIT C
TO STATE OF ALASKA'S RESPONSE TO LILLY'S MOTION IN LIMINE REGARDING RECENT REGULATORY COMMUNICATIONS AND DEVELOPMENTS

006232

www.lilly.com

Lilly

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

Phone 317 276 2000

October 5, 2007

Re: Safety data on Zyprexa® (olanzapine) and Symbyax® (olanzapine and fluoxetine HCl capsules) – Hyperglycemia, Weight Gain, and Hyperlipidemia

Dear Health Care Professional,

Eli Lilly and Company would like to inform you of important information being added to the Zyprexa® (olanzapine) and Symbyax® (olanzapine and fluoxetine HCl) labels. These labeling updates include new WARNINGS for Weight Gain and Hyperlipidemia and updated information in the WARNING for Hyperglycemia. These changes reflect results of recently completed pooled analyses of clinical trials in adults and adolescents as well as information from two published large studies of atypical antipsychotics, CATIE[1] and CAFE[2].

The new labeling language is detailed below. Monitoring of glucose, weight, and lipids is recommended during olanzapine and olanzapine/fluoxetine combination treatment. Guidelines published by the American Diabetes Association (ADA) following the consensus development conference[3] provide recommendations for the monitoring of blood glucose, weight, and lipid levels in those treated with atypical antipsychotics. Other highlights of the updated labeling include:

- Abnormal or borderline glucose levels at baseline are an important risk factor for further glucose increase.
- While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.
- Significantly greater mean increases in total cholesterol, LDL cholesterol, and triglycerides were observed in Zyprexa-treated patients compared with placebo-treated patients both with and without evidence of dyslipidemia at baseline.
- Labeling provides information on magnitude and distribution of weight gain over a two year period in Zyprexa-treated patients.
- Labeling also provides information on glucose, weight gain, and lipids from studies of Zyprexa for adolescent patients. Please note that Zyprexa and Symbyax are not approved currently for use in children and adolescents aged less than 18 years old.

006233

Eli Lilly and Company remains committed to providing you with the most current product information available for the management of your patients and we will continue our ongoing research and analyses in these areas.

Please refer to the full prescribing information for Zyprexa and Symbyax included with this letter.

Should you have any questions or would like additional information regarding this important safety information, please contact the Lilly medical department at 1-800-Lilly-Rx or your Eli Lilly and Company sales representative.

The Medical Community can further our understanding of adverse events by reporting all cases to the Agency via the MedWatch program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, via the MedWatch website at www.fda.gov/medwatch or by mail:

MEDWATCH
Food and Drug Administration
5515 Security Lane
Suite 5100, HFD-001
Rockville, MD 20852

Sincerely,

Tim Garnett, M.D.
Vice President,
Global Patient Safety
Eli Lilly and Company

006234

The following are the updated Hyperglycemia WARNINGS and the new Hyperlipidemia and Weight WARNINGS included in the Zyprexa label.

WARNINGS:

Zyprexa:
The following is updated language in the WARNINGS section of the Zyprexa package insert, and will be reflected in other materials.

Hyperglycemia — Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase I of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the two highest serum concentrations was 15.0 mg/dl.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse events, patients treated with antidiabetic agents, patients with a baseline random glucose level ≥200 mg/dL, and/or a baseline fasting glucose level ≥126 mg/dL). These patients had a statistically significantly greater mean increase in HbA_{1c} compared to placebo. In patients with baseline normal fasting glucose levels (<100 mg/dL), 2.2% (N= 543) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 3.4% (N= 293) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 17.4% (N=178) of those treated with

olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 11.5% (N=96) of those treated with placebo.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a statistically significantly greater mean change in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). In patients with baseline normal fasting glucose levels (<100 mg/dL), zero out of 124 (0%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 2 out of 14 (14.3%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus zero out of 13 (0%) of those treated with placebo.

Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus or having borderline increased blood glucose level (fasting 100–126 mg/dL, non-fasting 140–200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Hyperlipidemia — Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised.

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had statistically significant increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL,

4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting [illegible] no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse events, patients treated with lipid lowering agents, or patients with high baseline lipid levels. Table 1 shows categorical changes in fasting lipid values.

Table 1. Changes in Fasting Lipids Values from Adult Placebo-Controlled Olanzapine Monotherapy Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	745	39.6%[a]
		Placebo	402	26.1%
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Olanzapine	457	9.2%[a]
		Placebo	251	4.4%
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	135	39.3%[a]
		Placebo	65	20.0%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.6%[a]
		Placebo	402	9.5%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	392	2.8%
		Placebo	207	2.4%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Olanzapine	222	23.0%[a]
		Placebo	112	12.5%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	536	23.7%[a]
		Placebo	304	14.1%
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	154	0%
		Placebo	82	1.2%
	Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Olanzapine	302	10.6%
		Placebo	173	8.1%

[a] Statistically significant compared to placebo.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the mean increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), for fasting HDL cholesterol, no statistically significant

006237

differences were observed between olanzapine-treated patients and [illegible] patients. Table 2 shows categorical changes in fasting lipid values in adolescent patients.

Table 2. Changes in Fasting Lipids Values from Adolescent Placebo-Controlled Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	138	37.0%*
		Placebo	66	15.2%
	Normal to High (<90 mg/dL to >130 mg/dL)	Olanzapine	67	26.9%
		Placebo	28	10.7%
	Borderline to High (≥90 mg/dL and ≥130 mg/dL to >130 mg/dL)	Olanzapine	37	59.5%
		Placebo	17	35.3%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%*
		Placebo	66	4.5%
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%
		Placebo	43	2.3%
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	36	38.9%*
		Placebo	13	7.7%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%
		Placebo	63	11.1%
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%
		Placebo	44	4.5%
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%*
		Placebo	9	0%

* Statistically significant compared to placebo.

Weight Gain — Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight.

Olanzapine Monotherapy in Adults — In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg, which was statistically significantly different compared to an average 0.3 kg weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, which was statistically significantly different compared to 3% of placebo-treated patients, with a median exposure of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, which was statistically significantly different compared to 0.3% of placebo-treated patients, with a median exposure of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass

006238

Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in zero placebo-treated patients.

During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

Table 3 includes data on weight gain with olanzapine pooled from 68 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 3. Weight Gain with Olanzapine Use

Amount Gained kg (lb)	6 Weeks (N=2976) (%)	6 Months (N=1536) (%)	12 Months (N=778) (%)	24 Months (N=422) (%)
≤0	27	21	20	22
0-5 (0-11 lb)	57	34	25	22
5-10 (11-22 lb)	15	26	25	22
10-15 (22-33 lb)	2	12	16	18
>15 (>33 lb)	0	6	14	16

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescent patients (ages 13 to 17 years), including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine-treated patients gained an average of 4.6 kg, which was statistically significantly different compared to an average of 0.3 kg in placebo-treated patients, with a median exposure of 3 weeks; 40.6% of olanzapine-treated patients gained at least 7% of their baseline body weight, which was statistically significantly different compared to 9.8% of placebo-treated patients, with a median exposure of 4 weeks; 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 2.7% of placebo-treated patients, with a median exposure of 19 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories, but mean changes in weight were greater in adolescents with BMI categories above normal at baseline. Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to zero placebo-treated patients.

During long-term continuation therapy with olanzapine, 65% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.4 kg.

006239

Information for Patients:

Hyperglycemia — Patients should be advised of the potential risk of hyperglycemia-related adverse events. Patients should be monitored regularly for worsening of glucose control.

Weight Gain — Patients should be counseled that olanzapine is associated with weight gain. Patients should have their weight monitored regularly.

Exhibit C, Page 9 of 28
SOA Response to Lilly Motion in Limine Regarding Recent
Regulatory Communications and Developments
Case No. 3AN-06-5630 CI

The following are the updated Hyperglycemia WARNINGS and the new Hyperlipidemia and Weight WARNINGS included in the Symbyax label.

WARNINGS:

Symbyax:
The following is updated language in the WARNINGS section of the Symbyax package insert, and will be reflected in other materials.

Hyperglycemia — Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase I of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the two highest serum concentrations was 15.0 mg/dL.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, SYMBYAX was associated with a statistically significantly greater mean change in random glucose compared to placebo (8.65 mg/dL versus -3.86 mg/dL). In patients with baseline normal random glucose levels (<140 mg/dL), 2.3% of those treated with SYMBYAX were found to have high glucose levels (≥200 mg/dL) during SYMBYAX treatment and were statistically significantly different compared to 0.3% of those treated with placebo. In patients with baseline borderline random glucose levels (≥140 mg/dL and <200 mg/dL), 34.1% of those treated with SYMBYAX were found to have high glucose levels (≥200 mg/dL) during SYMBYAX treatment and were statistically significantly different compared to 3.6% of those treated with placebo. The difference in mean changes between SYMBYAX and placebo was greater in patients with evidence of glucose dysregulation at baseline (including those patients diagnosed with diabetes mellitus or related adverse events, patients treated with anti-diabetic agents,

006241

patients with a baseline random glucose level ≥200 mg/dL, or a baseline fasting glucose level ≥126 mg/dL). These patients had a greater mean increase in HbA_{1c}.

Controlled fasting glucose data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL vs 0.17 mg/dL).

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a statistically significantly greater mean change in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). In patients with baseline normal fasting glucose levels (<100 mg/dL), zero out of 124 (0%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 2 out of 14 (14.3%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus zero out of 13 (0%) of those treated with placebo.

Physicians should consider the risks and benefits when prescribing SYMBYAX to patients with an established diagnosis of diabetes mellitus or having borderline increased blood glucose level (fasting 100–126 mg/dL, nonfasting 140–200 mg/dL). Patients taking SYMBYAX should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Hyperlipidemia — Undesirable alterations in lipids have been observed with SYMBYAX use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using SYMBYAX, is advised.

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with SYMBYAX use. Significant increases in total cholesterol have also been seen with SYMBYAX use.

006242

Controlled fasting lipid data is limited for SYMBYAX.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, SYMBYAX-treated patients had an increase from baseline in mean random total cholesterol of 12.1 mg/dL compared to a statistically significantly different increase from baseline in mean random total cholesterol of 4.8 mg/dL for olanzapine-treated patients and a decrease in mean random total cholesterol of 5.5 mg/dL for placebo-treated patients. Table 3 shows categorical changes in nonfasting lipid values.

Table 3. Changes in Nonfasting Lipids Values from Controlled Clinical Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients (%)
Nonfasting Triglycerides	Increase by ≥50 mg/dL	OFC	174	67.8%
		Olanzapine	172	72.7%
	Normal to High (<150 mg/dL to ≥500 mg/dL)	OFC	57	0%
		Olanzapine	58	0%
	Borderline to High (≥150 mg/dL and <500 mg/dL to ≥500 mg/dL)	OFC	106	15.1%
		Olanzapine	103	8.7%
Nonfasting Total Cholesterol	Increase by ≥40 mg/dL	OFC	685	35%[a,b]
		Olanzapine	749	22.7%
		Placebo	390	9%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	OFC	256	8.2%[a,b]
		Olanzapine	279	2.9%
		Placebo	175	1.7%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	OFC	213	36.2%[a,b]
		Olanzapine	261	27.6%
		Placebo	111	9.9%

[a] Statistically significant compared to olanzapine.
[b] Statistically significant compared to placebo.

Controlled fasting lipid data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had statistically significant increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in

006243

patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse events, patients treated with lipid lowering agents, patients with high baseline lipid levels. Table 4 shows categorical changes in fasting lipid values.

Table 4. Changes in Fasting Lipids Values from Adult Placebo-Controlled Olanzapine Monotherapy Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	745	39.6%*
		Placebo	402	26.1%
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Olanzapine	457	9.2%*
		Placebo	251	4.4%
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	135	39.3%*
		Placebo	65	20.0%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.6%*
		Placebo	402	9.5%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	392	2.8%
		Placebo	207	2.4%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Olanzapine	222	23.0%*
		Placebo	112	12.5%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	536	23.7%*
		Placebo	304	14.1%
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	154	0%
		Placebo	82	1.2%
	Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Olanzapine	302	10.6%
		Placebo	173	8.1%

* Statistically significant compared to placebo.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the median increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), for fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Table 5 shows categorical changes in fasting lipid values in adolescent patients.

006244

Exhibit C, Page 13 of 28
SOA Response to Lilly Motion in Limine Regarding Recent
Regulatory Communications and Developments
Case No. 3AN-06-5630 CI

Table 5. Changes in Fasting Lipids Values from Adolescent Placebo-Controlled Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	138	37.0%*
		Placebo	66	15.2%
	Normal to High (<90 mg/dL to ≥130 mg/dL)	Olanzapine	67	26.9%
		Placebo	28	10.7%
	Borderline to High (≥90 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	37	59.5%
		Placebo	17	35.3%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%*
		Placebo	66	4.5%
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%
		Placebo	43	2.3%
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	36	38.9%*
		Placebo	13	7.7%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%
		Placebo	63	11.1%
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%
		Placebo	44	4.5%
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%*
		Placebo	9	0%

* Statistically significant compared to placebo.

Weight Gain — Potential consequences of weight gain should be considered prior to starting SYMBYAX. Patients receiving SYMBYAX should receive regular monitoring of weight.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, the mean weight increase for SYMBYAX-treated patients was statistically significantly greater than placebo-treated (4 kg vs -0.3 kg). Twenty-two percent of SYMBYAX-treated patients gained at least 7% of their baseline weight, with a median exposure of 6 weeks. This was statistically significantly greater than in placebo-treated patients (1.8%). Approximately 3% of SYMBYAX-treated patients gained at least 15% of their baseline weight, with a median exposure of 8 weeks. This was statistically significantly greater than in placebo-treated patients (0%). Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 2.5% of SYMBYAX-treated patients and zero placebo-treated patients.

Table 6 includes data on weight gain with olanzapine pooled from 68 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

006245

Table 6. Weight Gain with Olanzapine Use

Amount Gained kg (lb)	6 Weeks (N=2976) (%)	6 Months (N=1536) (%)	12 Months (N=778) (%)	24 Months (N=422) (%)
≤0	27	21	20	22
0.5 (0-1.1 lb)	57	34	25	22
5-10 (11-22 lb)	15	26	25	22
10-15 (22-33 lb)	2	12	16	18
>15 (>33 lb)	0	6	14	16

During long-term continuation therapy with olanzapine monotherapy (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescent patients (ages 13 to 17 years), including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine-treated patients gained an average of 4.6 kg, which was statistically significantly different compared to an average of 0.3 kg in placebo-treated patients, with a median exposure of 3 weeks; 40.6% of olanzapine-treated patients gained at least 7% of their baseline body weight, which was statistically significantly different compared to 9.8% of placebo-treated patients, with a median exposure of 4 weeks; 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 2.7% of placebo-treated patients, with a median exposure of 19 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories, but mean changes in weight were greater in adolescents with BMI categories above normal at baseline. Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to zero placebo-treated patients.

During long-term continuation therapy with olanzapine, 65% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.4 kg.

Information for Patients:

Hyperglycemia — Patients should be advised of the potential risk of hyperglycemia-related adverse events. Patients should be monitored regularly for worsening of glucose control.

006246

Weight Gain — Patients should be counseled that SYMBYAX is associated with weight gain. Patients should have their weight monitored regularly.

References:

1. Lieberman, JA, Stroup, TS, McEvoy, JP, S. Swartz, MS, Rosenheck, RA, Perkins, DO, Keefe, RSE, Davis, SM, Davis, CE, Lebowitz, BD, Severe, J, Hsiao, JK. 2005. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. New Engl J Med 353(12): 1209-1223.

2. McEvoy, JP, Lieberman,JA, Perkins, DO, Hamer, RM, Gu, H, Lazarus, A, Sweitzer, D, Olexy, C, Weiden, P, Strakowski, SD. 2007. Efficacy and Tolerability of Olanzapine, Quetiapine, and Risperidone in the Treatment of Early Psychosis: A Randomized, Double-Blind 52-Week Comparison. Am J Psychiatry 164:1050–1060.

3. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for Study of Obesity. 2004. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. Diabetes Care 27: 596-601. http://care.diabetesjournals.org/cgi/content/full/27/2/596

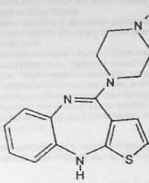
Zyprexa® (olanzapine) is indicated for the short-term and maintenance treatment of schizophrenia. Zyprexa is also indicated as monotherapy or in combination with lithium or valproate for the short-term treatment of acute mixed or manic episodes associated with Bipolar I Disorder and as maintenance treatment in bipolar disorder. Symbyax® (olanzapine and fluoxetine HCl capsules) is indicated for treatment of depressive episodes associated with bipolar disorder.

ZYPREXA® Olanzapine Tablets
ZYPREXA® ZYDIS® Olanzapine Orally Disintegrating Tablets
ZYPREXA® IntraMuscular Olanzapine for Injection

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis (see WARNINGS).

DESCRIPTION: ZYPREXA (olanzapine) is a psycholeptic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4 (4-methyl-1-piperzinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. The chemical structure is:



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

ZYPREXA: It aids are intended for administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 µmol), 5 mg (16 µmol), 7.5 mg (24 µmol), 10 mg (32 µmol), 15 mg (48 µmol), or 20 mg (64 µmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 µmol), 10 mg (32 µmol), 15 mg (48 µmol) or 20 mg (64 µmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben and sodium propyl paraben.

ZYPREXA IntraMuscular (olanzapine for injection) is intended for intramuscular use only.

Each vial provides for the administration of 10 mg (32 µmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

CLINICAL PHARMACOLOGY: Pharmacodynamics—Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_3$, (K_i=4, 11, and 5 nM, respectively); dopamine $D_{1/4}$ (K_i=11-31 nM); histamine H_1 (K_i=7 nM); and adrenergic α_1 receptors (K_i=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ (K_i=57 nM) and muscarinic M_{1-5} (K_i=73, 96, 132, 32, and 46 nM, respectively). Olanzapine binds weakly to $GABA_A$, BZD, and β adrenergic receptors (K_i>10 µM).

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism. The mechanism of action of olanzapine in the treatment of acute manic episodes associated with Bipolar I Disorder is unknown.

Antagonism at receptors other than dopamine and $5HT_2$ may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic-like effects. Olanzapine's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics—*Oral Administration*—Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about one week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age (see Special Populations).

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 92% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1-acid glycoprotein.

Metabolism and Elimination—Following a single oral dose of ^{14}C labeled olanzapine, 7% of the dose of radioactivity was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively, in the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-des-methyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Intramuscular Administration—ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is similar to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

Special Populations—*Renal Impairment*—Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment—Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Child's Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Age—In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in e (≥65 years) than in non-elderly subjects (≤65 years). Dosage should be used in dosing the elderly, especially if there are other that might additively influence drug metabolism and/or pharmacodynamic sensitivity (see DOSAGE AND ADMINISTRATION).

Gender—Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent dif between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status—Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications not routinely recommended.

Race—In vivo studies have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

Combined Effects—The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine (see DOSAGE AND ADMINISTRATION).

For specific information about the pharmacology of lithium or valproate, refer to the CLINICAL PHARMACOLOGY section of the package inserts for these other products.

CLINICAL EFFICACY DATA: Schizophrenia—The efficacy of oral olanzapine in the treatment of schizophrenia was established in 2 short-term (6-week) controlled trials of inpatients who met DSM-III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in one of the two trials, but this trial did not compare these two drugs on the full range of clinically relevant doses for both.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which are embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total, BPRS psychosis cluster, PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving two fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5 ± 2.5 mg/day, 10 ± 2.5 mg/day, and 15 ± 2.5 mg/day) on a once daily schedule, the two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high dose group over the medium dose group.

Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open label treatment for at least 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however, criteria were met for stopping the trial early due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months.

Bipolar Disorder—*Monotherapy*—The efficacy of oral olanzapine in the treatment of acute manic or mixed episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar disorder who had responded during an initial open-label treatment phase for about two weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to ≤12 and HAM-D 21 to ≤8 (absence during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to ≥15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Combination Therapy—The efficacy of oral olanzapine with concomitant lithium or valproate in the treatment of acute manic episodes was established in two controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course. The results of the trials follow:

(1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

Agitation Associated with Schizophrenia and Bipolar I Mania—The efficacy of intramuscular olanzapine for injection for the treatment of agitation was established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated inpatients from the diagnostic groups: schizophrenia and Bipolar I Disorder (manic or mixed episodes). Each of the trials included a single active comparator treatment group (one of either haloperidol injection (schizophrenia studies) or intramuscular injection (bipolar mania study). Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥14 on the 4-item Excited Component of the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least one individual item score ≥4 using a 1-7 scoring system (1=absent, 4=moderate, 7=extreme). In the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging from 13 to 32 (out of a maximum score of 35). Thus, patients suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to three injections during the 24 hour period of treatment period. However, patients could not receive the second injection until after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

(1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270), four fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the three highest doses. There were no significant pairwise differences for the 7.5 and 10 mg doses over the 5 mg dose.

(2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=311), one fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

(3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for Bipolar I Disorder (and currently displaying an acute manic or mixed episode with or without psychotic features) (n=201), one fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

Exhibit C, Page 17 of 28
Response to Lilly Motion in Limine Regarding Zyprexa
Regulatory Communications and Development
Case No. 3AN-06-5630 CI
006248

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

INDICATIONS AND USAGE: Schizophrenia—Oral ZYPREXA is indicated for the treatment of schizophrenia.

The efficacy of ZYPREXA was established in short-term (6-week) controlled trials of schizophrenic inpatients (see CLINICAL EFFICACY DATA).

The effectiveness of oral ZYPREXA at maintaining a treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo-controlled trial (see CLINICAL EFFICACY DATA). Nevertheless, the physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Bipolar Disorder—Acute Monotherapy—Oral ZYPREXA is indicated for the treatment of acute mixed or manic episodes associated with Bipolar I Disorder.

The efficacy of ZYPREXA was established in two placebo-controlled trials (one 3-week and one 4-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL EFFICACY DATA).

Maintenance Monotherapy—The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA after achieving a responder status for an average duration of two weeks was demonstrated in a controlled trial (see CLINICAL EFFICACY DATA). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Combination Therapy—The combination of oral ZYPREXA with lithium or valproate is indicated for the short-term treatment of acute mixed or manic episodes associated with Bipolar I Disorder.

The efficacy of ZYPREXA in combination with lithium or valproate was established in two placebo-controlled (6-week) trials with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL EFFICACY DATA).

Agitation Associated with Schizophrenia and Bipolar I Mania—ZYPREXA IntraMuscular is indicated for the treatment of agitation associated with schizophrenia and bipolar I mania. "Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

The efficacy of ZYPREXA IntraMuscular for the treatment of agitation associated with schizophrenia and bipolar I mania was established in 3 short-term (24 hours) placebo-controlled trials in agitated inpatients with schizophrenia or Bipolar I Disorder (manic or mixed episodes) (see CLINICAL EFFICACY DATA).

CONTRAINDICATIONS: ZYPREXA is contraindicated in patients with a known hypersensitivity to the product.

For specific information about the contraindications of lithium or valproate, refer to the CONTRAINDICATIONS section of the package inserts for these other products.

WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsych-ic drugs are at an increased risk of death compared to placebo. ZYPREXA is not approved for the treatment of patients with dem-ia-related psychosis (see BOX WARNING).

In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis—Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia—Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the two highest serum concentrations was 15.9 mg/dL.

Olanzapine Monotherapy in Adults—In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation or diabetes (patients diagnosed with diabetes mellitus or related adverse events, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥200 mg/dL, and/or a baseline fasting glucose level ≥126 mg/dL). These patients had a statistically significantly greater mean increase in HbA_{1c} compared to placebo. In patients with baseline normal fasting glucose levels (<100 mg/dL), 2.2% (N=543) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 1.4% (N=293) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 17.4% (N=178) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 11.5% (N=96) of those treated with placebo.

Glucose Monotherapy in Adolescents—The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a statistically significantly greater mean change in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). In patients with baseline normal fasting glucose levels (<100 mg/dL), zero out of 124 (0%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 2 out of 14 (14.3%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus zero out of 13 (0%) of those treated with placebo.

Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100-126 mg/dL, non-fasting 140-200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Hyperlipidemia—Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised.

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Olanzapine Monotherapy in Adults—In an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had statistically significant increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.3 mg/dL, 3.0 mg/dL, and 29.8 mg/dL, respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse events, patients treated with lipid lowering agents, or patients with high baseline lipid levels. Table 1 shows categorical changes in fasting lipid values.

Table 1. Changes in Fasting Lipids Values from Adult Placebo-Controlled Olanzapine Monotherapy Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by >50 mg/dL	Olanzapine	745	39.6%*
		Placebo	402	26.1%
	Normal to High (<150 mg/dL to >200 mg/dL)	Olanzapine	457	9.2%*
		Placebo	251	4.4%
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	135	39.3%*
		Placebo	65	20.0%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.6%*
		Placebo	402	9.5%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	392	2.8%
		Placebo	207	2.4%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Olanzapine	222	23.0%*
		Placebo	112	12.5%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	536	23.7%*
		Placebo	304	14.1%
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	154	0%
		Placebo	82	1.2%
	Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Olanzapine	302	10.6%
		Placebo	173	8.1%

* Statistically significant compared to placebo.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the mean increase in total cholesterol was 5.4 mg/dL.

Olanzapine Monotherapy in Adolescents—The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), for fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Table 2 shows categorical changes in fasting lipid values in adolescent patients.

Table 2. Changes in Fasting Lipids Values from Adolescent Placebo-Controlled Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	138	37.0%*
		Placebo	66	15.2%
	Normal to High (<90 mg/dL to >130 mg/dL)	Olanzapine	67	26.9%
		Placebo	28	10.7%
	Borderline to High (≥90 mg/dL and ≤130 mg/dL to >130 mg/dL)	Olanzapine	37	59.5%
		Placebo	17	35.3%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%*
		Placebo	66	4.5%
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%
		Placebo	43	2.3%
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥240 mg/dL)	Olanzapine	36	38.9%*
		Placebo	13	7.7%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%
		Placebo	63	11.1%
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%
		Placebo	44	4.5%
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%*
		Placebo	9	0%

* Statistically significant compared to placebo.

Weight Gain—Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight.

Olanzapine Monotherapy in Adults—In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg, which was statistically significantly different compared to an average 0.3 kg weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, which was statistically significantly different compared to 2% of placebo-treated patients, with a median exposure of 8 weeks. 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, which was statistically significantly different compared to 0.3% of placebo-treated patients, with a median exposure of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in zero placebo-treated patients.

During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

Table 3 includes data on weight gain with olanzapine pooled from 58 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 3. Weight Gain with Olanzapine Use

Amount Gained kg (lb)	6 Weeks (N=2976) (%)	6 Months (N=1536) (%)	12 Months (N=778) (%)	24 Months (N=422) (%)
≥0	27	21	20	22
0-5 (0-11 lb)	57	34	25	22
5-10 (11-22 lb)	15	26	25	22
10-15 (22-33 lb)	2	12	16	18
>15 (>33 lb)	0	6	14	16

Olanzapine Monotherapy in Adolescents—The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescent patients (ages 13 to 17 years), including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine-treated patients gained an average of 4.6 kg, which was statistically significantly different compared to an average of 0.3 kg in placebo-treated patients, with a median exposure of 3 weeks; 40.8% of olanzapine-treated patients gained at least 7% of their baseline body weight, which was statistically significantly different compared to 8.8% of placebo-treated patients, with a median exposure of 4 weeks; 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 2.7% of placebo-treated patients, with a median exposure of 19 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories, but mean changes in weight were greater in adolescents with BMI categories above normal at baseline. Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to zero placebo-treated patients.

During long-term continuation therapy with olanzapine, 65% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.4 kg.

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in associations with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

Exhibit C, Page 18 of 28
Response to Lilly Motion in Limine Regarding Zyprexa
Regulatory Communications and Developments
Case No. 3AN-06-5630 CI
006249

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia—A syndrome of potentially irreversible, involuntary dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

For specific information about the warnings of lithium or valproate, refer to the WARNINGS section of the package inserts for these other products.

PRECAUTIONS: General—Hepatotoxicity Effects—Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonistic properties. Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in non-agitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥20 mm/Hg) (see DOSAGE AND ADMINISTRATION). Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 oral olanzapine studies and in 0.3% (0/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the events occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs.

For oral olanzapine therapy, the risk of ortho-γ-2 hypotension and syncope may be minimized by initiating therapy with 5 mg OD (see DOSAGE AND ADMINISTRATION). A more gradual titration to the target dose should be considered if hypotension occurs.

For intramuscular olanzapine for injection therapy, patients should remain recumbent if dizziness or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation.

Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression (see Drug Interactions). Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine has not been studied and is therefore not recommended. If use of intramuscular olanzapine in combination with parenteral benzodiazepines is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

Seizures—During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hyperprolactinemia—As with other drugs that antagonize dopamine D_2 receptors, olanzapine elevates prolactin levels, and a modest elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats (see Carcinogenesis). However, neither clinical studies nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

Transaminase Elevations—In placebo-controlled clinical trials, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/242) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. In two of these patients, liver enzymes decreased toward normal despite continued treatment and in two others, enzymes decreased upon discontinuation of olanzapine. In two patients, one olanzapine-treated and one placebo-treated, both of whom had elevated transaminases at baseline, one olanzapine-treated patient, one olanzapine-treated patient, one olanzapine-treated patient

Nursing Mothers—In a study in lactating, healthy women olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving olanzapine should not breast-feed.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

Geriatric Use—Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (262) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient (see BOX WARNING, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: The information below is derived from a clinical trial database for olanzapine consisting of 8661 patients with approximately 4185 patient-years of exposure to oral olanzapine and 722 patients with exposure to intramuscular olanzapine for injection. This database includes: (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in schizophrenia and Alzheimer's disease, representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine premarketing bipolar mania trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5018 patients from 88 additional oral olanzapine clinical trials as of December 31, 2001; and (5) 722 patients who participated in intramuscular olanzapine for injection premarketing trials in agitated patients with schizophrenia, Bipolar I Disorder (manic or mixed episodes), or dementia. In addition, information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar mania trials with approximately 22 patient-years of exposure, is included below.

The conditions and duration of treatment with olanzapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatient and outpatient, fixed-dose and dose titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar mania or agitation. However, this information is also generally applicable to bipolar mania and agitation.

Adverse events during exposure are obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used initially to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported events do not include those event terms that were so general as to be uninformative. Events listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the events occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

Incidence of Adverse Events in Short-Term, Placebo-Controlled and Combination Trials—The following findings are based on premarketing trials of (1) oral olanzapine for schizophrenia, bipolar mania, a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease, and premarketing combination trials, and (2) intramuscular olanzapine for injection in agitated patients with schizophrenia or bipolar mania.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials—Schizophrenia—Overall, there was no difference in the incidence of discontinuation due to adverse events (5% for oral olanzapine vs 6% for placebo). However, discontinuations due to increases in SGPT were considered to be drug related (2% for oral olanzapine vs 0% for placebo) (see PRECAUTIONS).

Bipolar Mania Monotherapy—Overall, there was no difference in the incidence of discontinuation due to adverse events (2% for oral olanzapine vs 2% for placebo).

Agitation—Overall, there was no difference in the incidence of discontinuation due to adverse events (0.4% for intramuscular olanzapine for injection vs 0% for placebo).

Adverse Events Associated with Discontinuation of Treatment in Short-Term Combination Trials—Bipolar Mania Combination Therapy—In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse events were 11% for the combination of oral olanzapine with lithium or valproate compared to 2% for patients who remained on lithium or valproate monotherapy. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient were somnolence (2%), weight gain (1%), and peripheral edema (1%).

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials—The most commonly observed adverse events associated with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Oral Olanzapine in 5-Week Trials—SCHIZOPHRENIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=248)	Placebo (N=118)
Postural hypotension	5	2
Constipation	9	3
Weight gain	6	1
Dizziness	11	4
Personality disorder[1]	8	4
Akathisia	5	1

[1] Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

Common Treatment-Emergent Adverse Events Associated with the Use of Oral Olanzapine in 3-Week and 4-Week Trials—BIPOLAR MANIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=125)	Placebo (N=129)
Asthenia	15	6
Dry mouth	22	7
Constipation	11	5
Dyspepsia	11	5
Increased appetite	6	3
Somnolence	35	13
Dizziness	18	6
Tremor	6	3

There was one adverse event (somnolence) observed at an incidence of 5% or greater among intramuscular olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar mania was 8% for intramuscular olanzapine for injection and 3% for placebo.

Adverse Events Occurring at an Incidence of 2% or More Among Oral Olanzapine-Treated Patients in Short-Term, Placebo-Controlled Trials—Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 2% or more of patients treated with oral olanzapine (doses ≥2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

Table 4. Treatment-Emergent Adverse Events: Incidence in Short-Term, Placebo-Controlled Clinical Trials[1] with Oral Olanzapine

Body System/Adverse Event	Percentage of Patients Reporting Event		Body System/Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=332)	Placebo (N=294)		Olanzapine (N=332)	Placebo (N=294)
Body as a Whole			**Musculoskeletal System**		
Accidental Injury	12	8	Extremity pain		
Asthenia	10	9	(other than joint)	5	3
Fever	6	2	Joint pain	5	3
Back pain	5	2	**Nervous System**		
Chest pain	3	1	Somnolence	29	13
Cardiovascular System			Insomnia	12	11
Postural hypotension	3	1	Dizziness	11	4
Tachycardia	3	1	Abnormal gait	6	1
Hypertension	2	1	Tremor	4	3
Digestive System			Akathisia	3	2
Dry mouth	9	5	Hypertonia	3	2
Constipation	9	4	Articulation impairment	2	1
Dyspepsia	7	5	**Respiratory System**		
Vomiting	4	3	Rhinitis	7	6
Increased appetite	3	2	Cough increased	6	3
Hemic and Lymphatic System			Pharyngitis	4	3
			Special Senses		
Ecchymosis	5	3	Amblyopia	3	2
Metabolic and Nutritional Disorders			**Urogenital System**		
			Urinary incontinence	2	1
Weight gain	5	3	Urinary tract infection	2	1
Peripheral edema	3	1			

[1] Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion, depression, diarrhea, dysmenorrhea (denominator used was for females only [olanzapine, N=201; placebo, N=114]), hallucinations, headache, hostility, hyperkinesia, myalgia, nausea, nervousness, paranoid reaction, personality disorder (COSTART term for designating non-aggressive objectionable behavior), rash, thinking abnormal, weight loss.

Commonly Observed Adverse Events in Short-Term Combination Trials—In the bipolar mania combination placebo-controlled trials, the most commonly observed adverse events associated with the combination of olanzapine and lithium or valproate (incidence of ≥5% and at least twice placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Oral Olanzapine in 6-Week Combination Trials—BIPOLAR MANIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)
Dry mouth	33	9
Weight gain	26	7
Increased appetite	24	8
Dizziness	14	7
Back pain	8	4
Constipation	8	4
Speech disorder	7	1
Increased salivation	6	2
Amnesia	5	2
Paresthesia	5	2

Adverse Events Occurring at an Incidence of 2% or More Among Oral Olanzapine-Treated Patients in Short-Term Combination Trials—Table 5 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

Table 5. Treatment-Emergent Adverse Events: Incidence in Short-Term, Placebo-Controlled Combination Clinical Trials[1] with Oral Olanzapine

Body System/Adverse Event	Percentage of Patients Reporting Event		Body System/Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)		Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)
Body as a Whole			**Nervous System (cont.)**		
Asthenia	18	13	Speech disorder	7	1
Back pain	8	4	Amnesia	5	2
Accidental injury	4	2	Paresthesia	5	2
Chest pain	3	2	Apathy	4	3
Cardiovascular System			Confusion	4	1
Hypertension	2	1	Euphoria	3	2
Digestive System			Incoordination	2	0
Dry mouth	32	9	**Respiratory System**		
Increased appetite	24	8	Pharyngitis	4	1
Thirst	10	6	Dyspnea	3	1
Constipation	8	4	**Skin and Appendages**		
Increased salivation	6	2	Sweating	3	1
Metabolic and Nutritional Disorders			Acne	2	0
			Dry skin	2	0
Weight gain	26	7	**Special Senses**		
Peripheral edema	6	4	Amblyopia	9	5
Edema	2	1	Abnormal vision	2	0
Nervous System			**Urogenital System**		
Somnolence	52	27	Dysmenorrhea[2]	2	0
Tremor	23	13	Vaginitis[2]	2	0
Depression	18	17			
Dizziness	14	7			

[1] Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, abnormal dreams, abnormal ejaculation, agitation, akathisia, anorexia, anxiety, arthralgia, cough increased, diarrhea, dyspepsia, emotional lability, knee buckling, libido decreased, libido increased, menstrual disorder (denominator used was for females only [olanzapine, N=128; placebo, N=51]), myalgia, nausea, nervousness, pain, paranoid reaction, personality disorder, rash, rhinitis, sleep disorder, thinking abnormal, vomiting.

[2] Denominator used was for females only (olanzapine, N=128; placebo, N=51).

Exhibit C, Page 20 of 28
Response to Lilly Motion in Limine Regarding Regulatory Communications and Development
Case No. 3AN-06-5630 CI
006251

For specific information about the adverse reactions observed with lithium or valproate, refer to the ADVERSE REACTIONS *section of the package inserts for these other products.*

Adverse Events Occurring at an Incidence of 1% or More Among Intramuscular Olanzapine for Injection-Treated Patients in Short-Term, Placebo-Controlled Trials—Table 6 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred at 1% or more of patients treated with intramuscular olanzapine for injection (dose range of 2.5-10 mg/injection) and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania.

Table 6. Treatment-Emergent Adverse Events: Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trials with Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia or Bipolar Mania[1]

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Olanzapine (N=415)**	**Placebo (N=150)**
Body as a Whole		
Asthenia	2	1
Cardiovascular System		
Hypotension	2	0
Postural hypotension	1	0
Nervous System		
Somnolence	6	3
Dizziness	4	2
Tremor	3	1

[1] Events reported by at least 1% of patients treated with olanzapine for injection, except the following events which had an incidence equal to or less than placebo: agitation, anxiety, dry mouth, headache, hypertension, insomnia, nervousness.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials—Extrapyramidal Symptoms—The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia.

Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia—Acute Phase•

	Percentage of Patients Reporting Event			
	Placebo	Olanzapine 5 ± 2.5 mg/day	Olanzapine 10 ± 2.5 mg/day	Olanzapine 15 ± 2.5 mg/day
Parkinsonism[1]	15	14	12	14
Akathisia[2]	23	16	19	27

* No statistically significant differences.
[1] Percentage of patients with a Simpson-Angus Scale total score >3.
[2] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse events during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia.

Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Events Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia—Acute Phase

	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Dystonic events[1]	1	3	2	3
Parkinsonism events[2]	10	8	14	20
Akathisia events[3]	1	5	11*	10*
Dyskinetic events[4]	4	0	2	1
Residual events[5]	1	2	5	1
Any extrapyramidal event	16	15	25	32*

* Statistically significantly different from placebo.
[1] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.
[2] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
[3] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
[4] Patients with the following COSTART terms were counted in this category: buccolingual syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
[5] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with placebo in agitation. Patients in each dose group could receive up to three injections during the trials (see CLINICAL EFFICACY DATA). Patient assessments were conducted during the 24 hours following the initial dose of intramuscular olanzapine for injection. There were no statistically significant differences from placebo.

Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia•

	Percentage of Patients Reporting Event				
	Placebo	Olanzapine IM 2.5 mg	Olanzapine IM 5 mg	Olanzapine IM 7.5 mg	Olanzapine IM 10 mg
Parkinsonism[1]	0	0	0	0	3
Akathisia[2]	0	0	5	0	0

* No statistically significant differences.
[1] Percentage of patients with a Simpson-Angus total score >3.
[2] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse events in the same controlled clinical trial comparing fixed doses of intramuscular olanzapine for injection with placebo in agitated patients with schizophrenia. There were no statistically significant differences from placebo.

Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Events Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia•

	Percentage of Patients Reporting Event				
	Placebo (N=45)	Olanzapine IM 2.5 mg (N=48)	Olanzapine IM 5 mg (N=45)	Olanzapine IM 7.5 mg (N=46)	Olanzapine IM 10 mg (N=46)
Dystonic events[1]	0	0	0	0	0
Parkinsonism events[2]	0	2	0	0	0
Akathisia events[3]	0	2	0	0	0
Dyskinetic events[4]	0	0	0	0	0
Residual events[5]	0	0	0	0	0
Any extrapyramidal event	0	4	2	0	0

* No statistically significant differences.
[1] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.
[2] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
[3] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
[4] Patients with the following COSTART terms were counted in this category: buccolingual syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
[5] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

Other Adverse Events—The following table addresses dose relatedness for other adverse events rising data from a schizophrenia trial involving fixed dosage ranges of oral olanzapine. It enumerates the percentage of patients with treatment-emergent adverse events for the three fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse events for which there was a statistically significant trend.

Adverse Event	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Asthenia	15	8	9	20
Dry mouth	3	4	5	13
Nausea	9	3	2	9
Somnolence	16	20	30	39
Tremor	3	5	3	13

Additional Findings—In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of olanzapine in patients with schizophrenia or schizoaffective disorder, statistically significant differences among 3 dose groups were observed for the following safety outcomes: weight gain, prolactin elevation, fatigue and dizziness. Mean baseline to endpoint increase in weight (10 mg/day: 1.8 kg; 20 mg/day: 2.3 kg; 40 mg/day: 3 kg) was observed with significant differences between 10 vs 40 mg/day. Incidence of treatment-emergent prolactin elevation (>24.2 ng/mL [female] or >18.77 ng/mL [male]) at any time during the trial (10 mg/day: 31.2%, 20 mg/day: 42.7%, 40 mg/day: 51.1%) with significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day; fatigue (10 mg/day: 1.5%, 20 mg/day: 2.1%, 40 mg/day: 6.6%) with significant differences between 10 vs 40 and 20 vs 40 mg/day; and dizziness (10 mg/day: 2.6%, 20 mg/day: 1.6%, 40 mg/day: 6.6%) with significant differences between 20 vs 40 mg, was observed.

Additional Findings Observed in Clinical Trials—The following findings are based on clinical trials.

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials; intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (see PRECAUTIONS).

Laboratory Changes—An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in SGPT, SGOT, and GGT (see PRECAUTIONS). Olanzapine administration was also associated with increases in serum prolactin (see PRECAUTIONS), with an asymptomatic elevation of the neutrophil count in 0.3% of patients, and with an increase in CPK.

Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models (see ANIMAL TOXICOLOGY), careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

ECG Changes—Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine use was associated with a mean increase in heart rate of 2.4 beats per minute compared to no change among placebo patients. This slight tendency to tachycardia may be related to olanzapine's potential for inducing orthostatic changes (see PRECAUTIONS).

Other Adverse Events Observed During the Clinical Trial Evaluations of Olanzapine—Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with oral olanzapine (at multiple doses ≥1 mg/day) in clinical trials (8581 patients, 4185 patient-years of exposure). This listing may not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life threatening.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole—Frequent: dental pain and flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, and suicide attempt; *Rare:* chills and fever, hangover effect, and sudden death.

Cardiovascular System—Frequent: hypotension; *Infrequent:* atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, and ventricular extrasystoles; *Rare:* arteritis, heart failure, and pulmonary embolism.

Digestive System—Frequent: flatulence, increased salivation, and thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, and tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, and tongue discoloration.

Endocrine System—Infrequent: diabetes mellitus; *Rare:* diabetic acidosis and goiter.

Hemic and Lymphatic System—Infrequent: anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, and thrombocytopenia; *Rare:* normocytic anemia and thrombocythemia.

Metabolic and Nutritional Disorders—Infrequent: acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesterolemia, hyperglycemia, hyperlipemia, hypernatremia, hyperuricemia, hypocalcemia, hypokalemia, hyponatremia, lower extremity edema, and upper extremity edema; *Rare:* gout, hypoglycemia, hypernatremia, hyperuricemia, hypocalcemia, ketosis, and water intoxication.

Musculoskeletal System—Frequent: joint stiffness and twitching; *Infrequent:* arthritis, arthrosis, leg cramps, and myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, and rheumatoid arthritis.

Nervous System—Frequent: abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, and schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, cretinism, dementia, depersonalization, dysarthria, facial paralysis, hyperkinesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, ptosis, sociopathic, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, and withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, and tobacco misuse.

Respiratory System—Frequent: dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, and voice alteration; *Rare:* atelectasis, hiccup, hyperventilation, lung edema, and stridor.

Skin and Appendages—Frequent: sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, and vesiculobullous rash; *Rare:* hirsutism and pustular rash.

Special Senses—Frequent: conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, and tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, and pigment deposits lens.

Urogenital System—Frequent: vaginitis*; *Infrequent:* abnormal ejaculation*, amenorrhea*, breast pain, cystitis, decreased menstruation*, dysuria, female lactation*, glycosuria, gynecomastia, hematuria, impotence*, increased menstruation*, menorrhagia*, metrorrhagia*, polyuria, premenstrual syndrome*, pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged*, and vaginal hemorrhage*; *Rare:* albuminuria, breast enlargement, mastitis, and oliguria.

* Adjusted for gender.

Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with intramuscular olanzapine for injection (at one or more doses ≥2.5 mg/injection) in clinical trials (722 patients). This listing may not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients.

Body as a Whole—Frequent: injection site pain; *Infrequent:* abdominal pain and fever.

Cardiovascular System—Infrequent: AV block, heart block, and syncope.

Digestive System—Infrequent: diarrhea and nausea.

Hemic and Lymphatic System—Infrequent: anemia.

Metabolic and Nutritional Disorders—Infrequent: creatine phosphokinase increased, dehydration, and hyperkalemia.

Musculoskeletal System—Infrequent: twitching.

Nervous System—Infrequent: abnormal gait, akathisia, articulation impairment, confusion, and emotional lability.

Skin and Appendages—Infrequent: sweating.

Postintroduction Reports—Adverse events reported since market introduction that were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, neutropenia, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥300 mg/dL have been reported.

006252
Exhibit C, Page 21 of 28
SOA Response to Lilly Motion in Limine Regarding Regulatory Communications and Case No. 3AN-06-5630 CI

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class—Olanzapine is not a controlled substance.

Physical and Psychological Dependence—In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute dependence CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily oral dose (30 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily oral dose on a mg/m² basis.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE: Human Experience—In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and one patient experiencing torsus paste with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of lability in association with overdose of olanzapine alone. In one case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

Overdosage Management—The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. [Do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.] Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION: Schizophrenia—Usual Dose—Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since usually stable for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical assessment. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Doses in Special Populations—The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine (see CLINICAL PHARMACOLOGY, also see Use in Patients with Concomitant Illness and Drug Interactions under PRECAUTIONS). When indicated, dose escalation should be performed with caution in these patients.

Maintenance Treatment—While there is no body of evidence available to answer the question of how long the patient treated with olanzapine should remain on it, the effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo-controlled trial (see CLINICAL EFFICACY DATA). Patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

Bipolar Disorder—Usual Monotherapy Dose—Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Maintenance Monotherapy—The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of two weeks, was demonstrated in a controlled trial (see CLINICAL EFFICACY DATA). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Bipolar Mania Usual Dose in Combination with Lithium or Valproate—When administered in combination with lithium or valproate, oral olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals.

Short-term (6 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations—See Dosing in Special Populations under DOSAGE AND ADMINISTRATION, Schizophrenia.

Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)—After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

Agitation Associated with Schizophrenia and Bipolar I Mania—Usual Dose for Agitated Patients with Schizophrenia or Bipolar Mania—The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant (see CLINICAL EFFICACY DATA). If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., three doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension (see PRECAUTIONS, Hemodynamic Effects). Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended.

If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate (see Schizophrenia or Bipolar Disorder under DOSAGE AND ADMINISTRATION).

Intramuscular Dosing in Special Populations—A dose of 5 mg per injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg per injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine (see CLINICAL PHARMACOLOGY, also see Use in Patients with Concomitant Illness and Drug Interactions under PRECAUTIONS).

Administration of ZYPREXA IntraMuscular—ZYPREXA IntraMuscular is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for preparation of ZYPREXA IntraMuscular with Sterile Water for Injection—Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. ZYPREXA IntraMuscular reconstituted with Sterile Water for Injection should be used immediately (within 1 hour) after reconstitution. Discard any unused portion.

The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

Dose (mg) Olanzapine	Volume of Injection, mL Withdraw total contents of vial
10	2
7.5	1.5
5	1
2.5	0.5

Physical Incompatibility Information—ZYPREXA IntraMuscular should be reconstituted only with Sterile Water for Injection. ZYPREXA IntraMuscular should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed. Lorazepam injection should not be used to reconstitute ZYPREXA IntraMuscular as this combination results in a delayed reconstitution time. ZYPREXA IntraMuscular should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

HOW SUPPLIED: The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. The tablets are available as follows:

	TABLET STRENGTH					
	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	20 mg
Tablet No. Identification	4132 LILLY 4132	4115 LILLY 4115	4116 LILLY 4116	4117 LILLY 4117	4415 LILLY 4415	4420 LILLY 4420
NDC Codes: Bottles 30	NDC 0002-4132-30	NDC 0002-4115-30	NDC 0002-4116-30	NDC 0002-4117-30	NDC 0002-4415-30	NDC 0002-4420-30
Blisters-ID* 100	NDC 0002-4132-33	NDC 0002-4115-33	NDC 0002-4116-33	NDC 0002-4117-33	NDC 0002-4415-33	NDC 0002-4420-33
Bottles 1000	NDC 0002-4132-04	NDC 0002-4115-04	NDC 0002-4116-04	NDC 0002-4117-04	NDC 0002-4415-04	NDC 0002-4420-04

* Identi-Dose® (unit dose medication, Lilly).

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:

ZYPREXA ZYDIS Tablets	TABLET STRENGTH			
	5 mg	10 mg	15 mg	20 mg
Tablet No. Debossed*	4453 5	4454 10	4455 15	4456 20
NDC Codes Dose Pack 30 (Child-Resistant)	NDC 0002-4453-85	NDC 0002-4454-85	NDC 0002-4455-85	NDC 0002-4456-85

ZYPREXA is a registered trademark of Eli Lilly and Company.
ZYDIS is a registered trademark of Catalent Pharma Solutions.
ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Catalent Pharma Solutions, United Kingdom, SNS ERU.

ZYPREXA IntraMuscular is available in:
NDC 0002-7597-01 (Rx, V-7597) – 10 mg vial (1s)

Store ZYPREXA tablets, ZYPREXA ZYDIS, and ZYPREXA IntraMuscular vials (before reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP]. Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP] for up to 1 hour if necessary. Discard any unused portion of reconstituted ZYPREXA IntraMuscular. The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect ZYPREXA tablets and ZYPREXA ZYDIS from light and moisture. Protect ZYPREXA IntraMuscular from light, do not freeze.

ANIMAL TOXICOLOGY: In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily oral dose on a mg/m² basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a mg/m² basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily oral dose on a mg/m² basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a mg/m² basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

Literature revised October 1, 2007

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Indianapolis, IN 46285, USA

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Exhibit C, Page 22 of 28
FDA Response to Lilly Motion in Limine Regarding Recall Communications and Development
Regulatory Consultants
Case No. 3AN-06-5630 CI

SYMBYAX® (olanzapine and fluoxetine HCl capsules)

WARNING

Suicidality and Antidepressant Drugs—Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SYMBYAX or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SYMBYAX is not approved for use in pediatric patients. (See WARNINGS, Clinical Worsening and Suicide Risk, PRECAUTIONS, Information for Patients, and PRECAUTIONS, Pediatric Use.)

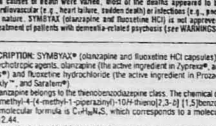
Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infections (e.g., pneumonia) in nature. SYMBYAX (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with dementia-related psychosis (see WARNINGS).

DESCRIPTION: SYMBYAX® (olanzapine and fluoxetine HCl capsules) combines 2 psychotropic agents, olanzapine (the active ingredient in Zyprexa®, and Zyprexa Zydis®) and fluoxetine hydrochloride (the active ingredient in Prozac®, Prozac Weekly™, and Sarafem®).

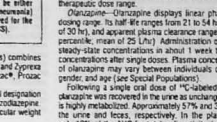
Olanzapine belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44.

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI). The chemical designation is (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)oxy] propylamine hydrochloride. The molecular formula is $C_{17}H_{18}F_3NO{\cdot}HCl$, which corresponds to a molecular weight of 345.

The chemical structures are:



olanzapine



fluoxetine hydrochloride

Olanzapine is a yellow crystalline solid, which is practically insoluble in water. Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

SYMBYAX capsules are available for oral administration in the following strength combinations:

	3 mg/ 25 mg	6 mg/ 25 mg	6 mg/ 50 mg	12 mg/ 25 mg	12 mg/ 50 mg
olanzapine equivalent	3	6	6	12	12
fluoxetine base equivalent	25	25	50	25	50

Each capsule also contains pregelatinized starch, gelatin, dimethicone, titanium dioxide, sodium lauryl sulfate, edible black ink, red iron oxide, yellow iron oxide, and/or black iron oxide.

CLINICAL PHARMACOLOGY: Pharmacodynamics—Although the exact mechanism of SYMBYAX is unknown, it has been proposed that the activation of 2 neurotransmitter neural systems (serotonin, norepinephrine, and dopamine) is responsible for its enhanced antidepressant effect. This is supported by animal studies in which the olanzapine/fluoxetine combination has been shown to produce synergistic increases in norepinephrine and dopamine release in the prefrontal cortex compared with either component alone, as well as increases in serotonin.

Olanzapine is a psychotropic agent with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$, (K_i=4, 11, and 5 nM, respectively), dopamine D_{1-4} (K_i=11 to 31 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors (K_i=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ (K_i=57 nM) and muscarinic M_{1-5} (K_i=73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds weakly to $GABA_A$, BZD, and β-adrenergic receptors (K_i>10 μM). Fluoxetine is an inhibitor of the serotonin transporter and is a weak inhibitor of the norepinephrine and dopamine transporters.

Antagonism at receptors other than dopamine and $5HT_2$ may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic-like effects. The antagonism of histamine H_1 receptors by olanzapine may explain the somnolence observed with this drug. The antagonism of α_1-adrenergic receptors by olanzapine may explain the orthostatic hypotension observed with this drug. Fluoxetine has relatively low affinity for muscarinic, α-adrenergic, and histamine H_1 receptors.

Pharmacokinetics—Fluoxetine (administered as a 60-mg single dose or 60 mg daily for 8 days) caused a small increase in the mean maximum concentration of olanzapine (16%) following a 5-mg dose, and a decrease in the mean area under the curve (17%) and a small decrease in mean apparent clearance of olanzapine (16%). In another study, a similar decrease in apparent clearance of olanzapine of 14% was observed following olanzapine doses of 6 or 12 mg with concomitant fluoxetine doses of 25 mg or more. The decrease in clearance reflects an increase in bioavailability. The terminal half-life is not affected, and therefore the time to reach steady state should not be altered. The overall steady-state plasma concentrations of olanzapine and fluoxetine when given as the combination in the therapeutic dose ranges were comparable with those typically attained with each of the monotherapies. The small change in olanzapine clearance, observed in both studies, likely reflects the inhibition of a minor metabolic pathway for olanzapine via CYP2D6 by fluoxetine, a potent CYP2D6 inhibitor, and was not deemed clinically significant. Therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination.

Absorption and Bioavailability—SYMBYAX—Following a single oral 12-mg/50-mg dose of SYMBYAX, peak plasma concentrations of olanzapine and fluoxetine occur at approximately 4 and 6 hours, respectively. The effect of food on the absorption and bioavailability of SYMBYAX has not been evaluated. The bioavailability of olanzapine given as Zyprexa, and the bioavailability of fluoxetine given as Prozac were not affected by food. It is unlikely that there would be a significant food effect on the bioavailability of SYMBYAX.

Olanzapine—Olanzapine is well absorbed and reaches peak concentration approximately 6 hours following an oral dose. Food does not affect the rate or extent of olanzapine absorption when olanzapine is given as Zyprexa. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation.

Fluoxetine—Following a single oral 40-mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine given as Prozac, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant.

Distribution—SYMBYAX—The in vitro binding to human plasma proteins of the olanzapine/fluoxetine combination is similar to the binding of the individual components.

Olanzapine—Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α-acid glycoprotein.

Fluoxetine—Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α$_1$-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated (see PRECAUTIONS, Drugs highly bound to plasma proteins).

Metabolism and Elimination—SYMBYAX—SYMBYAX therapy yielded steady-state concentrations of norfluoxetine similar to those seen with fluoxetine in the therapeutic dose range.

Olanzapine—Olanzapine displays linear pharmacokinetics over the clinical dosing range of 5 to 20 mg/day. Ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr) Administration of olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single dosing. Plasma concentration, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age (see Special Populations).

Following a single oral dose of ^{14}C-labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and CYP450-mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYP1A2/ CYP2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6-mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Fluoxetine—Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Fluoxetine is extensively metabolized in the liver to its only identified active metabolite, norfluoxetine, via the CYP2D6 pathway. A number of unidentified metabolites exist.

In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical Issues Involving Metabolism and Elimination—The complexity of the metabolism of fluoxetine has several consequences that may potentially affect the clinical use of SYMBYAX.

Variability in metabolism—A subset (about 7%) of the population has reduced activity of the drug metabolizing isozyme CYP2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants (TCAs). In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine or *R*-fluoxetine at rates achieved by extensive metabolizers of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with extensive metabolizers, the total sum at steady state of the plasma concentrations of the 4 enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative non-routable pathways (non-CYP2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine and olanzapine, like that of a number of other compounds including TCAs and other selective serotonin antidepressants, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (see PRECAUTIONS, Drug Interactions).

Accumulation and slow elimination—The relatively slow elimination of fluoxetine (elimination half-life of 4 to 6 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of drug and active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because the metabolism of fluoxetine is not proportional to dose. However, norfluoxetine appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine.

Special Populations—*Geriatric*—Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in geriatric patients. Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity.

In a study involving 14 elderly (≥ 65 years) patients receiving olanzapine, the clearance was about 1.5 times greater in elderly women than in elderly men. The disposition of single doses of fluoxetine in healthy elderly subjects (≥ 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Renal Impairment—The pharmacokinetics of SYMBYAX has not been studied in patients with renal impairment. However, olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not routinely required.

Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on olanzapine metabolite elimination has not been studied.

In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.

Hepatic Impairment—Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in patients with hepatic impairment. The lowest starting dose should be considered for patients with hepatic impairment (see PRECAUTIONS, Use in Patients with Concomitant Illness and DOSAGE AND ADMINISTRATION, Special Populations).

Although the presence of hepatic impairment may significantly increase the clearance of olanzapine, a study of the effect of impaired liver function in subjects (N=6) with clinically significant cirrhosis (Childs-Pugh Classification A and B) revealed little effect on the pharmacokinetics of olanzapine.

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean half-life of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects.

Gender—Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between male and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status—Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely required.

Race—No SYMBYAX pharmacokinetic study was conducted to investigate the effects of race. In vivo studies have shown that exposures to olanzapine are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race, therefore, are not routinely required.

Combined Effects—The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance of olanzapine in young smoking males, for example, may be 3 times faster than that in elderly nonsmoking females. SYMBYAX dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of the olanzapine component (see DOSAGE AND ADMINISTRATION, Special Populations).

CLINICAL STUDIES: The efficacy of SYMBYAX for the treatment of depressive episodes associated with bipolar disorder was established in 2 identically designed, 8-week, randomized, double-blind, controlled studies of patients who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for Bipolar I Disorder, Depressed (allowing flexible dosing of SYMBYAX (6/25, 6/50, or 12/50 mg/day), olanzapine (5 to 20 mg/day), and placebo). These studies included patients (≥18 years of age) with or without psychotic symptoms and with or without a rapid cycling course.

The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 to 60. The primary outcome measure of these studies was the change from baseline to endpoint in the MADRS total score. In both studies, SYMBYAX was statistically significantly superior to both olanzapine monotherapy and placebo in reductions of the MADRS total score. The results of the studies are summarized below (Table 1).

Table 1: MADRS Total Score
Mean Change from Baseline to Endpoint

	Treatment Group	Baseline Mean	Change to Endpoint Mean[1]
Study 1	SYMBYAX (N=40)	30	-19[2]
	Olanzapine (N=182)	32	-12
	Placebo (N=181)	31	-10
Study 2	SYMBYAX (N=42)	32	-18[2]
	Olanzapine (N=169)	33	-14
	Placebo (N=174)	31	-9

[1] Negative number denotes improvement from baseline.
[2] Statistically significant compared to both olanzapine and placebo.

INDICATIONS AND USAGE: SYMBYAX is indicated for the treatment of depressive episodes associated with bipolar disorder. The efficacy of SYMBYAX was established in 2 identically designed, 8-week, randomized, double-blind clinical studies.

Unlike with unipolar depression, there are no established guidelines for the length of time patients with bipolar disorder experiencing a major depressive episode should be treated with agents containing antidepressant drugs.

The effectiveness of SYMBYAX for maintaining antidepressant response in this patient population beyond 8 weeks has not been established in controlled clinical studies. Physicians who elect to use SYMBYAX for extended periods should periodically reevaluate the benefits and long-term risks of the drug for the individual patient.

CONTRAINDICATIONS: *Hypersensitivity*—SYMBYAX is contraindicated in patients with a known hypersensitivity to the product or any component of the product.

Monoamine Oxidase Inhibitors (MAOI)—There have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes) in patients receiving fluoxetine in combination with an MAOI, and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore,

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Regulatory Communications and Development
0062544

SYMBYAX should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) (see CLINICAL PHARMACOLOGY, Accumulation and slow elimination)] should be allowed after stopping SYMBYAX before starting an MAOI.

Pimozide—Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

Thioridazine—Thioridazine should not be administered with SYMBYAX or administered within a minimum of 5 weeks after discontinuation of SYMBYAX (see WARNINGS, Thioridazine).

WARNINGS—*Clinical Worsening and Suicide Risk*—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug versus placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 2

Table 2

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuation of Treatment with SYMBYAX, for a description of the risks of discontinuation of SYMBYAX).

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for SYMBYAX should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

It should be noted that SYMBYAX is not approved for use in treating any indications in the pediatric population.

Screening Patients for Bipolar Disorder—A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SYMBYAX is approved for use in treating bipolar depression.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SYMBYAX (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with dementia related psychosis (see BOX WARNING).

In olanzapine placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

Cerebrovascular Adverse Events (CVAE), including Stroke, in Elderly Patients with Dementia-Related Psychosis—Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia—Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in fasting glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the two highest serum concentrations was 15.0 mg/dL.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, SYMBYAX was associated with a statistically significantly greater mean change in random glucose compared to placebo (8.65 mg/dl, versus -3.86 mg/dL). In patients with baseline normal random glucose levels (<140 mg/dL), 2.3% of those treated with SYMBYAX were found to have high glucose levels (≥200 mg/dL) during SYMBYAX treatment and were statistically significantly different compared to 0.3% of those treated with placebo. In patients with baseline borderline random glucose levels (≥140 mg/dL and <200 mg/dL), 34.1% of those treated with SYMBYAX were found to have high glucose levels (≥200 mg/dL) during SYMBYAX treatment and were statistically significantly different compared to 3.5% of those treated with placebo. The difference in mean changes between SYMBYAX and placebo was greater in patients with evidence of glucose dysregulation at baseline (including those patients diagnosed with diabetes mellitus or related adverse events, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥200 mg/dL, or a baseline fasting glucose level ≥126 mg/dL). These patients had a greater mean increase in HbA_{1c}.

Controlled fasting glucose data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.7 mg/dL vs 0.17 mg/dL).

Olanzapine Monotherapy in Adolescents—The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (5 weeks) or bipolar (manic or mixed episodes) (3 weeks), olanzapine was associated with a statistically significantly greater mean change in fasting glucose levels compared to placebo (2.68 mg/dl, versus -2.59 mg/dL). In patients with baseline normal fasting glucose levels (<100 mg/dL), zero out of 121 (0%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 2 out of 14 (14.3%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 0 out of 8 (0%) of those treated with placebo.

Physicians should consider the risks and benefits when prescribing SYMBYAX to patients with an established diagnosis of diabetes mellitus, or having borderline increased fasting glucose level (fasting 100-126 mg/dL, nonfasting 140-200 mg/dL). Patients taking SYMBYAX should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspected drug.

Hyperlipidemia—Undesirable alterations in lipids have been observed with SYMBYAX use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using SYMBYAX, is advised.

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with SYMBYAX use. Significant increases in total cholesterol have also been seen with SYMBYAX use.

Controlled fasting lipid data is limited for SYMBYAX.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, SYMBYAX-treated patients had an increase from baseline in mean random total cholesterol of 12.1 mg/dL compared to a statistically significantly different increase from baseline in mean random total cholesterol of 4.8 mg/dL for olanzapine-treated patients and a decrease in mean random total cholesterol of 5.5 mg/dL for placebo-treated patients. Table 3 shows categorical changes in nonfasting lipid values.

Table 3: Changes in Nonfasting Lipids Values from Controlled Clinical Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Nonfasting Triglycerides	Increase by ≥50 mg/dL	OFC	174	67.8%
		Olanzapine	172	72.7%
	Normal to High (<150 mg/dL to ≥500 mg/dL)	OFC	57	0%
		Olanzapine	58	0%
	Borderline to High (≥150 mg/dL and <500 mg/dL to ≥500 mg/dL)	OFC	106	15.1%
		Olanzapine	103	8.7%
Nonfasting Total Cholesterol	Increase by ≥40 mg/dL	OFC	685	35%*
		Olanzapine	749	22.7%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Placebo	390	9%
		OFC	255	8.2%*
		Olanzapine	279	2.9%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Placebo	175	1.7%
		OFC	213	36.2%*
		Olanzapine	261	27.6%
		Placebo	111	9.9%

* Statistically significant compared to placebo

Controlled fasting lipid data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had statistically significant increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse events, patients treated with lipid lowering agents, or patients with high baseline lipid levels. Table 4 shows categorical changes in fasting lipid values.

Table 4: Changes in Fasting Lipids Values from Adult Placebo-Controlled Olanzapine Monotherapy Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	745	39.6%*
		Placebo	492	26.1%
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Olanzapine	457	9.2%*
		Placebo	251	4.4%
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	135	39.3%*
		Placebo	65	20.0%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.6%*
		Placebo	402	9.5%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	392	2.8%
		Placebo	207	2.4%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Olanzapine	222	23.0%*
		Placebo	112	12.5%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	536	23.7%*
		Placebo	304	14.1%
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	154	0%
		Placebo	82	1.2%
	Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Olanzapine	302	10.6%
		Placebo	173	8.1%

* Statistically significant compared to placebo

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the median increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents—The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), for fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Table 5 shows categorical changes in fasting lipid values in adolescent patients.

Table 5: Changes in Fasting Lipids Values from Adolescent Placebo-Controlled Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	138	37.0%*
		Placebo	66	15.2%
	Normal to High (<90 mg/dL to ≥130 mg/dL)	Olanzapine	67	26.9%
		Placebo	28	10.7%
	Borderline to High (≥90 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	37	59.5%
		Placebo	17	35.3%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%*
		Placebo	66	4.5%
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%
		Placebo	43	2.3%
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	36	38.9%*
		Placebo	13	7.7%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%
		Placebo	63	11.1%
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%
		Placebo	44	4.5%
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%*
		Placebo	9	0%

* Statistically significant compared to placebo

Weight Gain—Potential consequences of weight gain should be considered prior to starting SYMBYAX. Patients receiving SYMBYAX should receive regular monitoring of weight.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, the mean weight increase for SYMBYAX-treated patients was statistically significantly greater than placebo-treated patients (4 kg vs -0.3 kg). Twenty-two percent of SYMBYAX-treated patients gained at least 7% of their baseline weight, with a median exposure of 6 weeks. This was statistically significantly greater than in placebo-treated patients (1.8%). Approximately 3% of SYMBYAX-treated patients gained at least 15% of their baseline weight, with a median exposure of 9 weeks. This was statistically significantly greater than in placebo-treated patients (0%). Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 2.5% of SYMBYAX-treated patients and zero placebo-treated patients.

Table 6 includes data on weight gain with olanzapine pooled from 86 clinical trials. The data in each column represent data from those patients who completed treatment periods of the durations specified.

Subject to Protective Order Regarding Lilly Information
Regulatory Communications and Developments
Case No. 3:04-md-1596 Document 2465-3 Filed 04/24/08 Page 24 of 28
SCSD_MDL_1596_0006630 CI
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Table 8: Weight Gain with Olanzapine Use

Among Patients Age (Yrs)	4 Weeks (N=29/76) (%)	6 Months (N=15/38) (%)	12 Months (N=5/18) (%)	24 Months (N=4/22) (%)
≤9	37	21	20	22
0-5 (9-11 lb)	37	26	25	22
5-10 (11-22 lb)	17	12	16	18
10-15 (22-33 lb)	7	14	16	14
>15 (>33 lb)	3	7	0	0

During short-term combination therapy with olanzapine monotherapy (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 3.4 kg.

Olanzapine Monotherapy in Adolescents—The safety and efficacy of olanzapine used alone (monotherapy) in adolescents have not been established in patients under the age of 18 years. In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescent patients (ages 13 to 17 years), including those with schizophrenia (5 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine-treated patients gained an average of 4.6 kg, which was statistically significantly different compared to an average of 0.3 kg in placebo-treated patients, with a median exposure of 3 weeks; 40.6% of olanzapine-treated patients gained at least 7% of their baseline body weight, which was statistically significantly different compared to 9.8% of placebo-treated patients; with a median exposure of 4 weeks; 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 2.7% of placebo-treated patients; with a median exposure of 19 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories, but mean changes in weight were greater in adolescents with BMI categories above normal at baseline. Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to zero placebo-treated patients.

During long-term continuation therapy with olanzapine, 85% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.4 kg.

Orthostatic Hypotension—SYMBYAX may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some patients, syncope, especially during the initial dose-titration period.

In the bipolar depression studies, statistically significantly more orthostatic changes occurred with the SYMBYAX group compared to placebo and olanzapine groups. Orthostatic systolic blood pressure decrease of at least 30 mm Hg occurred in 7.3% (9/82), 1.4% (5/346), and 1.4% (5/352) of the SYMBYAX, olanzapine and placebo groups, respectively. Among the group of controlled clinical studies with SYMBYAX, an orthostatic systolic blood pressure decrease of ≥30 mm Hg occurred in 4% (21/512) of SYMBYAX-treated patients, 5% (10/204) of fluoxetine-treated patients, 2% (16/644) of olanzapine-treated patients, and 2% (8/445) of placebo-treated patients. In this group of studies, the incidence of syncope in SYMBYAX-treated patients was 0.4% (2/571) compared to placebo 0.2% (1/477).

In a clinical pharmacology study of SYMBYAX, three healthy subjects were discontinued from the trial after experiencing severe, but self-limited, hypotension and bradycardia that occurred 2 to 3 hours following a single 12-mg/50-mg dose of SYMBYAX. Reactions consisting of this combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in at least three other healthy subjects treated with oral formulations of olanzapine (one oral, two intramuscular). In controlled clinical studies, the incidence of patients with a ≥20 bpm decrease in orthostatic pulse concomitantly with a ≥20 mm Hg decrease in orthostatic systolic pressure was 0.4% (2/545) in the SYMBYAX group, 0.2% (1/455) in the placebo group, 0.8% (5/659) in the olanzapine group, and 0% (0/370) in the fluoxetine group.

SYMBYAX should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Allergic Events and Rash—In SYMBYAX premarketing controlled clinical studies, the overall incidence of rash or allergic events in SYMBYAX-treated patients [4.6% (26/571)] was similar to that of placebo [5.2% (25/477)]. The majority of the cases of rash and/or allergic event were mild; however, three patients discontinued (one due to rash, which was moderate in severity, and two due to allergic events, one of which included face edema).

In fluoxetine US clinical studies, 7 of 10,782 fluoxetine-treated patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical studies, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and elevated transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In fluoxetine premarketing clinical studies, 2 patients are known to have developed a severe cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a reaction to erythema multiforme or toxic epidermal necrolysis. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of fluoxetine, systemic events, possibly related to vasculitis, have been reported in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possible allergic phenomena for which an alternative etiology cannot be identified, SYMBYAX should be discontinued.

Serotonin Syndrome—The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including SYMBYAX treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of SYMBYAX with MAOIs intended to treat depression is contraindicated (*see* CONTRAINDICATIONS, Monoamine Oxidase Inhibitors (MAOI) and PRECAUTIONS, Drug Interactions).

If concomitant treatment of SYMBYAX with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* PRECAUTIONS, Drug Interactions).

The concomitant use of SYMBYAX with serotonin precursors (such as tryptophan) is not recommended (*see* PRECAUTIONS, Drug Interactions).

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscular rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If after recovering from NMS, a patient requires treatment with an antipsychotic, the patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia—A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the relative incidence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses (≤300 mg chlorpromazine equivalents) or even after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the process that is causing the underlying pathology. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

The incidence of dyskinetic movement in SYMBYAX-treated patients was infrequent. The mean score on the Abnormal Involuntary Movement Scale (AIMS) across clinical studies involving SYMBYAX-treated patients decreased from baseline. Nonetheless, SYMBYAX should be prescribe in a manner most likely to minimize the risk of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on SYMBYAX, drug discontinuation should be considered. However, some patients may require treatment with SYMBYAX despite the presence of the syndrome. The need for continued treatment should be reassessed periodically.

Thioridazine—A study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators. Whether olanzapine, which is metabolized by the debrisoquin hydroxylation is felt to depend on the low level of CYP2D6 isozyme activity. Thus, this study suggests that drugs that inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (*see* PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QT, interval, which is associated with serious ventricular arrhythmias such as torsades de pointes-type arrhythmias and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism (*see* CONTRAINDICATIONS, Thioridazine).

PRECAUTIONS: General—*Concomitant Use of Olanzapine and Fluoxetine Products*—SYMBYAX contains the same active ingredients that are in Symbyax and Zyprexa Zydis (olanzapine) and in Prozac, Prozac Weekly, and Sarafem (fluoxetine HCl). Caution should be exercised when prescribing these medications concomitantly with SYMBYAX.

Abnormal Bleeding—Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (*see* DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of SYMBYAX with NSAIDs, aspirin, or other drugs that affect coagulation.

Mania/Hypomania—In the two controlled bipolar depression studies there was no statistically significant difference in the incidence of manic events (manic reaction or manic depressive reaction) between SYMBYAX- and placebo-treated patients. In one of the studies, the incidence of manic events was 2% (7/352) in SYMBYAX-treated patients compared to 0% (5/184)] in placebo-treated patients. In the other study, the incidence was 3% (4/146) in SYMBYAX-treated patients compared to 0% [15/193)] in placebo-treated patients. This limited controlled trial experience of SYMBYAX in the treatment of bipolar depression precludes any definitive conclusion at this time until additional data is obtained. Because of this and the cyclical nature of bipolar disorder, patients should be monitored closely for the development of symptoms of mania/hypomania (*see* PRECAUTIONS, Activation).

Body Temperature Regulation—Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic drugs. Appropriate care is advised when prescribing SYMBYAX. Patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

Cognitive and Motor Impairment—Somnolence was a commonly reported adverse event associated with SYMBYAX treatment, occurring at an incidence of 22% in SYMBYAX patients compared with 11% in placebo patients. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them adversely.

Discontinuation of Treatment with SYMBYAX—During marketing of fluoxetine, a component of SYMBYAX, and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, [illegible] nausea and/or vomiting, and sweating. While these events are generally self-limiting, there have been reports of serious withdrawal symptoms [illegible] when fluoxetine has been abruptly discontinued. It is therefore recommended that SYMBYAX be tapered rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy, which may minimize the risk of discontinuation symptoms with this drug (*see* DOSAGE AND ADMINISTRATION).

Dysphagia—Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Half-Life—Because of the long elimination half-lives of fluoxetine and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* CLINICAL PHARMACOLOGY, Accumulation and slow elimination).

Hyperprolactinemia—As with other drugs that antagonize dopamine D_2 receptors, SYMBYAX elevates prolactin levels, and a modest elevation persists during administration; however, possibly associated clinical manifestations (e.g., galactorrhea and breast enlargement) were infrequently observed.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds that increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats (*see* Carcinogenesis). However, neither clinical studies nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

Hyponatremia—Hyponatremia has been observed in SYMBYAX premarketing clinical studies. In controlled trials, no SYMBYAX-treated patients had a treatment-emergent serum sodium level below 130 mmol/L. However, the frequency of serum sodium below the reference range occurred at an incidence of 2% (10/500) of SYMBYAX-treated patients compared with 0.3% (2/600) of placebo patients. In open label studies, 0.3% (5/1889) of these SYMBYAX-treated patients had a treatment-emergent serum sodium below 130 mmol/L.

Cases of hyponatremia with serum sodium lower than 110 mmol/L) have been reported with fluoxetine. The hyponatremia appeared to be reversible when fluoxetine was discontinued. Although these cases were complex with varying possible etiologies, most were probably due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In 7 placebo controlled clinical trials in patients ≥60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

Seizures—Seizures occurred in 0.2% (4/2066) of SYMBYAX-treated patients during open-label premarketing clinical studies. No seizures occurred in the premarketing controlled SYMBYAX studies. Seizures have also been reported with both olanzapine and fluoxetine monotherapy. Therefore, SYMBYAX should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of ≥65 years of age.

Transaminase Elevations—In controlled trials, asymptomatic elevations of hepatic transaminases [ALT (SGPT), AST (SGOT), and GGT] and alkaline phosphatase have been observed with SYMBYAX. In the SYMBYAX-controlled database, ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 6.3% (31/495) of patients exposed to SYMBYAX compared with 0.5% (2/384) of the placebo patients and 4.5% (25/560) of olanzapine-treated patients. The difference between SYMBYAX and placebo was statistically significant. None of these 31 SYMBYAX-treated patients experienced jaundice and three had transient elevations >200 IU/L.

In olanzapine placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared with 0% (0/115) of the placebo patients. None of these patients experienced jaundice. In 2 of these patients, liver enzymes decreased toward normal despite continued treatment, and in 2 others, enzymes decreased upon discontinuation of olanzapine. In the remaining 2 patients, 1, seropositive for hepatitis C, had persistent enzyme elevations for 4 months after discontinuation, and the other had insufficient follow-up to determine if enzymes ever normalized.

Within the larger olanzapine premarketing database of about 2400 patients with baseline SGPT ≤90 IU/L, the incidence of SGPT elevation to >200 IU/L was 2% (59/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued. Among all 2500 patients in olanzapine clinical trial studies, approximately 1% (23/2500) discontinued treatment due to transaminase increases.

Rare postmarketing reports have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with diagnoses and predisposing conditions associated with limited hepatic functional reserve, and in patients who are taking medications associated with potential hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant liver disease (*see* Laboratory Tests).

Use in Patients with Concomitant Illness—Clinical experience with SYMBYAX in patients with concomitant systemic illnesses is limited (*see* CLINICAL PHARMACOLOGY, Renal impairment and Hepatic impairment). The following precautions for the individual components may be applicable to SYMBYAX.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical studies, SYMBYAX was associated with constipation, dry mouth, tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events were not often the basis for study discontinuations; SYMBYAX should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, a history of paralytic ileus, or related conditions.

In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse events were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse events was also significantly greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised (*see* BOX WARNING and WARNINGS).

As with other CNS-active drugs, SYMBYAX should be used with caution in elderly patients with dementia. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised (*see* BOX WARNING and WARNINGS).

SYMBYAX has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during this premarket testing.

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006256

Caution is advised when using SYMBYAX in cardiac patients and in patients with diseases or conditions that could affect hemodynamic responses (see WARNINGS, Orthostatic Hypotension).

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower dose of the fluoxetine component of SYMBYAX should be used in patients with cirrhosis. Caution is advised when SYMBYAX should be used in patients with cirrhosis. Caution is advised when using SYMBYAX in patients with diseases or conditions that could affect its metabolism (see CLINICAL PHARMACOLOGY, Hepatic Impairment and DOSING AND ADMINISTRATION, Special Populations).

Olanzapine and fluoxetine pharmacokinetics do not differ significantly in patients with mild renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not routinely required (see CLINICAL PHARMACOLOGY, Renal Impairment).

Information for Patients—Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SYMBYAX and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for SYMBYAX. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SYMBYAX:

Clinical Worsening and Suicide Risk—Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is increased or decreased. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Hyperglycemia—Patients should be advised of the potential risk of hyperglycemia-related adverse events. Patients should be monitored regularly for worsening of glucose control.

Weight Gain—Patients should be counseled that SYMBYAX may cause weight gain. Patients should have their weight monitored regularly.

Serotonin Syndrome—Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of SYMBYAX and triptans, tramadol or other serotonergic agents.

Abnormal Bleeding—Patients should be cautioned about the concomitant use of SYMBYAX and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding (see PRECAUTIONS, Abnormal Bleeding).

Alcohol—Patients should be advised to avoid alcohol while taking SYMBYAX.

Cognitive and Motor Impairment—As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them adversely.

Concomitant Medication—Patients should be advised to inform their physician if they are taking Prozac®, Prozac Weekly™, Sarafem®, fluoxetine, Zyprexa®, or Zyprexa Zydis®. Patients should also be advised to inform their physicians if they are taking or plan to take any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions.

Heat Exposure and Dehydration—Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Nursing—Patients, if taking SYMBYAX, should be advised not to breast-feed.

Orthostatic Hypotension—Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol (see WARNINGS and Drug Interactions).

Pregnancy—Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during SYMBYAX therapy.

Rash—Patients should be advised to notify their physician if they develop a rash or hives while taking SYMBYAX.

Treatment Adherence—Patients should be advised to take SYMBYAX exactly as prescribed, and to continue taking SYMBYAX as prescribed even after their mood symptoms improve. Patients should be advised that they should not alter their dosing regimen, or stop taking SYMBYAX, without consulting their physician.

Patient information is printed at the end of this insert. Physicians should discuss the drug-related risks with their patients and instruct them to read the Medication Guide before starting therapy with SYMBYAX and each time their prescription is refilled.

Laboratory Tests—Periodic assessment of transaminases is recommended in patients with significant hepatic disease (see Transaminase Elevations).

Drug Interactions—The risks of using SYMBYAX in combination with other drugs have not been systematically evaluated in psychiatric patients. The drug-drug interactions of the individual components are applicable to SYMBYAX. As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or induction, and others) is a possibility. Caution is advised if the concomitant administration of SYMBYAX and other CNS-active drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status (see CLINICAL PHARMACOLOGY, Accumulation and slow elimination).

Antihypertensive Agents—Because a small risk of inducing orthostatic hypotension exists, SYMBYAX may enhance the effects of certain antihypertensive agents (see WARNINGS, Orthostatic Hypotension).

Anti-Parkinsonian Agents—The olanzapine component of SYMBYAX may antagonize the effects of levodopa and dopamine agonists.

Benzodiazepines—Multiple doses of olanzapine did not influence the pharmacokinetics of diazepam and its active metabolite N-desmethyldiazepam. However, the coadministration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine.

When concomitantly administered with fluoxetine, the half-life of diazepam may be prolonged in some patients (see CLINICAL PHARMACOLOGY, Accumulation and slow elimination). Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

Biperiden—Multiple doses of olanzapine did not influence the pharmacokinetics of biperiden.

Carbamazepine—Carbamazepine therapy (200 mg BID) causes an approximate 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of SC carbamazepine may cause an even greater increase in olanzapine clearance.

Patients on stable doses of carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following anticonvulsant concentration fluoxetine treatment

inhibition of concomitant fluoxetine treatment

Clozapine—Elevation of blood levels of clozapine has been observed in patients receiving concomitant fluoxetine.

Electroconvulsive therapy (ECT)—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment (see Seizures).

Ethanol—Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The coadministration of ethanol with SYMBYAX may potentiate sedation and orthostatic hypotension.

Fluvoxamine—Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine C_{max} following fluvoxamine administration of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of the olanzapine component of SYMBYAX should be considered in patients receiving concomitant treatment with fluvoxamine.

Haloperidol—Elevation of blood levels of haloperidol has been observed in patients receiving concomitant fluoxetine.

Lithium—Multiple doses of olanzapine did not influence the pharmacokinetics of lithium.

There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored in patients taking SYMBYAX concomitantly with lithium.

Monoamine oxidase inhibitors—See CONTRAINDICATIONS

Phenytoin—Patients on stable doses of phenytoin have developed elevated plasma levels of phenytoin with clinical phenytoin toxicity following initiation of concomitant fluoxetine.

Pimozide—Clinical studies of pimozide with other antidepressants demonstrate an increase in drug interaction or QT_c prolongation. While a specific study with pimozide and fluoxetine has not been conducted, a similar risk of drug interactions or QT_c prolongation warrants restricting the concurrent use of pimozide and fluoxetine. Concomitant use of fluoxetine and pimozide is contraindicated (see CONTRAINDICATIONS).

Serotonergic drugs—Based on the mechanism of action of SNRIs and SSRIs, including SYMBYAX, and the potential for serotonin syndrome, caution is advised when SYMBYAX is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see WARNINGS, Serotonin Syndrome). The concomitant use of SYMBYAX with other SSRIs, SNRIs or tryptophan is not recommended (see Tryptophan).

Tryptophan—Multiple doses of olanzapine did not affect the pharmacokinetics of tryptophan.

Thioridazine—See CONTRAINDICATIONS and WARNINGS, Thioridazine.

Tricyclic antidepressants (TCAs)—Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

In two fluoxetine studies previously stable plasma levels of imipramine and desipramine have increased >2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. The dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when SYMBYAX is coadministered or has been recently discontinued (see Drugs metabolized by CYP2D6 and TCAs and Antidepressants, Sedatives, and other stimulation).

Triptans—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of SYMBYAX with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS, Serotonin Syndrome).

Tryptophan—Five patients receiving fluoxetine in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Valproate—In vitro studies using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. Thus, a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

Warfarin—Warfarin (20-mg single dose) did not affect olanzapine pharmacokinetics. Single-dose olanzapine did not alter the pharmacodynamics of warfarin.

Altered anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin (see PRECAUTIONS, Abnormal Bleeding). Patients receiving warfarin therapy should receive careful coagulation monitoring when SYMBYAX is initiated or stopped.

Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.)—Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding (see PRECAUTIONS, Abnormal Bleeding). Thus, patients should be cautioned about the use of such drugs concurrently with SYMBYAX.

Drugs metabolized by CYP2D6—In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP2D6. Thus, clinically significant interactions between olanzapine and drugs principally metabolized by this enzyme.

Fluoxetine exhibits the potent inhibition of CYP2D6, and makes individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous five weeks. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for a decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (including but not limited to, flecainide, propafenone, vitabrivine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated thioridazine plasma levels, thioridazine should not be administered with fluoxetine or within a minimum of five weeks after fluoxetine has been discontinued (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors (MAOI) and WARNINGS, Thioridazine).

Drugs metabolized by CYP3A—In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

In an in vivo interaction study between SYMBYAX and midazolam, a CYP3A substrate, fluoxetine was found to be a moderate inhibitor of midazolam metabolism. Coadministration of midazolam and fluoxetine resulted in a 3- and 4-fold increase in midazolam C_{max} and AUC, respectively, and a 2.5-fold increase in midazolam half-life. Caution should be exercised when midazolam is coadministered with fluoxetine.

Effect of olanzapine on drugs metabolized by other CYP enzymes—In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, and CYP2C19. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

The effect of other drugs on olanzapine—Fluoxetine, an inhibitor of CYP2D6, decreases olanzapine clearance a small amount (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Fluvoxamine, an inhibitor of CYP1A2, decreases olanzapine clearance (see Drug Interactions, Fluvoxamine). The effect of CYP1A2 inhibitors, such as fluvoxamine and some fluoroquinolone antibiotics, on SYMBYAX has not been evaluated. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, no dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

Drugs highly bound to plasma proteins—The in vitro binding of SYMBYAX to human plasma proteins is similar to the individual components. The interaction between SYMBYAX and other highly protein-bound drugs has not been fully evaluated. Because fluoxetine is highly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is highly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other highly bound drugs (see CLINICAL PHARMACOLOGY, Distribution and PRECAUTIONS, Drug Interactions).

Carcinogenesis, Mutagenesis, Impairment of Fertility—No carcinogenicity, mutagenicity, or fertility studies were conducted with SYMBYAX. The following data are based on findings in studies performed with the individual components.

Carcinogenesis—Olanzapine—Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, and 30/20 mg/kg/day [equivalent to 0.8 to 5 times the maximum recommended human daily dose (MRHD) on a mg/m² basis] and 0.25, 2, and 8 mg/kg/day (equivalent to 0.06 to 2 times the MRHD on a mg/m² basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, and 4 mg/kg/day (equivalent to 0.25, 1, 4, and 8 mg/kg/day (females) (equivalent to 0.1 to 2 and 0.1 to 4 times the MRHD on a mg/m² basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one study in female mice at 8 mg/kg/day (2 times the MRHD on a mg/m² basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2 to 5 times the MRHD on a mg/m² basis). In this study there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at 2 mg/kg/day or more and in rats dosed at ≥4 mg/kg/day (0.5 and 2 times the MRHD on a mg/m² basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasia has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the finding of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, Hyperprolactinemia).

Fluoxetine—The dietary administration of fluoxetine to rats and mice for two years at doses of up to 10 and 12 mg/kg/day, respectively (approximately 1.2 and 0.7 times, respectively, the MRHD on a mg/m² basis), produced no evidence of carcinogenicity.

Mutagenesis—Olanzapine—No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test, in the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Fluoxetine—Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assays, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of Fertility—SYMBYAX—Fertility studies were not conducted with SYMBYAX. However, in a repeat-dose rat toxicology study of three months duration, ovary weight was decreased in females treated with the low-dose (2 and 4 mg/kg/day (1 and 0.5 times the MRHD on a mg/m² basis), respectively) and high-dose (4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m² basis), respectively) combinations of olanzapine and fluoxetine. Decreased ovary weight, and corpora lutea/ degeneration and uterine atrophy were observed to a greater extent in the females receiving the high-dose combination than in females receiving either olanzapine or fluoxetine alone. In a 3-month repeat-dose dog toxicology study, reduced epididymal sperm and reduced testicular and prostate weights were observed with the high-dose combination of olanzapine and fluoxetine (5 and 5 mg/kg/day (9 and 2 times the MRHD on a mg/m² basis), respectively) and with olanzapine alone (5 mg/kg/day or 9 times the MRHD on a mg/m² basis).

Olanzapine—In a fertility and reproductive performance study in male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the MRHD on a mg/m² basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male-mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the MRHD on a mg/m² basis). Diestrous was prolonged and precoital time was delayed at 1.1 mg/kg/day (0.6 times the MRHD on a mg/m² basis); therefore, olanzapine may produce a delay in ovulation.

Fluoxetine—Two fertility studies conducted in adult rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m² basis) indicated that fluoxetine had no adverse effects on fertility (see Pediatric Use).

Pregnancy—Pregnancy Category C—SYMBYAX—Embryo fetal development studies were conducted in rats and rabbits with olanzapine and fluoxetine alone and in low-dose and high-dose combinations. In rats, the doses were: 2 and 4 mg/kg/day (low-dose) [1 and 0.5 times the MRHD on a mg/m² basis, respectively], and 4 and 8 mg/kg/day (high-dose) [2 and 1 times the MRHD on a mg/m² basis, respectively]. In rabbits, the doses were 4 and 4 mg/kg/day (low-dose) [4 and 1 times the MRHD on a mg/m² basis, respectively], and 8 and 8 mg/kg/day (high-dose) [8 and 2 times the MRHD on a mg/m² basis, respectively]. In these studies, olanzapine and fluoxetine were also administered alone at the high-doses (4 and 8 mg/kg/day, respectively, in the rat; 8 and 8 mg/kg/day, respectively, in the rabbit). In the rabbit, there was no evidence of teratogenicity; however, the high-dose combination produced decreases in fetal weight and retarded skeletal ossification in conjunction with maternal toxicity. Similarly, in the rat there was no evidence of teratogenicity; however, a decrease in fetal weight was observed with the high-dose combination.

In a pre- and postnatal study conducted in rats, olanzapine and fluoxetine were administered during pregnancy and throughout lactation in combination (low-dose: 2 and 4 mg/kg/day [1 and 0.5 times the MRHD on a mg/m² basis], respectively, high-dose: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m² basis], respectively, and alone: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m² basis], respectively). Administration of the high-dose combination resulted in a marked elevation in offspring mortality and growth retardation in comparison to the same doses of olanzapine and fluoxetine administered alone. These effects were not observed with the low dose combination; however, there

Case No. 3:11-cv-05630 CI
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006257

were a few cases of testicular degeneration and atrophy, depletion of epididymal sperm and infertility in the male progeny. The effects of the high-dose combination on postnatal endpoints could not be assessed due to high progeny mortality.

There are no adequate and well-controlled studies with SYMBYAX in pregnant women.

SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Olanzapine—In reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the MRHD on a mg/m^2 basis, respectively), no evidence of teratogenicity was observed. In a rat teratology study, early resorptions and decreased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD on a mg/m^2 basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the MRHD on a mg/m^2 basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled clinical studies with olanzapine in pregnant women. Seven pregnancies were observed during premarketing clinical studies with olanzapine, including two resulting in normal births, one resulting in neonatal death due to a cardiovascular defect, three therapeutic abortions, and one spontaneous abortion.

Fluoxetine—In embryo fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times the MRHD on a mg/m^2 basis, respectively) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup death during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis).

Nonteratogenic Effects—Neonates exposed to fluoxetine and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately 6-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

When treating a pregnant woman with fluoxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Labor and Delivery—*SYMBYAX*—The effect of SYMBYAX on labor and delivery in humans is unknown. Parturition in rats was not affected by SYMBYAX. SYMBYAX should be used during labor and delivery only if the potential benefit justifies the potential risk.

Olanzapine—Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery in humans is unknown.

Fluoxetine—The effect of fluoxetine on labor and delivery in humans is unknown. Fluoxetine crosses the placenta; therefore, there is a possibility that fluoxetine may have adverse effects on the newborn.

Nursing Mothers—*SYMBYAX*—There are no adequate and well-controlled studies with SYMBYAX in nursing mothers or infants. No studies have been conducted to examine the excretion of olanzapine or fluoxetine in breast milk following SYMBYAX treatment. It is recommended that women not breast-feed when receiving SYMBYAX.

Olanzapine—In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose.

Fluoxetine—Fluoxetine is excreted in human breast milk. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on fluoxetine developed crying, irritable disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the 2nd day of feeding.

Pediatric Use—Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of SYMBYAX in a child or adolescent must balance the potential risks with the clinical need.

Fluoxetine—Significant toxicity, including myotoxicity, long-term neurobehavioral and reproductive toxicity, and impaired bone development, has been observed following administration of fluoxetine animals to fluoxetine. Some of these effects occurred at clinically relevant exposures.

In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats beginning (Postnatal Day 21) through adulthood (Day 90), male and female sexual development was delayed at all doses, and growth (body weight gain, femur length) was decreased during the dosing period in animals receiving the highest dose. At the end of the treatment period, serum levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolization and hypospermia) was observed at the high dose. When animals were evaluated after a recovery period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased reactivity at all doses and learning deficit at the high dose) and reproductive functional impairment (decreased mating at all doses and impaired fertility at the high dose) were seen; in addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were found in the high dose group, indicating that the reproductive organ effects seen at the end of treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dose in this study were approximately 0.1-0.2, 1-2, and 5-10 times, respectively, the average exposure in pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat exposures to the major metabolite, norfluoxetine, were approximately 0.3-0.8, 1-8, and 3-20 times, respectively, pediatric exposure at the MRD.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg, intraperitoneal) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These doses did not affect overall growth (body weight gain or femoral length). The doses administered to juvenile mice in this study are approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area (mg/m^2) basis.

In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric MRD on a mg/m^2 basis. Because of the early dosing period in this study, the significance of these findings to the general pediatric use in humans is uncertain.

Geriatric Use—*SYMBYAX*—Clinical studies of SYMBYAX did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION).

Olanzapine—Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263 patients) were ≥65 years of age. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared with younger patients. Studies in patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared with younger patients with schizophrenia. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients, extra caution and close monitoring for cerebrovascular events should be exercised (see BOX WARNING, WARNINGS, PRECAUTIONS, Use in Patients with Concomitant Illness; and DOSAGE AND ADMINISTRATION, Special Populations).

As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient.

Fluoxetine—US fluoxetine clinical studies (10,782 patients) included 687 patients ≥65 years of age and 93 patients ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients.

ADVERSE REACTIONS: The information below is derived from a premarketing clinical study database for SYMBYAX consisting of 2066 patients with various diagnoses with approximately 1061 patient-years of exposure. The conditions and duration of treatment with SYMBYAX varied greatly and included (in overlapping categories) open label and double-blind phases of studies, outpatients and outpatients, fixed-dose and dose-titration studies, and short-term or long-term exposure.

Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories.

In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The data in the tables represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is possible that events reported during therapy were not necessarily related to drug exposure.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing clinician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Incidence in Controlled Clinical Studies—The following findings are based on the short-term, controlled premarketing studies in various diagnoses including bipolar depression.

Adverse events associated with discontinuation of treatment—Overall, 10% of the patients in the SYMBYAX group discontinued due to adverse events compared with 4.6% for placebo. Table 7 enumerates the adverse events leading to discontinuation associated with the use of SYMBYAX (incidence of at least 1% for SYMBYAX and greater than that for placebo).

Adverse events occurring at an incidence of 2% or more in controlled clinical studies—Table 8 enumerates the treatment-emergent adverse events associated with the use of SYMBYAX (incidence of at least 2% for SYMBYAX and twice or more that for placebo).

Table 8: Treatment-Emergent Adverse Events: Incidence in Controlled Clinical Studies

Body System/ Adverse Event[1]	Percentage of Patients Reporting Event		
	SYMBYAX		Placebo
	Bipolar Depression (N=86)	SYMBYAX-Controlled (N=571)	(N=477)
Body as a Whole			
Asthenia	13	15	3
Accidental injury	5	3	2
Fever	4	3	1
Cardiovascular System			
Hypertension	2	2	1
Tachycardia	2	2	0
Digestive System			
Diarrhea	19	8	7
Dry mouth	16	11	6
Increased appetite	13	16	4
Tooth disorder	1	2	1
Metabolic and Nutritional Disorders			
Weight gain	17	21	3
Peripheral edema	4	8	1
Edema	0	5	0
Musculoskeletal System			
Joint disorder	1	2	
Twitching	6	2	
Arthralgia	5	2	
Nervous System			
Somnolence	21	22	11
Tremor	9	8	3
Thinking abnormal	6	6	3
Libido decreased	4	2	1
Hyperkinesia	2	1	1
Personality disorder	2	1	1
Sleep disorder	2	1	1
Amnesia	1	3	0
Respiratory System			
Pharyngitis	4	6	3
Dyspnea	1	2	1
Special Senses			
Amblyopia	5	4	2
Ear pain	2	1	1
Otitis media	2	0	0
Speech disorder	0	2	0
Urogenital System			
Abnormal ejaculation[2]	7	2	1
Impotence[2]	4	2	1
Anorgasmia	3	1	0

[1] Included are events reported by at least 2% of patients taking SYMBYAX except the following events, which had an incidence on placebo (SYMBYAX: abdominal pain, abnormal dreams, agitation, akathisia, anorexia, anxiety, apathy, back pain, chest pain, constipation, cough increased, depression, dizziness, dysmenorrhea (adjusted for gender), dyspepsia, flatulence, flu syndrome, headache, hypertonia, insomnia, manic reaction, myalgia, nausea, nervousness, pain, palpitation, paresthesia, rash, rhinitis, sexuality, sweating, vomiting.

[2] Adjusted for gender.

Additional Findings Observed in Clinical Studies—The following findings are based on clinical studies.

Effect on cardiac repolarization—The mean increase in QT$_c$ interval for SYMBYAX-treated patients (4.9 msec) in clinical studies was significantly greater than that for placebo-treated (-0.9 msec) and olanzapine-treated (0.6 msec) patients, but was not significantly different from fluoxetine-treated (3.7 msec) patients. There were no differences between patients treated with SYMBYAX, placebo, olanzapine, or fluoxetine in the incidence of QT$_c$ prolongation (≥500 msec).

Laboratory changes—In SYMBYAX clinical studies, SYMBYAX was associated with asymptomatic mean increases in alkaline phosphatase, cholesterol, GGT, and uric acid compared with placebo (see PRECAUTIONS, Transaminase Elevations).

SYMBYAX was associated with a slight decrease in hemoglobin that was statistically significantly greater than that seen with placebo, olanzapine, and fluoxetine.

An elevation in serum prolactin was observed with SYMBYAX. This elevation was not statistically different than that seen with olanzapine (see PRECAUTIONS, Hyperprolactinemia).

Sexual dysfunction—In the pool of controlled SYMBYAX studies, there were higher rates of the treatment-emergent adverse events decreased libido, anorgasmia, impotence and abnormal ejaculation in the SYMBYAX group than in the placebo group. One case of decreased libido led to discontinuation in the SYMBYAX group. In the controlled studies that contained a fluoxetine arm, the rates of decreased libido and abnormal ejaculation in the SYMBYAX group were less than the rates in the fluoxetine group. None of the differences were statistically significant.

Sexual dysfunction, including priapism, has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible effects.

Vital signs—Tachycardia, bradycardia, and orthostatic hypotension have occurred in SYMBYAX-treated patients (see WARNINGS, Orthostatic Hypotension). The mean pulse of SYMBYAX-treated patients was reduced by 1.6 beats/min.

Additional findings—In a single 8-week randomized, double-blind, fixed-dose, study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of olanzapine in patients with schizophrenia or schizoaffective disorder, statistically significant differences among 3 dose groups were observed for the following safety outcomes: weight gain, prolactin elevation, fatigue and dizziness. Mean baseline to endpoint increase in weight (10 mg/day: 1.9 kg; 20 mg/day: 2.3 kg; 40 mg/day: 4.1 kg) was observed with significant differences between 10 vs 40 mg/day. Incidence of treatment-emergent prolactin elevation ≥24.2 ng/mL (female) or

Case No. 3AN-06-5630 Ci
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...ng 77 mg/dL (male) at any time during the trial (10 mg/day: 31.2%, 20 mg/day: 40.7%, 40 mg/day: 61.1%) with significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day; fasting ≥150 mg/dL: 1.3%, 20 mg/day: 2.1%, 40 mg/day: 6.8%) and (fasting ≥200 mg/dL: 0.6%, 20 mg/day: 1.6%, 40 mg/day: 6.0%) with significant differences between 20 vs 40 mg, was observed.

Other Events Observed in Clinical Studies—Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking SYMBYAX in clinical studies except (1) those listed in the body or footnotes of Tables 7 and 8 above or elsewhere in labeling, (2) those for which the COSTART terms were uninformative or misleading, (3) those events for which a causal relationship to SYMBYAX use was considered remote, and (4) events occurring in only 1 patient treated with SYMBYAX and which did not have a substantial probability of being acutely life-threatening.

Events are classified within body system categories using the following definitions: frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients, infrequent adverse events are those occurring in 1/100 to 1/1000 patients, and rare events are those occurring in <1/1000 patients.

Body as a Whole—Frequent: chills, infection, neck pain, neck rigidity, photosensitivity reaction, *Infrequent:* cellulitis, cyst, hernia, intentional injury, intentional overdose, malaise, moniliasis, overdose, pelvic pain, suicide attempt, *Rare:* diabetes, tolerance decreased.

Cardiovascular System—Frequent: migraine, vasodilatation, *Infrequent:* arrhythmia, bradycardia, cerebral ischemia, electrocardiogram abnormal, hypotension, QT-interval prolonged, *Rare:* angina pectoris, atrial arrhythmia, atrial fibrillation, bundle branch block, congestive heart failure, myocardial infarct, peripheral vascular disorder, T-wave inverted.

Digestive System—Frequent: increased salivation, thirst, *Infrequent:* cholelithiasis, colitis, eructation, esophagitis, gastritis, gastroenteritis, gingivitis, hepatomegaly, nausea and vomiting, peptic ulcer, periodontal abscess, stomatitis, tooth caries, *Rare:* aphthous stomatitis, fecal incontinence, gastrointestinal hemorrhage, gum hemorrhage, intestinal obstruction, liver fatty deposit, pancreatitis.

Endocrine System—Infrequent: hypothyroidism

Hemic and Lymphatic System—Frequent: ecchymosis; *Infrequent:* anemia, leukocytosis, lymphadenopathy, *Rare:* coagulation disorder, leukopenia, purpura, thrombocythemia.

Metabolic and Nutritional—Frequent: generalized edema, weight loss; *Infrequent:* alcohol intolerance, dehydration, glycosuria, hyperlipemia, hypoglycemia, hypokalemia, obesity, *Rare:* acidosis, bilirubinemia, creatinine increased, gout, hypercalcemia, hypoglycemic reaction

Musculoskeletal System—Infrequent: arthritis, bone disorder, generalized spasm, leg cramps, tendinous contracture, tenosynovitis, *Rare:* arthrosis, bursitis, myasthenia, myopathy, osteoporosis, rheumatoid arthritis.

Nervous System—Infrequent: abnormal gait, ataxia, buccoglossal syndrome, cogwheel rigidity, coma, confusion, depersonalization, dysarthria, emotional lability, euphoria, extrapyramidal syndrome, hostility, hyperthesia, hypokinesia, incoordination, movement disorder, myoclonus, neuralgia, neurosis, vertigo, *Rare:* brain stem syndrome, aphasia, dystonia, libido increased, subarachnoid hemorrhage, withdrawal syndrome.

Respiratory System—Frequent: bronchitis, lung disorder; *Infrequent:* apnea, asthma, epistaxis, hiccup, hyperventilation, laryngitis, pneumonia, voice alteration, yawn, *Rare:* emphysema, hemoptysis, laryngismus.

Skin and Appendages—Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, pruritis, psoriasis, skin discoloration, vesiculobullous rash; *Rare:* exfoliative dermatitis, maculopapular rash, seborrhea, skin ulcer.

Special Senses—Frequent: abnormal vision, taste perversion, tinnitus; *Infrequent:* abnormality of accommodation, conjunctivitis, deafness, diplopia, dry eyes, eye pain, mydosis; *Rare:* eye hemorrhage.

Urogenital System—Frequent: breast pain, menorrhagia[1], urinary frequency, urinary incontinence, urinary tract infection; *Infrequent:* amenorrhea[1], breast enlargement, breast neoplasm, cystitis, dysuria, female lactation[1], fibrocystic breast[1], hematuria, hypermenorrhea[1], leukorrhea[1], menopause[1], metrorrhagia[1], oliguria, ovarian disorder[1], polyuria, urinary retention, urinary urgency, urination impaired, vaginal hemorrhage[1], vaginal moniliasis[1], vaginitis[1], *Rare:* breast carcinoma, breast engorgement, endometrial disorder[1], gynecomastia[1], kidney calculus, uterine fibroids enlarged

[1] Adjusted for gender.

Other Events Observed with Olanzapine or Fluoxetine Monotherapy—The following adverse events were not observed in SYMBYAX treated patients during premarketing clinical studies but have been reported with olanzapine or fluoxetine monotherapy: agitated amnesia, choleastic jaundice, diabetic coma, dyskinesia, eosinophilic pneumonia, erythema multiforme, hepatitis, idiosyncratic hepatitis, jaundice, neutropenia, priapism, pulmonary embolism, rhabdomyolysis, serotonin syndrome, serum sickness-like reaction, sudden unexpected death, suicidal ideation, vasculitis, venous thromboembolic events (including pulmonary embolism and deep venous thrombosis), violent behaviors. Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

DRUG ABUSE AND DEPENDENCE: *Controlled Substance Class*—SYMBYAX is not a controlled substance.

Physical and Psychological Dependence—SYMBYAX, as with fluoxetine and olanzapine, has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical studies did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of SYMBYAX (e.g., development of tolerance, incrementation of dose, or drug-seeking behavior).

In studies in rats and rhesus monkeys designed to assess abuse and dependence potential, olanzapine alone was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence at oral doses up to 15 (rat) and 8 (monkey) times the MRHD (20 mg) on a mg/m² basis.

OVERDOSAGE: SYMBYAX—During premarketing clinical studies of the olanzapine/fluoxetine combination, overdose of both fluoxetine and olanzapine were reported in five study subjects. Four of the five subjects experienced loss of consciousness (3) or coma (1). No fatalities occurred.

Since the marked introduction of olanzapine in October 1996, adverse event cases involving combination use of fluoxetine and olanzapine have been reported to Eli Lilly and Company. An overdose of combination therapy is defined as confirmed or suspected ingestion of a dose of olanzapine 20 mg or greater in combination with a dose of fluoxetine 80 mg or greater. As of 1 February 2000, 12 cases of combination therapy overdose were reported, most of which involved additional substances. Adverse events associated with these reports included somnolence; impaired consciousness (coma, lethargy); impaired neurologic function (ataxia, confusion, convulsions, dysarthria); arrhythmias; and fatality. Fatalities have been confounded by exposure to additional substances including alcohol, thioridazine, oxycodone, and propoxyphene.

Olanzapine—In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia as well as a patient that experienced sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

Fluoxetine—Worldwide exposure to fluoxetine is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdose, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdose were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown outcome. One of the 6 fatalities was a 9-year old boy who had a history of OCD, Tourette's Syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion is the most common method of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams, which was non-lethal.

Other important adverse events reported with fluoxetine overdose (single or multiple drugs) included coma, delirium, ECG abnormalities (such as QT-interval prolongation and ventricular tachycardia, including torsades de pointes type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like events, pyrexia, stupor, and syncope.

Management of Overdose—In managing overdose, the possibility of multiple drug involvement should be considered. In case of acute overdose, establish and maintain an airway and ensure adequate ventilation, which may include intubation. Induction of emesis is not recommended as the possibility of obtundation, seizures, or dystonic reactions of the head and neck following overdose may create a risk for aspiration. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

A specific precaution involves patients who are taking or have recently taken SYMBYAX and may have ingested excessive quantities of a TCA (tricyclic antidepressant). In such cases, accumulation of the parent TCA and/or an active metabolite may increase the possibility of serious sequelae and extend the time needed for close medical observation.

Due to the large volume of distribution of olanzapine and fluoxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidote for either fluoxetine or olanzapine overdose is known. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Do not use epinephrine, dopamine, or other sympathomimetics with β-agonist activity, since beta stimulation may worsen hypotension/shock in the case of olanzapine-induced alpha blockade.

The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*.

DOSAGE AND ADMINISTRATION: SYMBYAX should be administered once daily in the evening, generally beginning with the 6-mg/25-mg capsule. While food has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of SYMBYAX has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with SYMBYAX in a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg (see CLINICAL STUDIES).

The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies. Special Populations—The starting dose of SYMBYAX is 6 mg/25 mg - 6 mg/25 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of SYMBYAX (female gender, geriatric age, nonsmoking status) or those patients who may be pharmacodynamically sensitive to olanzapine. When indicated, dose escalation should be performed with caution in these patients. SYMBYAX has not been systematically studied in patients over 65 years of age or in patients <18 years of age (see WARNINGS: Orthostatic Hypotension, PRECAUTIONS, Pediatric Use, and Geriatric Use, and CLINICAL PHARMACOLOGY, Pharmacokinetics).

Treatment of Pregnant Women During the Third Trimester—Neonates exposed to fluoxetine, a component of SYMBYAX, and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering fluoxetine in the third trimester.

Discontinuation of Treatment with SYMBYAX—Symptoms associated with discontinuation of fluoxetine, a component of SYMBYAX, and other SSRIs and SNRIs, have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually, conclusion of therapy which may minimize the risk of discontinuation syn... with this drug.

HOW SUPPLIED: SYMBYAX capsules are supplied in 3/25-, 6/25-, 6/50-, 12/25-, and 12/50-mg (mg equivalent olanzapine/mg equivalent fluoxetine*) strengths.

SYMBYAX	CAPSULE STRENGTH				
	3 mg/ 25 mg	6 mg/ 25 mg	6 mg/ 50 mg	12 mg/ 25 mg	12 mg/ 50 mg
Color	Peach & Light Yellow	Mustard Yellow & Light Yellow	Mustard Yellow & Light Yellow	Red & Light Yellow	Red & Light Grey
Capsule No.	PU3230	PU3231	PU3233	PU3232	PU3234
Identification	Lilly 3230 3/25	Lilly 3231 6/25	Lilly 3233 6/50	Lilly 3232 12/25	Lilly 3234 12/50
NDC Codes					
Bottles 30	0002 3230 30	0002 3231 30	0002 3233 30	0002 3232 30	0002 3234 30
Bottles 100		0002 3231 02	0002 3233 02	0002 3232 02	0002 3234 02
Bottles 1000		0002 3231 04	0002 3233 04	0002 3232 04	0002 3234 04
Blisters (DP)30		0002 3231 33	0002 3233 33	0002 3232 33	0002 3234 33

* Fluoxetine base equivalent.
† IDENTI-DOSE®, Unit Dose Medication, Lilly.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Keep tightly closed and protect from moisture.

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Indianapolis, IN 46285

www.SYMBYAX.com

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Medication Guide

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families, or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the US Food and Drug Administration for all antidepressants.

PV 5083 AMP

Patient information revised June 21, 2007

SYMBYAX® (olanzapine and fluoxetine HCl capsules) PV 5418 AMP

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EXHIBIT D

TO STATE OF ALASKA'S RESPONSE TO LILLY'S MOTION IN LIMINE REGARDING RECENT REGULATORY COMMUNICATIONS AND DEVELOPMENTS

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
-v-	)	CAUSE NO.
	)	3AN-06-5630 CIV
ELI LILLY & COMPANY,	)	
	)	
Defendant.	)	

The videotaped deposition upon oral examination of ROBIN PITTS WOJCIESZEK, a witness produced and sworn before me, Nancy M. Kottenstette, Notary Public in and for the County of Marion, State of Indiana, taken on behalf of the Plaintiff at the offices of Ice Miller, One American Square, Suite 3100, Indianapolis, Indiana, on December 11, 2007, at 9:37 a.m., pursuant to all applicable rules.

C O N F I D E N T I A L

Page 14

A And Symbyax.
Q Okay. Let's first talk about the first item in the notice of deposition, which is regarding Lilly's responses to a letter from FDA in March of 2007, which was the subject of Plaintiff's Second Set of Interrogatories and Document Requests to Defendants in the Alaskan litigation. And I'm going to hand you -- I'll hand you what we'll have marked as Plaintiff's Exhibit 2.
(Plaintiff's Exhibit 2 was marked for identification.)
Q And this appears to be a copy of a fax of a letter. It bears several dates on the front page, the earliest in time of which was March 28, 2007, and I noticed that on the very last page there is an electronic signature of Thomas Laughren at FDA that's dated March 28, 2007. Do you see that?
A Yes, I do.
Q Was this letter faxed to you on March 28, 2007?
A Yes, it was.
Q Okay. And once you received this letter, who did you distribute copies to?
A I distributed to individuals within the regulatory affairs department in addition to those key individuals on the team who are responsible for

Page 15

this supplemental application.
Q And who were those key members responsible for the supplemental application?
A They would be the medical director of the Zyprexa team.
Q Who was?
A Sara Corya.
Q Okay. How does she spell her last name?
A C-O-R-Y-A.
Q Okay.
A The Zyprexa global brand development team leader at the time was Eric Baclet.
Q Anyone else?
A Of course, my supervisor, Greg Brophy.
Q Okay.
A And, again, those -- there was a core team of probably over 20 individuals, too, who are involved in just the overall data package who were also communicated, but those were the key individuals.
Q Now, the letter from FDA makes reference to a number of regulatory filings with FDA by Lilly regarding Symbyax; correct?
A Correct.
Q And Symbyax is a combination drug containing both Zyprexa and Prozac; correct?

Page 16

A That's correct.
Q Or, I guess, the generic terms would be containing both olanzapine and fluoxetine; correct?
A That's correct.
Q Did I pronounce that last one correctly?
A Yes, you did.
Q Okay. And in those regulatory submissions, Lilly was seeking approval from FDA to market the combination drug Symbyax for use in treatment resistant depression or TRD; is that correct?
A That's correct.
Q Okay. And it indicates that these prior submissions had occurred in September of 2006, in November of 2006, December of 2006, and February of 2007; correct?
A That's correct.
Q Okay. And am I correct that those submissions made by Lilly to FDA included information from clinical studies of the combination drug?
A That's correct.
Q Okay. And among other things, that clinical data included information regarding changes in the blood glucose of patients who were exposed to the combination drug as compared to people who were just receiving placebo; is that correct?

Page 17

A That's correct.
Q And since those submissions occurred in the fall of 2006, the studies that contained that data would have been concluded sometime before that; correct?
A That's correct.
Q And do you know when it was that those clinical studies were done which contained the data that was submitted to FDA in the submissions that are referenced here?
A They had completed over numerous years, but the last study that completed, which was to support the indication which was HDAO, completed in the fall of 2005.
Q Fall of 2005. And that was the latest of those studies; correct?
A That's correct.
Q And what was -- what would have been the earliest of those studies?
A I don't recall. They were -- some of the studies that we included in the submission were also submitted with the original application for Symbyax in 2002.
Q Okay. I want to make sure I understand. So that the submissions that occurred in the fall of 2006 to support the additional indication for

Page 18

treatment resistant depression included data from studies that had been conducted in support of the original Symbyax submission in 2002 as well as other studies after that point, the last of which had been completed by the fall of 2005. Is that a fair statement?
A That's a fair statement, yes.
Q Okay. And the earliest of those studies that had been done in support of the 2002 submission, I presume, would have been completed sometime before 2002; is that correct?
A That's correct.
Q Do you know when it was that they would have been completed?
A I don't know the exact dates, but, typically, they're done about six months prior to a submission.
Q So probably 2001 sometime?
A Some of them were, yes.
Q Okay. Do you know what the date -- at least a month, date of the 2000 submission for Symbyax?
A If I recall, it was November of 2002. It was prior to my responsibility --
Q Okay.
A -- around the application.

Page 19

Q Okay. So it'd be fair to say that the data that's being referenced here in this letter is the data that was generated between, say, early 2002 and 2005 in that time frame; correct?
A Majority of the data, yes.
Q Okay. Now, in order to approve Symbyax for use in treatment resistant depression, FDA needed to approve the labeling for the drug; correct?
A Correct.
Q Okay. And on the first page of the letter in -- there's a bolded heading that states "Updated Information on Risks of Weight Gain, Hyperglycemia, and Hyperlipidemia." Do you see that?
A Yes, I do.
Q In the first paragraph right after that heading, it states "A primary concern with this application and the primary basis for our not taking a final action is our view that we lack important safety information needed to adequately update the labeling with all relevant risk information. In particular, we are concerned that the labeling is deficient with regard to information about weight gain, hyperglycemia, and hyperlipidemia that is associated with olanzapine use, whether taken alone or in combination with fluoxetine. You

Page 20

must fully address these concerns before we will be able to take a final action on this application."
Do you see that language that I read?
A Yes.
Q And I read it correctly; correct?
A Yes, you did.
Q And it was clear, was it not, that the concerns about weight gain, hyperglycemia, and hyperlipidemia that it's referring to in connection with Symbyax had to deal with the Zyprexa portion of the drug and not the Prozac portion; correct?
A That's correct.
Q Okay. And, in fact, FDA has not requested any change in the labeling of Prozac regarding weight gain, hyperglycemia, and hyperlipidemia recently, have they?
A No, they have not.
Q Okay. Now, if I could direct your attention to the following page, in the first full paragraph on that page, FDA is talking about the data that they would like to see presented in the labeling; correct?
MR. KANTRA: Objection to the form.
A What they're asking for is regarding -- if you look at the previous paragraph, it's an extension of

Page 21

what type of information that they would like to see prior to making any labeling change.
Q Ah, okay. Good point. So the FDA is telling you before they can approve a labeling change to allow for a further indication of treatment resistant depression they wanted to see the type of data that they're referring to in the first full paragraph on page 2; correct? Is that a fair statement?
A That's -- that's a fair statement.
Q Okay.
A Yes.
Q And what they said in that paragraph was "Regarding data displays, an overall strategy will be to subgroup patients on the basis of their status at baseline so that clinicians can better understand the risks associated with treatment of patients falling into different risk categories. For example, we note that your proposed Symbyax label includes information only on proportions of patients who are relatively normal at baseline with regard to random blood glucose (less than 140 milligrams per deciliter); i.e, 2.9 percent of such patients receiving OFC had on-treatment levels greater than or equal to

EXHIBIT E

TO STATE OF ALASKA'S RESPONSE TO LILLY'S MOTION IN LIMINE REGARDING RECENT REGULATORY COMMUNICATIONS AND DEVELOPMENTS

006264

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

AMERICAN DIABETES ASSOCIATION
AMERICAN PSYCHIATRIC ASSOCIATION
AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
NORTH AMERICAN ASSOCIATION FOR THE STUDY OF OBESITY

Antipsychotic medications are an important component in the medical management of many psychotic conditions. With the introduction of the second-generation antipsychotics (SGAs) over the last decade, the use of these medications has soared. Although the SGAs have many notable benefits compared with their earlier counterparts, their use has been associated with reports of dramatic weight gain, diabetes (even acute metabolic decompensation, e.g., diabetic ketoacidosis [DKA]), and an atherogenic lipid profile (increased LDL cholesterol and triglyceride levels and decreased HDL cholesterol).

Because of the close associations between obesity, diabetes, and dyslipidemia and cardiovascular disease (CVD), there is heightened interest in the relationship between the SGAs and the development of these major CVD risk factors. To gain a better understanding of this relationship, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity convened a consensus development conference 19–21 November 2003 on the subject of antipsychotic drugs and diabetes. An eight-member panel heard presentations from 14 experts drawn from the areas of psychiatry, obesity, and diabetes. Presentations were also made by a representative from the U.S. Food and Drug Administration (FDA) and by representatives from the AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, and Pfizer pharmaceutical companies. In addition, before the conference, the consensus panel was given copies of most of the known peer-reviewed, English language clinical studies published in this area, as well as additional articles from animal studies, other papers and abstracts were reviewed at the conference.

With this information, the panel developed a consensus position on the following questions:

1. What is the current use of antipsychotic drugs?
2. What is the prevalence of obesity, prediabetes, and type 2 diabetes in the populations in which the SGAs are used?
3. What is the relationship between the use of these drugs and the incidence of obesity or diabetes?
4. Given the above risks, how should patients be monitored for the development of significant weight gain, dyslipedemia, and diabetes, and how should they be treated if diabetes develops?
5. What research is needed to better understand the relationship between these drugs and significant weight gain, dyslipedemia, and diabetes?

1. WHAT IS THE CURRENT USE OF ANTIPSYCHOTIC DRUGS?

— Antipsychotic medications (Table 1) are the mainstay of treatment for psychotic illnesses and are also widely used in many other psychiatric conditions. Introduced ~50 years ago, these medications have helped millions of people manage their symptoms. For people who respond well, antipsychotics can mean the difference between leading an engaged, fulfilling community life and being severely disabled.

The first-generation antipsychotics (FGAs) are still widely available and are effective at treating positive symptoms of psychosis, such as hallucinations and delusions. FGAs do not, however, adequately alleviate many other common and important aspects of psychotic illness, such as negative symptoms (e.g., withdrawal, apathy, poverty of speech), cognitive impairment, and affective symptoms. In addition, all FGAs can produce significant extrapyramidal side effects at clinically effective doses. These side effects, which include dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia, can make treatment intolerable for some people, leading to subjective distress, diminished function, stigma, and nonadherence.

The effort to find more effective medications with fewer and less-severe side effects led to the development of the SGAs, often referred to as the "atypical antipsychotics." SGAs have fewer or no extrapyramidal side effects at clinically effective doses. Many of these newer medications are also more effective than the older agents at treating the negative, cognitive, and affective symptoms of psychotic illnesses.

The six currently available SGAs vary in their efficacy, formulation, biochemistry, receptor binding, and side effect profiles. One of them, clozapine, is clearly the most effective antipsychotic. However, clozapine is only indicated after other medications have failed or in patients at high risk for suicidal behavior, largely because it can cause agranulocytosis.

In general, SGAs are better tolerated and more effective than the FGAs. Aside from clozapine, they have become the first-line agents for their indicated use and

From the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity.
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Abbreviations: CVD, cardiovascular disease; DKA, diabetic ketoacidosis; FDA, Food and Drug Administration; FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics.

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Exhibit E, Page 2 of 7
SOA Response to Lilly Motion in Limine Regarding Recent Regulatory Communications and Developments
Case No. 3AN-06-5630 CI

Zyprexa MDL Plaintiffs' Exhibit No 02368

006265

ZY200381764
Page 1

Table 1—*Antipsychotic medications*

	Generic name	Trade name	Year approved
Commonly used FGAs	Chlorpromazine	Thorazine	—
	Perphenazine	Trilafon	—
	Trifluoperazine	Stelazine	—
	Thiothixene	Navane	—
	Haloperidol	Haldol	—
	Fluphenazine	Prolixin	—
SGAs	Clozapine	Clozaril	1989
	Risperidone	Risperdal	1993
	Olanzapine	Zyprexa	1996
	Quetiapine	Seroquel	1997
	Ziprasidone	Geodon	2001
	Aripiprazole	Abilify	2002

are increasingly being used off-label. In current practice, people who are likely to be treated with an SGA include those with schizophrenia spectrum disorders, bipolar disorder, dementia, psychotic depression, autism, and developmental disorders and, to a lesser extent, individuals with conditions such as delirium, aggressive behavior, personality disorders, and posttraumatic stress disorder. These psychiatric conditions are common and often require lifelong treatment. In the U.S., the prevalence of schizophrenia and related conditions is ~ 1%, the prevalence of bipolar disorders is ~ 2%, and the prevalence of major depression is ~ 8%. The SGAs are therefore widely used medications, and their use has important public health ramifications.

2. WHAT IS THE PREVALENCE OF OBESITY, PRE-DIABETES, AND TYPE 2 DIABETES IN THE POPULATIONS IN WHICH THE SGAs ARE USED?

— It is difficult to determine whether the prevalence of these metabolic disorders is increased in these psychiatric populations independent of drug treatment. Most of the available data are derived from studies of individuals with schizophrenia, and even in this condition, the evidence is very limited. Data from most studies suggest that the prevalence of both diabetes and obesity among individuals with schizophrenia and affective disorders is ~1.5–2.0 times higher than in the general population. Many characteristics of people with schizophrenia, such as sedentary behavior, may contribute to the apparently higher prevalence of metabolic abnormalities. However, none of these studies controlled for all of the major diabetes risk factors. For example, BMI and family history of diabetes were rarely determined, nor were the control populations appropriately matched for these and other variables. Thus, it is unclear whether psychiatric conditions per se, independent of other known diabetes risk factors, account for the increased prevalence.

There are limited data evaluating the metabolic profile and diabetes risk of drug-naïve subjects with schizophrenia. In a small cohort of adults with schizophrenia untreated with medications, visceral fat content (which is correlated with insulin resistance) was threefold higher than in age- and BMI-matched control subjects. In another study, the same investigators found that drug-naïve patients presenting with their first episode of schizophrenia had an increased prevalence of impaired fasting glucose, were more insulin resistant, and had higher plasma levels of glucose, insulin, and cortisol than did matched control subjects.

Overall, the limited amount of epidemiological data suggest an increased prevalence of obesity, impaired glucose tolerance, and type 2 diabetes in people with psychiatric illness. Whether this is a function of the illness itself versus its treatment is unknown. Studies using the proper diagnoses of glucose intolerance and more complete risk factor characterization are necessary in order to resolve this issue.

3. WHAT IS THE RELATIONSHIP BETWEEN THE USE OF THESE DRUGS AND THE INCIDENCE OF OBESITY OR DIABETES?

— Recognition of an association between SGAs and diabetes was first derived from case reports of severe, sometimes fatal, acute diabetic decompensation, including DKA. Subsequent drug surveillance and retrospective database analyses suggest there is an association between specific SGAs and both diabetes and obesity. This potential relationship is of considerable clinical concern because obesity and diabetes are important risk factors for CVD, and the relative risk of CVD mortality is significantly greater in people with psychiatric disorders than in the general population. High rates of smoking and physical inactivity may also contribute to the excess mortality. Therefore, if SGA therapy further increases the risk for obesity and type 2 diabetes, this should be of major clinical concern.

Although there are significant shortcomings in many of the studies examining the relationships between the SGAs and obesity or diabetes, clear-cut trends can be identified.

Obesity

There is considerable evidence, particularly in patients with schizophrenia, that treatment with SGAs can cause a rapid increase in body weight in the first few months of therapy that may not reach a plateau even after 1 year of treatment. There is, however, considerable variability in weight gain among the various SGAs (Table 2). At 10 weeks of therapy, estimated average weight gain with drug treatment compared with placebo varies from ~0.5 to 5.0 kg. Limited data suggest that in humans, most of the weight gained

Table 2—*SGA's and metabolic abnormalities*

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+ + +	+	+
Olanzapine	+ + +	+	+
Risperidone	+ +	D	D
Quetiapine	+ +	D	D
Aripiprazole*	+/−	−	−
Ziprasidone*	+/−	−	−

+ = increase effect; − = no effect; D = discrepant results. *Newer drugs with limited long-term data.

Exhibit E, Page 3 of 7
SOA Response to Lilly Motion in Limine Regarding Recent
Regulatory Communications and Developments
Case No. 3AN-06-5630 CI

Zyprexa MDL Plaintiffs' Exhibit No 02368

006266

ZY200381765
Page 2

is fat. Data derived from a canine model indicated that certain SGAs increase total visceral fat mass and intrahepatic lipid content.

The mechanism(s) responsible for weight gain associated with SGA therapy are unknown. Weight gain occurs when more energy is ingested than is expended. Therefore, weight gain is due to increased energy intake, decreased energy expenditure, or both. Even a small, chronic imbalance between energy intake and expenditure can lead to large changes in body weight over time. For example, ingestion of ~500 kcal/day more than is expended can account for the largest average weight gain reported with SGA therapy (4.5 kg at 10 weeks). This amount of daily increase in energy intake represents the calories in a normal-size candy bar plus a soda or in an ice cream dessert. Hunger and satiety may be altered in people taking SGAs because of the known binding affinities of these drugs to serotonin, norepinephrine, dopamine, and particularly histamine-H1 receptors. All of these receptors have been implicated in the control of body weight.

Weight gain and changes in body composition may account for many of the purported metabolic complications associated with SGA therapy, e.g., insulin resistance, pre-diabetes, diabetes, and dyslipidemia. A possible direct effect of SGAs on β-cell function and insulin action in liver and muscle tissue could also be involved, as discussed below.

Diabetes

Numerous case reports have documented the onset or exacerbation of diabetes, including the occurrence of hyperglycemic crises, following initiation of therapy with many of the SGAs.

Several of these events occurred within a few weeks of initiating drug treatment. In some, but not all cases, hyperglycemia promptly resolved after the medication was discontinued. Several reports documented recurrent hyperglycemia after another challenge with the same drug. Additional cases of diabetes or hyperglycemia have been reported through MedWatch into the FDA's Adverse Event Reporting System.

Large retrospective cohort studies have been reported that estimate the prevalence of diabetes in patients using SGAs. These reports relied on a variety of methods for determining the diagnosis of diabetes, such as ICD-9 codes and data on prescriptions for diabetes medications. In addition, several cross-sectional studies of patients taking different SGAs, "switch studies" of patients changed from one medication to another, and one prospective randomized controlled trial evaluating SGA therapy on parameters of insulin sensitivity and glycemic control have been conducted. Despite limitations in study design, the data consistently show an increased risk for diabetes in patients treated with clozapine or olanzapine compared with patients not receiving treatment with FGAs or with other SGAs. The risk in patients taking risperidone and quetiapine is less clear; some studies show an increased risk for diabetes, while others do not. The two most recently approved SGAs, aripiprazole and ziprasidone, have relatively limited epidemiological data, but available clinical trial experience with these drugs has not shown an increased risk for diabetes (Table 2).

One possible mechanism for hyperglycemia is impairment of insulin action (i.e., insulin resistance). Drug-induced insulin resistance may occur because of weight gain or a change in body fat distribution or by a direct effect on insulin-sensitive target tissues. Patients treated with olanzapine and clozapine have higher fasting and postprandial insulin levels than patients treated with FGAs, even after adjusting for body weight. To date, studies in humans have not shown adverse effects of any antipsychotic medication on β-cell function, but this issue has not been adequately studied in individuals with psychiatric illnesses.

Dyslipidemia

An additional related consequence of SGA use is their effect on serum lipids. Although the data are limited, the available evidence suggests that changes in serum lipids are concordant with changes in body weight. Clozapine and olanzapine, which produce the greatest weight gain, are associated with the greatest increases in total cholesterol, LDL cholesterol, and triglycerides and with decreased HDL cholesterol. Aripiprazole and ziprasidone, which are associated with the least amount of weight gain, do not seem to be associated with a worsening of serum lipids. Risperidone and quetiapine appear to have intermediate effects on lipids (Table 2).

[redacted] cited above, a number of factors should be considered when choosing among the antipsychotic medications. These include the nature of the patient's psychiatric condition, specific target signs and symptoms, past history of drug response (both therapeutic and adverse), patient preference, history of treatment adherence, medication effectiveness, psychiatric and medical comorbidities, availability of appropriate formulations (e.g., fast-dissolving oral, short- or long-acting intramuscular), need for special monitoring, and cost of and access to medications. Nonetheless, the risks of obesity, diabetes, and dyslipidemia have considerable clinical implications in this patient population and should also influence drug choice.

Even for those medications associated with an increased risk of metabolic side effects, the benefit to specific patients could outweigh the potential risks. For example, clozapine has unique benefits for treatment-refractory patients and those at significant risk for suicidal behavior. Since treatment response in many psychiatric conditions is heterogeneous and unpredictable, physicians and patients can benefit from the availability of a broad array of different therapeutic agents.

4. GIVEN THE ABOVE RISKS, HOW SHOULD PATIENTS BE MONITORED FOR THE DEVELOPMENT OF SIGNIFICANT WEIGHT GAIN, DYSLIPIDEMIA, AND DIABETES, AND HOW SHOULD THEY BE TREATED IF DIABETES DEVELOPS? —

Given the serious health risks, patients taking SGAs should receive appropriate baseline screening and ongoing monitoring. Clinicians who prescribe SGAs for patients with psychiatric illnesses should have the capability of determining a patient's height and weight (BMI) and waist circumference. These values should be recorded and tracked for the duration of treatment. Clinicians should also encourage patients to monitor and chart their own weight. It is particularly important to monitor any alteration in weight following a medication change. The patients' psychiatric illness should not discourage clinicians from addressing the metabolic

Exhibit E, Page 4 of 7
SOA Response to Lilly Motion in Limine Regarding Recent Regulatory Communications and Developments
Case No. 3AN-06-5630 CI

Zyprexa MDL Plaintiffs' Exhibit No. 02368

006267

ZY200381766
Page 3

Table 3—*Monitoring protocol for patients on SGAs**

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

*More frequent assessments may be warranted based on clinical status

complications for which these patients are at increased risk.

Baseline monitoring

The panel recommends that baseline screening measures be obtained before, or as soon as clinically feasible after, the initiation of any antipsychotic medication (Table 3). These include

- Personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease
- Weight and height (so that BMI can be calculated)
- Waist circumference (at the level of the umbilicus)
- Blood pressure
- Fasting plasma glucose
- Fasting lipid profile

These assessments can determine if the patient is overweight (BMI 25.0–29.9) or obese (BMI >30), has pre-diabetes (fasting plasma glucose 100–125 mg/dl) or diabetes (fasting plasma glucose ≥126 mg/dl), hypertension (blood pressure >140/90 mmHg), or dyslipidemia. If any of these conditions are identified, appropriate treatment should be initiated. Psychiatrists should not hesitate to refer the patient to the appropriate health care professional or specialist knowledgeable about these disorders.

The panel recommends that nutrition and physical activity counseling be provided for all patients who are overweight or obese, particularly if they are starting treatment with an SGA that is associated with significant weight gain. Referral to a health care professional or program with expertise in weight management may also be appropriate.

Table 4—*DKA clinical presentation*

Rapid onset of
- Polyuria, polydipsia
- Weight loss
- Nausea, vomiting
- Dehydration
- Rapid respiration
- Clouding of sensorium, even coma

Health professionals, patients, family members, and caregivers should be aware of the signs and symptoms of diabetes and especially those associated with the acute decompensation of diabetes such as DKA (Table 4). The latter is a life-threatening condition and always requires immediate treatment. Patients, family members, and caregivers also need to know that treatment with some SGAs may be associated with significant weight gain and a heightened risk of developing diabetes and dyslipidemia. For patients with, or at higher risk for, diabetes and in those treated with other medications that may increase these risks (e.g., valproate, lithium, Depo-Provera), it may be preferable to initiate treatment with an SGA that appears to have a lower propensity for weight gain and glucose intolerance (Table 2). Potential for weight gain should also be considered in the choice of other psychiatric and nonpsychiatric medications.

Follow-up monitoring

The patient's weight should be reassessed at 4, 8, and 12 weeks after initiating or changing SGA therapy and quarterly thereafter at the time of routine visits (Table 3). If a patient gains ≥5% of his or her initial weight at any time during therapy, one should consider switching the SGA. In such a situation, the panel recommends cross-titration to be the safest approach; abrupt discontinuation of an antipsychotic drug should generally be avoided. When switching from one antipsychotic drug to another, it is preferable to discontinue the current medication in a gradual fashion. The profile of the subsequent drug will determine the initial dose and escalation strategy. Particular consideration should be given before discontinuing clozapine because of the potential for serious psychiatric sequelae.

Fasting plasma glucose, lipid levels, and blood pressure should also be assessed 3 months after initiation of antipsychotic medications. Thereafter, blood pressure and plasma glucose values should be obtained annually or more frequently in those who have a higher baseline risk for the development of diabetes or hypertension. In those with a normal lipid profile, repeat testing should be performed at 5-year intervals or more frequently if clinically indicated.

Although limited data are available in children and adolescents regarding the risks of diabetes when SGAs are given, these patients should have their height, in addition to weight, measured at regular intervals and their BMI calculated. BMI percentile adjusted for age and sex should be used to determine if excessive weight gain has occurred, and if present, a change in therapy should be considered.

For people who develop worsening glycemia or dyslipidemia while on antipsychotic therapy, the panel recommends considering switching to an SGA that has not been associated with significant weight gain or diabetes (Table 2). All patients with diabetes should be referred to an American Diabetes Association–recognized diabetes self-management education program, if available. Referral to a clinician with experience treating people with diabetes is recommended. These patients should carry diabetes identification.

Immediate care or consultation is required for patients with symptomatic or severe hyperglycemia (glucose values >300 mg/dl), symptomatic hypoglycemia, or glucose levels ≤60 mg/dl, even in the absence of symptoms. The presence of

Exhibit E, Page 5 of 7
SOA Response to Lilly Motion in Limine Regarding Recent
Regulatory Communications and Developments
Case No. 3AN-06-5630 CI

Zyprexa MDL Plaintiffs' Exhibit No 02368

006268

ZY200381767
Page 4

symptoms of DKA (Table 4), requires immediate evaluation and treatment.

Blood pressure, lipid, and glycemic goals of therapy for people with diabetes apply equally to those who also have psychiatric disorders. However, all goals need to be individualized. The benefits and risks of different therapeutic agents used in the treatment of diabetes and its comorbidities should be considered in the context of the patient's psychiatric condition and treatment.

In summary, the panel recommends the following:

- Consideration of metabolic risks when starting SGAs
- Patient, family, and care giver education
- Baseline screening
- Regular monitoring
- Referral to specialized services, when appropriate

5. WHAT RESEARCH IS NEEDED TO BETTER UNDERSTAND THE RELATIONSHIP BETWEEN THESE DRUGS AND SIGNIFICANT WEIGHT GAIN, DYSLIPIDEMIA, AND DIABETES?

— Evidence for weight gain and abnormalities of glucose and lipid metabolism in patients taking SGAs is in part derived from case-control studies, pharmacovigilance (e.g., through MedWatch), and database reviews. Many of these studies suffer from their retrospective nature, heterogeneity of methodology, selection or ascertainment bias, and absence of appropriate or well-characterized control subjects. Comparison studies among SGAs are also limited by relatively short periods of study, by failure to control for a possible treatment sequence bias in "switchover" studies, and by not always using clinically equivalent dosages of the medications.

Trials with SGAs should be randomized and controlled, preferably using drug-naive subjects. Weight gain and measures of glucose and lipid metabolism should be thoroughly evaluated. Study subjects should be well-characterized in terms of their baseline risk factors for diabetes, obesity, and lipid disorders and their degree of baseline impairment in insulin sensitivity and β-cell function. The duration of exposure to the various SGAs should be carefully controlled. Future research studies should focus on the following:

- Baseline body composition in untreated patients with psychiatric disorders and changes that occur during treatment with SGAs need to be better characterized. This would include measures of fat versus fat-free mass and visceral and subcutaneous adipose stores, using valid methods to measure body fat (e.g., magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry).
- The contribution of altered neuroendocrine function (e.g., hypothalmic-pituitary-adrenal axis activation) to alterations in body composition and abnormalities in glucose and lipid metabolism needs further study to distinguish the acute effects of stress from the underlying disease process.
- Studies are needed that examine glucose and lipid metabolism as they relate to alterations in insulin sensitivity in peripheral and hepatic tissues (e.g., euglycemic-hyperinsulinemic clamp with labeled glucose infusions), alterations in β-cell function (hyperglycemic clamp or frequently sampled intravenous glucose tolerance test), and alterations in lipid metabolism (using tracer infusions).
- Large prospective studies should be conducted to identify baseline and early treatment factors that predict the later occurrence of abnormalities in body weight and composition and disorders of glucose and lipid metabolism during treatment with these drugs.
- Additional studies are needed to identify whether there are baseline characteristics that predict acute, life-threatening complications (e.g., DKA, pancreatitis).
- Additional data are needed to determine whether the risks of therapy are increased in certain ethnic groups (e.g., African Americans).
- Studies determining the effect of SGAs in various psychiatric disorders are needed to clarify the disease-related risk for the development of weight gain and metabolic disturbances.
- Alterations in energy intake and expenditure as contributors to weight gain in the psychiatric population and how these processes are altered by treatment with SGAs should be studied.
- Studies are needed to determine [illegible] and glucose [illegible] metabolism are due to central nervous system or peripheral tissue actions of the SGAs. Valuable information on the direct effects of SGAs on different body tissue compartments might be obtained from studies in appropriate animal models.
- Studies of the genetic markers that are associated with, and may be causally related to, the metabolic disturbances occurring in treated patients with psychiatric disorders (e.g., 5-HT_{2C}, histamine-H1 receptor alleles) are needed.

SUMMARY — The SGAs are of great benefit to a wide variety of people with psychiatric disorders. As with all drugs, SGAs are associated with undesirable side effects. One constellation of adverse effects is an increased risk for obesity, diabetes, and dyslipidemia. The etiology of the increased risk for metabolic abnormalities is uncertain, but their prevalence seems correlated to an increase in body weight often seen in patients taking an SGA. Direct drug effects on β-cell function and insulin action could also be involved, since there is insufficient information to rule out this possibility. In the general population, being overweight or obese also carries a much higher risk of diabetes and dyslipidemia.

These three adverse conditions are closely linked, and their prevalence appears to differ depending on the SGA used. Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine appear to have intermediate effects. Aripiprozole and ziprasidone are associated with little or no significant weight gain, diabetes, or dyslipidemia, although they have not been used as extensively as the other agents.

The choice of SGA for a specific patient depends on many factors. The likelihood of developing severe metabolic disease should also be an important consideration. When prescribing an SGA, a commitment to baseline screening and follow-up monitoring is essential in order to mitigate the likelihood of developing CVD, diabetes, or other diabetes complications.

Exhibit E, Page 6 of 7
SOA Response to Lilly Motion in Limine Regarding Recent Regulatory Communications and Developments
Case No. 3AN-06-5630 CI

Zyprexa MDL Plaintiffs' Exhibit No. 02368

006269

ZY200381768
Page 5

APPENDIX

Consensus panel

Eugene Barrett, MD, PhD, Chair, Lawrence Blonde, MD, Stephen Clement, MD, John Davis, MD, John Devlin, MD, John Kane, MD, Samuel Klein, MD, William Torrey, MD.

Support

This conference was supported in part by an educational grant from AstraZeneca, Bristol-Myers Squibb Co., Janssen Pharmaceutical Products, Eli Lilly and Co. and Pfizer, Inc.

Disclosure

These panel members have declared receiving research grant support, honoraria, or consulting fees from the following companies in the previous year. Eugene Barrett (BMS, Pfizer), Lawerence Blonde (BMS, Lilly, Novartis, Pfizer), Stephen Clement (Pfizer); John Kane (AstraZeneca, BMS, Janssen, Lilly, Novartis, Pfizer).

Presenters at the conference

David Allison, PhD, Richard Bergman, PhD, John Buse, MD, PhD, Patrizia Cavazzoni, MD, Fred Fiedorek, MD, Rohan Ganguli, MD, Andrew Greenspan, MD, David Kendall, MD, Ron Leonge, MD, Antony Loebel, MD, Patrick Lustman, PhD, Herbert Meltzer, MD, John Newcomer, MD, Judy Racoosin, MD, Bryan Roth, MD, Michael Sernyak, MD, Jogin Thakore, MB, Donna Wirshing, MD, William Wirshing, MD.

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Exhibit E, Page 7 of 7
SOA Response to Lilly Motion in Limine Regarding Recent Regulatory Communications and Developments
Case No. 3AN-06-5630 CI

Zyprexa MDL Plaintiffs' Exhibit No 02368

006270

ZY200381769
Page 6

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By Peggy S. Crowe
Date 2/14/08

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006271

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

Filed in the Trial Courts
STATE OF ALASKA, THIRD DISTRICT
FEB 11 2008
Clerk of the Trial Courts
By _____ Deputy

Plaintiff,

vs.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-5630 CIV

NOTICE OF FILING PLAINTIFF'S OBJECTIONS TO DEFENDANT'S PAGE/LINE COUNTER DESIGNATIONS UNDER SEAL

On this date the State of Alaska is filing a pleading titled "Plaintiff's Objections to Defendant's Page/Line Counter Designations." Because one or more exhibits filed with this pleading may be confidential documents under the Court's April 6, 2007 oral ruling, the State of Alaska is submitting this pleading and the attached exhibits under seal.

DATED this 11 day of February, 2008.

FELDMAN ORLANSKY & SANDERS
Counsel for Plaintiff

BY Eric Sanders (ESD)
Eric T. Sanders
AK Bar No. 7510085

Separate Envelope Filed

See Judge Rindner's order of 6/13/08, pages 18 & 19, #12

Documents unsealed clwade 8/11/08

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Case # 06-05630 CR/CI

Case Title: SOA v. Lilly & Co.

Type of Document Enclosed: 1st Opp to Def. Pose/Lone Counsel Desination

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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

Filed in the Trial Courts
STATE OF ALASKA, THIRD DISTRICT

FEB 11 2008

Clerk of the Trial Courts
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STATE OF ALASKA,

Plaintiff,

vs.

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Defendant.

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Eric T. Sanders
AK Bar No. 7510085

See Judge Rindner's order of 4/13/08 pages 18:19, #13

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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

PLAINTIFF'S OBJECTIONS TO DEFENDANT'S PAGE/LINE COUNTER DESIGNATIONS

Plaintiff respectfully submits its specific objections to Defendant's Counter Designations of deposition testimony on the grounds set forth below:

Exhibit 1; Deposition of Charles Beasley, Jr. M.D (Vol. I)

START (PAGE:LINE)	END (PAGE:LINE)	OBJECTION
83:2	83:8	Non-responsive
109:15	109:16	Non-responsive
114:9	114:24	Not necessary for fairness
142:24	143:7	Not necessary for fairness
143:21	143:23	Not necessary for fairness
144:1	144:12	Not necessary for fairness
148:5	148:18	Non-responsive
149:20	149:24	Non-responsive
184:23	185:15	Not necessary for fairness

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006272B

Exhibit 1 Charles Beasley Jr. M.D | Exhibit 2 harles Beasley Jr. M.D | Alan Breier, M.D. | Alan Breier, M.D.

186:24	187:10	Not necessary for fairness
202:17	203:9	Not necessary for fairness
208:20	209:10	Not necessary for fairness
210:2	210:5	Not necessary for fairness
210:6	210:11	Not necessary for fairness
210:16	211:13	Not necessary for fairness
234:5	234:17	Not necessary for fairness; non-responsive
235:8	235:12	Non-responsive
236:2	236:2	Non-responsive
236:19	236:22	Non-responsive
243:24	243:24	Non-responsive
248:5	248:10	Non-responsive
253:11	253:13	Non-responsive
258:24	258:24	Non-responsive
272:18	272:22	Not necessary for fairness; lack of foundation; speculation
391:3	391:7	Not necessary for fairness
391:10	391:18	Not necessary for fairness

Exhibit 2; Deposition of Charles Beasley, Jr. M.D (Vol. II)

START (PAGE:LINE)	END (PAGE:LINE)	OBJECTION
446:13	446:16	Non-responsive

Exhibit 3; Deposition of Alan Breier, M.D., (Vol. 1)

START (PAGE:LINE)	END (PAGE:LINE)	OBJECTION
27:14	28:12	Not necessary for fairness
95:6	95:23	Non-responsive
96:5	96:8	Not necessary for fairness
96:11	97:11	Not necessary for fairness

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97:14	98:12	Not necessary for fairness
98:15	98:16	Not necessary for fairness
98:19	100:20	Not necessary for fairness
105:21	105:24	Non-responsive
112:4	112:10	Non-responsive
122:1	122:17	Not necessary for fairness; speculation
140:12	140:14	Not necessary for fairness
140:17	140:24	Not necessary for fairness
141:3	141:18	Not necessary for fairness
163:22	164:3	Not necessary for fairness
164:6	164:10	Not necessary for fairness
164:16	165:13	Not necessary for fairness
189:23	190:8	Non-responsive
201:10	202:2	Non-responsive
222:1	223:1	Non-responsive
291:9	291:24	Non-responsive
304:4	304:17	Non-responsive
352:21	352:22	Non-responsive
353:6	353:12	Non-responsive

Exhibit 4; Deposition of Alan Breier, M.D. (Vol. II)

START (PAGE:LINE)	END (PAGE:LINE)	OBJECTION
428:17	428:22	Non-responsive
428:23	429:8	Non-responsive
433:10	433:21	Non-responsive
451:15	451:16	Non-responsive
451:19	452:17	Non-responsive
457:12	458:10	Non-responsive
480:4	480:6	Non-responsive
526:6	526:9	Non-responsive
526:12	526:22	Non-responsive

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Exhibit 5; Deposition of John Lechleiter, Ph.D.

START (PAGE:LINE)	END (PAGE:LINE)	OBJECTION
92:17	92:19	Non-responsive
111:23	112:9	Non-responsive
149:3	14912	Non-responsive
267:16	268:11	Non-responsive
280:10	280:18	Non-responsive
286:22	287:2	Non-responsive
293:7	293:10	Non-responsive
300:13	300:21	Non-responsive

Exhibit 6; Deposition of David Thomas Noesges

START (PAGE:LINE)	END (PAGE:LINE)	OBJECTION
165:10	165:11	Non-responsive
173:2	173:4	No preceding question
173:19	173:21	No preceding question
195:24	196:6	No preceding question
209:14	209:21	Not necessary for fairness

Exhibit 7; Deposition of Sidney Taurel

START (PAGE:LINE)	END (PAGE:LINE)	OBJECTION
60:10	60:17	Non-responsive
74:1	74:3	Not necessary for fairness
74:5	75:7	Not necessary for fairness
77:17	79:8	Not necessary for fairness; non-responsive; no preceding question
80:22	81:1	Question with no answer

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85:2	86:19	No question preceding designated portion; not necessary for fairness; non-responsive
94:11	95:4	Not necessary for fairness; non-responsive
120:6	121:7	No preceding question; non-responsive
123:6	123:21	Non-responsive
168:23	169:6	Non-responsive
187:18	188:3	Non-responsive
202:5	202:22	Non-responsive
213:3	213:19	Foundation; speculation
220:19	221:4	No preceding question; non-responsive
237:8	237:15	Non-responsive
245:21	246:10	Non-responsive
246:19	247:4	Non-responsive
247:22	247:24	Non-responsive
248:15	249:8	Non-responsive
249:14	249:15	Non-responsive
249:17	249:19	Non-responsive
259:19	260:2	Non-responsive
293:17	294:5	Non-responsive
294:19	295:3	Non-responsive
306:11	306:18	Non-responsive
307:4	307:9	Non-responsive
308:9	308:14	Foundation; mischaracterizes document
309:21	310:8	Non-responsive
336:10	336:18	Non-responsive
336:22	337:3	Not necessary for fairness
337:7	337:11	Not necessary for fairness
337:13	337:18	Not necessary for fairness
350:18	351:7	Non-responsive
354:21	355:9	Not necessary for fairness

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366:2	366:4	Not necessary for fairness; non-responsive
366:6	366:16	Not necessary for fairness; non-responsive
367:11	367:24	Non-responsive
368:13	368:22	Non-responsive
396:6	396:17	Non-responsive
409:3	409:8	Non-responsive

Exhibit 8; Deposition of Gary Tollefson

START (PAGE:LINE)	END (PAGE:LINE)	OBJECTION
82:8	82:15	Non-responsive
225:22	226:4	Non-responsive
226:16	227:5	Non-responsive
250:4	250:7	No answer designated
270:19	271:4	Non-responsive
276:21	277:15	Non-responsive

DATED this 11 day of February, 2008.

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Exhibit 2 Charles Beasley Jr. M.D
Alan Breier, M.D.
Exhibit 4 Alan Breier, M.D.
John Lechleiter, Ph.D

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WESTBROOK & BRICKMAN, LC
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Charles Beasley Jr. M.D
Exhibit 2
Charles Beasley Jr. M.D
Alan Breier, M.D.
Exhibit 4
Alan Breier, M.D.
John Lechleiter, Ph.D

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK
IN RE: MDL-1596
ZYPREXA PRODUCTS
LIABILITY LITIGATION
THIS DOCUMENT RELATES TO:
ALL CASES

C O N F I D E N T I A L

- - -

July 26, 2006

- - -

Videotape deposition of
CHARLES BEASLEY, JR., M.D.

- - -

GOLKOW LITIGATION TECHNOLOGIES
1600 John F. Kennedy Boulevard
Suite 1210
Philadelphia, Pennsylvania 19103
(877) DEPS-USA

Page 82

And with respect to diabetes, the same.
Clearly cases were observed in what we would call temporal association, individuals in the clinical trials did develop diabetes, a small number, and we did not, in looking at all the data, see the compound as -- given the data that we had, as there being an increased or excessive development within our clinical trial database.
Q. With respect to the weight issue, your labeling did not inform physicians that for all patients treated with olanzapine for any amount of time 40 percent gained more than or equal to 7 percent of the body weight; is that correct?
MR. SEE: Object to the form.
A. Well --
Q. You got to answer that question "yes" or "no" or "I don't know?"
A. Well, it, specifically, did not. What our label did --
Q. Thank you.
MR. SEE: You can finish your answer.
A. Did inform physicians about, from my perspective, was a rather excellent characterization of the weight gain. And we indicated that 56 percent of individuals treated long-term in our clinical studies overall, gained 7 percent or more body weight.
MR. ALLEN: Object to everything after "it did not" as nonresponsive.
MR. SUGGS: I join in the objection.
QUESTIONS BY MR. SUGGS:
Q. Your labeling also did not, specifically, inform physicians that patients who remained on olanzapine for 12 months gained an average of 24 pounds at the end of those 12 months, correct?
A. No, it did not.
Q. Okay. And on Page 8 at the bottom there's a -- in the last paragraph, there's a heading that says Laboratory Anolytes?

Page 84

A. Yes.
Q. And what does that phrase mean?
A. This would refer to all of those things that are measured in blood or urine, specific measurements such as sodium, glucose, or white blood cells, that are measured in a laboratory.
Q. And, in fact, the laboratory testing that was done on HGAJ subjects showed that there was a statistically significant increased incidence of high glucose and also high cholesterol; isn't that correct?
MR. SEE: Object to the form.
A. Again, without benefit of looking at the -- at the entirety of the data, my only recollection is with regard to a analysis of the, what we call the categorical incidence of elevated glucoses relative to haloperidol, based on what we call anytime data. I recall this number as being statistically significant. That is one number that needs to be appropriately put in the context of, actually, about nine

Page 85

analyses.
Q. You say "based on what we call anytime data I recall this number as being statistically significant." What was "this number" that you're referring to?
A. I believe it was the percentage of individuals who showed a shift from a normal glucose to what would be considered a high glucose.
Q. Okay. And you were aware of that at what point in time?
A. I don't know the specific. It would have been when the data were analyzed.
Q. It would be sometime between when the data was cutoff in February of 1995 and when it was submitted to FDA in September of 1995, correct?
A. That would have been correct.
MR. SUGGS: Okay. Let me show you a computer printout from that time. I'm handing you what's been previously marked as Plaintiff's Exhibit 1605.

Exhibit 1, Page 2 of 18
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006280

Exhibit 6 David Noesges
Exhibit 2 Charles Beasley Jr. M.D.
Exhibit 3 Alan Breier, M.D.
Exhibit 4 Alan Breier, M.D.
John Lechleiter, Ph.D

Page 106

you point out to the group that "not everybody gained weight, but there are some patients who gained a substantial amount. In fact, that's the most consistent nontherapeutic physical finding you're talking about." Do you see that?
A. Yes, I do.
Q. Then there's a question from a Dr. Casey -- was that Dr. Daniel Casey?
A. Yes, it was.
Q. And he was one of your outside experts, correct?
A. Yes.
Q. And is he a psychiatrist or endocrinologist?
A. He's a psychiatrist.
Q. But he has a special interest in this issue of whether diabetes is related to antipsychotic drugs, correct?
A. I think he has -- I believe that he has published or at least presented data on this issue.
Q. Okay. And had he as of that time or did this become a matter of interest

Page 107

to him after 1995, if you know?
A. I don't believe it was an interest of his. And I say that because I know that his interest at that time was particularly in the area of tardive dyskinesia.
Q. Okay. But in any event, at this meeting in December of 1995, Dr. Casey asked you after you told him about the weight gain, he says quote, "Did any develop diabetes?" And I'm just going to read the interchange that goes on there. You responded by saying, "Very few people have developed type II diabetes during the time of this trial. We have over 400,000 patient days of olanzapine exposure, and the rate for diabetes, a couple of these cases I know are type I who got out of control. Treatment-emergent diabetes, does," and then you're interrupted by Dr. Potkin who asked, "Does that happen more often on olanzapine?" And then there's a response by Todd Sanger, who said, "I don't believe it did." Who is Mr. Sanger?

Page 108

A. Dr. Sanger was the chief statistician for the project.
Q. Okay. And then you went on to say quote, "We don't have comparative data long term for haloperidol analyzed at this point. We need six-week data."
Then Todd Sanger jumped in and said, "We had 16 cases of treatment-emergent diabetes, which is .6 percent, of all 2500 patients. This is adverse event."
Then you jumped in and said, "Spontaneous adverse event."
And then Dr. Potkin -- by the way, he was another one of the outside consultants?
A. That's correct.
Q. Okay. And where was he from?
A. I believe he was from a university in southern California, although I'm not sure which institution.
Q. Do you know if he's still there?
A. I'm not sure.

Page 109

Q. Was he a psychiatrist or an endocrinologist?
A. He's a psychiatrist.
Q. Okay. Anyway, Dr. Potkin asked quote, "You were measuring glucose all along?" You see that question?
A. Yes.
Q. And then your response to him was, "And we don't see anything," correct?
A. That's correct.
Q. You made no mention of the results of that computer printout that we discussed some minutes before, correct?
A. No, I did not. This was a statement made that was based on interpreting the totality of our data.
MR. SUGGS: Move to strike that portion of your answer which is nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. You would agree with me, wouldn't you, sir, that the advisory committee of your outside consultants -- by the way, these folks were all hired and

to have; isn't that correct?
A. It is intended to be a summary of the data that would allow the effective and safe use of the medication. That is correct.
Q. And it's absolutely necessary that the information in there is complete and accurate, correct?
A. Again, it's important that it allow for the safe and effective use of the medication. From a concept of complete, again, all 1.5 million pages can't be contained.
So the intent is that it is a summary of the most pertinent information that will allow the drug to be prescribed appropriately.
Q. And the doctor uses that information contained in the package insert to weigh both the risks and the benefits of using a drug and make an evaluation as to whether it is appropriate for him to prescribe that drug to his patient, correct?
A. That's correct.

Q. Okay. And in the labeling there is a hierarchy of significance of information about adverse reactions or potential safety issues, is there not?
MR. SEE: Object to the form.
A. There are a series of different sections in the U.S. label.
Q. For example, there's, there can be a warning section in the drug label, correct?
A. Generally, there is a warning section.
Q. And there's also what's referred to as a precaution section, correct?
A. That's correct.
Q. And there's also what's referred to as an adverse reaction section, correct?
A. That is correct.
Q. And that is a decreasing hierarchy of significant, if the you will, is it not?
MR. SEE: Objection to the form.

A. I'm not exactly sure what you mean by significance. If I may?
Q. Sure.
A. Significance could be the extent of which there is understood to be an association, so degree of association. That can be one thing that you might mean by significance.
The other thing that you could mean by significance would be the clinically significance of an -- of an individual term or observed event.
If you mean the latter, then those three sections don't have decreasing significance.
Q. Okay. Well, if, for example, your -- if, for example, you've got an adverse reaction or that can occur with a drug, let's call it syndrome X, okay? If you've got syndrome X that's -- and it's listed in the --
MR. SUGGS: I want to wait for the fire engine to go by.
MR. ALLEN: That won't be the

last one of those either.
MR. SUGGS: There was one this morning at 5:30.
MR. ALLEN: We have at least three a day.
MR. SUGGS: I heard the one this morning at 5:30. Okay. I think we're safe now. Let me go back to my question.
QUESTIONS BY MR. SUGGS:
Q. Let's assume that a particular drug has something bad that can happen with it that's called syndrome X. Okay? If it's just listed in the adverse reaction section, then that means that it has been seen, syndrome X has been seen in people who have used the drug, correct, and it really means not much more than that, isn't that true?
MR. SEE: Object to the form.
A. It means that it has been seen. I believe that the standard language that the Food and Drug Administration would include in a preamble to that is that that

Page 142

from literature, for example, as well as other sources.
Q. Okay. And are you aware, sir, that it's generally estimated that only 1 percent, maybe 10 percent of the number of adverse events that, actually, occur in the use of a drug ever get reported?
MR. SEE: Object to the form.
A. The literature that I am familiar with estimated between 1 in 5 and 1 in 30 cases would be reported. This was in this time frame when I was more involved with doctors Funk and Hornbuckle. I believe that more recent literature has suggested it may be as low as one in a hundred.
Q. Okay. So if, for example, you got ten adverse event reports of -- I'll use syndrome X that we were talking about before, based on the current literature that would indicate that probably out in the real world there's maybe a hundred times that amount, which would be what, a thousand?
MR. SEE: Object to the form.
Q. I take it back. You said one

Page 143

in a hundred.
A. I said you would multiply, and the best understanding that I have of the literature is that there is not a good estimator for what this is, but you could multiply by between 5 and 100, that would be the range.
Q. Okay, between 5 and 100.
A. So if you had 10 it might be 50.
Q. Or it might be --
A. Or it might be a hundred -- thousand.
Q. Okay.
A. A pretty wide range.
Q. Okay. In any event, the main thing is though, that if you get one adverse event report you've got to assume that there's a bunch more out there.
MR. SEE: Object to the form.
Q. How big that bunch is we're not sure about but there's, probably, a bunch more out there, right?
MR. SEE: Object to the form.

Page 144

A. There may be. One thing that we take into consideration when we consider that, and it's supported by some of the literature, is to what extent the drug -- a drug is having an event reported is new, how serious the event is, and to what extent the event has been described in either the medical literature or the -- or the public nontechnical literature.
So there are a number of things that we take into consideration when we do an estimate of this range.
Q. Okay. If I could direct your attention, sir, to page, I believe it's 14. And as it turns outs there is --
A. May I --
Q. -- there's two sets of numbers on these pages.
A. May I, just since I opened this document up.
Q. Sure.
A. It has refreshed my memory with respect to the reporting structure for Doctors Hornbuckle and Fung. There is a

Page 145

reference to Edmundo, so I believe that they would have reported to Dr. Muniz.
Q. How do you spell that?
A. I must confess I have difficulty with spelling Beasley on occasion, so, I believe it would be M-U-N-I-Z.
Q. Okay.
MR. ALLEN: Or something thereabout.
A. It's a -- he's originally from the Dominican Republic. It's a Latin name. It's hard for me to spell.
Q. If I could direct your attention to Page 14, and I'm referring to the bottom most number of Page 14.
A. Okay.
Q. I believe you're on the same.
A. Is it --
Q. It has two numbers, one -- it's my 14 as opposed to the 13 that was on the original document. You're there. This is the section on showing blood sugar elevation, correct?
A. Clintrace Database. This

Page 146

would be spontaneous adverse events, yes.
Q. Showing blood sugar elevation, correct?
A. Actually, not necessarily. For example, you see the term "ketosis."
Q. Right.
A. That might not refer to an actual case of blood sugar increase. These were terms that were thought to be possibly related, not definitely related. Some of them are clearly definitely related.
Q. In any event, whoever prepared this report, well, Doctors Hornbuckle and Fung, have a bold heading there entitled Blood Sugar Elevation, correct?
A. That's correct.
Q. And then below that they have six different subcategories, including hyperglycemia, diabetes mellitus, diabetic acidosis, diabetic coma, ketosis, and glucose tolerance decreased, correct?
A. That's correct.
Q. And then below that they have

Page 147

another bold heading that says Unduplicated Reports, correct?
A. That's correct.
Q. And that totals the numbers of each of those categories, correct?
A. Again, not technically. For example, if we take the first column it's 27, 28, 29, 30, 32, but yet the number is 28.
Q. Let me restate, it totals the unduplicated reports?
A. Yes.
Q. Okay. And it shows that if you looked at all four quarters of -- or I guess eight quarters from '96 to '98 there were a total 194 unduplicated reports of what they had grouped together as blood sugar elevation, correct?
A. That's correct.
Q. Okay. And again, using the numbers we've talked about before, if we multiplied by -- well, the numbers we talked before in terms of what the range might be with respect to what's happening out in the real world. If we multiply the 194 by 5

Page 148

that's almost a thousand and if we multiply by a hundred it would be almost 20,000 cases of blood sugar elevation, correct?
A. That is correct. As I said, there are -- there are things that influence how we use these numbers in our multipliers. We would have thought about the midrange to potentially the upper range for, let's say, hyperglycemia or glucose tolerance decreased for the terms of diabetic acidosis and diabetic coma, we would have thought that these would be much toward the lower end of the range, again, because these are more serious.
So we would have, in general, if we were trying to do our best estimate, apply different correction factors or different ranges of correction factors.
MR. ALLEN: Object to everything after "that is correct" as nonresponsive.
Q. If you look, though, at group, the same grouping that Doctors Fung and Hornbuckle created for this report, we

Page 149

would have a range of between, roughly, a thousand and 20,000 unduplicated reports of events in that grouping, correct?
MR. SEE: Object to the form.
A. If we used the -- and I think you have correctly used the five to a hundred rounding off to 200.
Q. Okay. Very good. Do you recall that by December of 1998, which was just a couple months after this -- well, let me back up for a second.
With respect to Exhibit 988. The one you have there. It's marked confidential on every page. Was it standard drill at Eli Lilly to mark reports of adverse event reports as confidential?
MR. SEE: Object to the form.
A. Actually, I don't know whether all such reports would be so marked. Clearly these are information that are, the reports themselves and analysis similar to this are not confidential because they are shared with Food and Drug Administration and other regulatory bodies.

Page 182

I do have concerns regarding making any connections between olanzapine induced weight gain and hyperglycemia. Therefore, in my opinion, I would not include your following statement, quote, Patients who gain weight may develop insulin resistance which may lead to hyperglycemia and diabetes, end quote. Do you see that language, sir?

A. Yes, I did.

Q. Were you made aware that Dr. Kinon had made that recommendation that the marketing department not state that patients who gain weight may develop insulin resistance which may lead to hyperglycemia and diabetes?

MR. SEE: Object to the form.

THE WITNESS: If I can -- I think I got the question right. Was I made aware that Dr. Kinon had sent this e-mail?

MR. SUGGS: Yes.

A. I don't recall that.

Q. Okay. Did you work with Dr. Kinon?

Page 183

A. Minimally. Dr. Kinon was in the U.S. Affiliate, one of the physicians in the U.S. Affiliate that worked with olanzapine. Some of my -- so I did have some interaction with him, as I was a consultant to the team, but not on a daily basis.

MR. SUGGS: Okay. Well, let's talk a little bit about the teams who were working on Zyprexa. I'm going to hand you what's been previously marked as MDL Plaintiff's Exhibit 8042.

(Whereupon, Deposition Exhibit(s) 8042 previously marked, was presented to the witness.)

MR. SUGGS: Which for the record is a November 29, 1999, e-mail from Michele Sharp to Gail Uminger, which then copies several other e-mails.

QUESTIONS BY MR. SUGGS:

Q. The first of which is an e-mail on November 28, 1999, from Edmundo

Page 184

Muniz to Michael Clayman, Timothy Franson with copies to Gregor Brophy, Kenneth Hornbuckle, Kenneth Kwong, correct?

THE WITNESS: I was trying to look at the -- at the e-mail. Could you, again, direct me to, I guess --

MR. SUGGS: I'm directing you to the e-mail that was sent by Edmundo Muniz on November 28, 1999, to Michael Clayman, Timothy Franson with copies to Gregory Brophy, Kenneth Hornbuckle, Kenneth Kwong.

THE WITNESS: Yes.

QUESTIONS BY MR. SUGGS:

Q. Okay. And I believe you said earlier that Mr. Muniz -- am I pronouncing his name, right?

A. Muniz, Dr. Muniz, but yes.

Q. He was head of the pharmacovigilance department; is that correct?

A. That's correct.

Q. And who was Michael Clayman, one of the recipients of this?

Page 185

A. He was -- I believe at the time, he would have been the International Director for regulatory.

Q. Okay. And who is Timothy Franson?

A. And Timothy Franson, at the time, I believe, was the head of regulatory for the United States.

Q. Okay. And who is Gregory Brophy?

A. And Gregory Brophy would have been one of the regulatory people for the United States that interacted, specifically, with the Neuropharmacology division of the FDA.

Q. Okay. And then the other recipients of that e-mail were Kenneth Hornbuckle and Kenneth Kwong, both of whom we've discussed before, correct?

A. That's correct.

Q. And in his e-mail Dr. Muniz says, "Mike and Tim, below you will find the summary of issues discussed this week regarding hyperglycemia and Zyprexa. There

Page 186

are two types of initiatives," and then he lists what those two different types are, correct?
A. There are two types of initiatives, yes.
Q. And the first is a, what he refers to, as a cross-functional team -- pardon me -- cross-functional action team led by Alan Breier. Do you see that?
A. Yes, I do.
Q. And it states that the goal of this team is to bring to the same table all the groups and functions working to address the hyperglycemia issue, correct?
A. Yes.
Q. And the hyperglycemia issue was the fact that by November of 1999 there were published medical articles linking hyperglycemia with Zyprexa and you also had a number of adverse event reports linking hyperglycemia and Zyprexa, correct?
MR. SEE: Object to the form.
A. Yes, that would be correct.
Q. And, in fact, as we saw

Page 187

earlier, your clinical trials back in 1995 showed a statistically significant increased incidence of hyperglycemia with use of Zyprexa?
MR. SEE: Object to the form.
Q. Correct?
A. And I disagree with that. As we discussed, there was one finding in one clinical trial of many analysis showing that finding.
Q. Okay. He goes on to state in his memo, "This Action Team has a Steering Committee formed by N. Ascroft, A. Breier, J. Caro, R. DiMarchi, C. Fibiger, S. Paul, G. Probst and G Tollefson," correct?
A. Correct.
Q. And could you identify who N. Ascroft was?
A. She was, I believe, in medical plans so she was serving as a coordinator for the group.
Q. And Dr. Alan Breier, we've talked about him before. But I don't believe we've discussed his medical specialty. Do

Page 188

you know what it is?
A. He is a psychiatrist.
Q. Who is J. Caro?
A. J. Caro was, I believe, the head of the preclinical diabetes area and diabetes metabolism area.
Q. Who is R. Demarchi?
A. I do not recall what his, he's a Ph.D. I don't recall if he was a chemist or a pharmacokinetics.
Q. And who is C. Fibiger?
A. That would be Chris Fibeger, he was the head of preclinical psychopharmacology at the time.
Q. And who is S. Paul?
A. That, I believe, would have been Steve Paul, who was -- I don't know if as of yet he was the head of Lilly Research Laboratories or not.
Q. And who is G. Probst?
A. G. Probst was the head of toxicology.
Q. And Dr. Tollefson, we've talked about before. Do you know what his

Page 189

title was at that point?
A. I, again, think he was president of the -- of the Neuroscience Unit.
Q. And do you know what his medical specialty was?
A. Psychiatry.
Q. Okay. In that cross-functional action team, which was to bring to the same table all the groups and functions working to address the hyperglycemia issue, there wasn't, in what you've described to me, a single endocrinologist there?
A. That would have been Dr. Caro, a very eminent diabetologist.
Q. Okay. And the second type of initiative was the regulatory slash PHV and the Zyprexa team as described by Dr. Muniz, correct?
A. That's correct.
Q. Now, when it says regulatory slash PHV, is that regulatory pharmacovigilance?
A. That's correct.

Exhibit 1, Page 8 of 18
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006286

Exhibit 6 David Noesges
Exhibit 2 Charles Beasley Jr. M.D.
Exhibit 3 Alan Breier, M.D.
Exhibit 4 Alan Breier, M.D.
John Lechleiter, Ph.D

post-marketing safety surveillance of hyperglycemia, exploring the possibility of using GPRD to conduct database analysis, what's GPRD?

A. That is a database that, I believe, is available in the UK. So this was an intended epidemiologic study.

Q. Okay. And then Item D -- pardon me -- Item C rather, was "discuss Zyprexa label at a GPLC session and evaluate potential proactive regulatory strategies." Did I read that correctly?

A. Yes.

Q. Am I correct that GPLC stands for Global Product Labeling Committee?

A. That's correct.

Q. And what was the Global Product Labeling Committee?

A. This is a committee made up of a number of individuals holding fairly senior positions within the company. At the time it was chaired by, I believe, Dr. Clayman, so --

Q. I'm sorry?

A. Dr. Clayman.

Q. Okay.

A. So it was a regulatory -- it was, essentially, a regulatory committee. But members from various components of medical, toxicology, adme, manufacturing and other individuals that would ultimately make decisions, approve or disapprove labeling changes.

MR. ALLEN: Objection to portions of the answer as completely nonresponsive and unnecessary.

Q. Is marketing a member of the GPLC?

A. No.

Q. Is legal?

A. There is legal representation, yes.

Q. Okay. Are there regular minutes kept of GPL meetings?

A. I believe there are, yes.

Q. Okay. Do you have any explanation for why such minutes have not been produced in this litigation?

MR. SEE: Object to the form.

A. I wouldn't know that, no.

Q. If you wanted to get the minutes of Global Product Labeling Committee meetings that related to Zyprexa, how would you go about getting those?

A. I would, probably, contact the chairman of the committee who, I'm sure, would contact the secretary, who -- I don't know if there's an archivist --

Q. Okay.

A. -- available.

Q. And it's your understanding that Dr. Clayman is the head of the Global Product Labeling Committee?

A. Not at this time, no.

Q. Okay. Was he, though, back in, say, 2000?

A. I do not recall the specific time at which he transitioned off that position.

Q. Do you know who succeeded him?

A. It is currently co-chaired by

Dr. Franson and Dr. Breier.

Q. Okay. And do you know how long Dr. Breier has been a co-chair of that labeling committee?

A. I'm not sure of the specific length.

Q. Do you have an approximation?

A. It's been a short number of years --

Q. Okay.

A. -- since the time that he became chief medical officer, I believe.

Q. Okay. And do you recall when it was he became chief medical officer?

A. And again, because I can't recall when he -- and again, I think it's approximately, several years.

Q. Okay.

A. Two would be an approximate number.

Q. And was the Zyprexa label the subject of a GPLC session in the weeks or months following this e-mail?

A. I don't recall.

Page 206

Q. Did you ever give a presentation to the Global Product Labeling Committee on Zyprexa labeling?
A. I think I was, probably, present for discussions about the molecule at GPLC, I cannot recall the specifics of those conversations.
Q. Okay.
A. I may have been simply in attendance as opposed to doing a presentation.
MR. SUGGS: Let me hand you what's been previously marked as Plaintiff's Exhibit 990.
(Whereupon, Deposition Exhibit(s) 990 previously marked, was presented to the witness.)
MR. SUGGS: For the record this is a seven-page document, the first page of which is labeled Confidential, Do Not Forward, To be distributed only by Global Operations Labeling Department,

Page 207

Indianapolis, Attachment E.
QUESTIONS BY MR. SUGGS:
Q. And, Dr. Beasley, if I could refer you to the second physical page of the document.
A. Um-hum.
Q. There is a heading towards the top of the page below the confidential label that says, "Olanzapine Labeling Change on Hyperglycemia For February 21, 2000, GPLC Meeting." Do you see that?
A. Yes, I do.
Q. And have you seen this document before?
A. Yes, I have.
Q. When was the last time you saw it?
A. Sometime during the last week.
Q. And if you could direct your attention to the last physical page, there is a box there referring to consultation process?
A. Yes.

Page 208

Q. And it says "reviewed by," and it has, "Global Product Physician Charles Beasley," with the date of February 15, 2000?
A. Yes.
Q. And does that refresh your recollection that you would have seen this document or reviewed it back in February of 2000?
A. Oh, I'm very certain that I was very much involved in putting this document together. A technical correction, I was not the Global Product Physician, as I have explained. I was a consultant, not part of the team.
Q. Okay.
A. But I consulted to the team.
Q. Okay. And apparently this was also reviewed by Kenneth Kwong?
A. Yes.
Q. Okay. And did you and Dr. Kwong prepare this document?
A. Physically we didn't, but we certainly had input into this proposal.
Q. Who would have?

Page 209

A. This --
Q. I'm sorry. Go ahead.
A. This would have arisen from the work that we'd undertaken that I discussed previously.
Q. Okay. By that you mean your review of the spontaneous data, the published literature, the clinical trials and so forth?
A. And this component, specifically, the clinical trial data.
Q. Okay. And who -- you said you weren't sure that you, actually, put this physically together. Did you -- did you and Dr. Kwong write the text of what's contained in here?
A. I don't recall who, specifically, wrote this text. It -- it well may not have been us, I think, that probably wrote what's contained up in the -- or parts of what is contained in the top box here.
Q. And regardless of whether you personally drafted the text that's in here, would it be fair to say you not only reviewed but approved this language?

Page 210

A. Yes.
Q. Okay. And by approving it you believed that what was stated in there was accurate and truthful, correct?
A. At the time --
Q. Sure. That's all you can do.
A. -- yes, recognizing that the basis for the specific numbers that had been included in here were from the very first preliminary analysis of our clinical trial data.
MR. ALLEN: Object to everything after "yes" as nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. I'm not sure what you meant when you said that the basis for the specific numbers that had been included in here were from the very first preliminary analysis of our clinical trial data. Can you explain that?
A. Yes. Thank you. The numbers contained in here were brought forward for review by GPLC and we clearly suggested and

Page 211

thought that a labeling change was appropriate. The basis for this, as I said, is someplace between 50 and a hundred studies.
I brought forward to, I believe, Dr. Breier and Dr. Tollefson and other individuals the results of the very first successful run of that data. And so that was the basis for what went in here.
Q. Okay.
A. It's very much like the first time that you run a long column of numbers on an adding machine and get a result.
Q. Okay. Below the title there's a box that says, "Proposal of the Product Team and PhV."
A. Yes.
Q. Okay. Now, you said earlier that you were not really a member of the product team but were a consultant or was -- you were a consultant for --
A. I was a consultant to --
Q. -- the product team. Did this proposal have to get signed off on by

Page 212

somebody in the product team before it was put forward as a proposal?
A. I think that was the case, but I'm not familiar with whether there was an explicit sign-off or who would have been the sign-off individuals.
Q. And who was in charge -- who was the lead person on the product team, was that Dr. Breier?
A. That would have been Dr. Breier.
Q. Okay. In that section of the proposal it states that the, "Spontaneous reporting rate for hyperglycemia, less than .01 percent, is currently in the Core Data Sheet as a Core Adverse Event in the Adverse Drug Reaction Table." What was the Core Data Sheet?
THE WITNESS: The core -- and I'm sorry, but I was listening to you and I just was not following where you were -- where you were reading.
MR. SUGGS: At the very top

Page 213

of that box that's of the proposal.
THE WITNESS: Okay.
QUESTIONS BY MR. SUGGS:
Q. And my question was what is the Core Data Sheet?
A. The Core Data Sheet is a -- is an internal document that is used as the basis for labeling internationally. To some extent from a efficacy perspective but, primarily, from a safety perspective.
It lists those things that are the absolute minimum for inclusion in all actual product labeling throughout the world.
Q. Okay.
A. Product labels, unless a regulator says, "No, you can't put that in."
Q. Okay. And you state here that, The proposal was to add the following information regarding hyperglycemia to the Core Data Sheet in a particular section, correct?
A. That's correct.
Q. And then below that follows the new statement, correct?

Exhibit 1, Page 11 of 18
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006289

Exhibit 6 David Noesges
Exhibit 2 Charles Beasley Jr. M.D
Exhibit 3 Alan Breier, M.D.
Exhibit 4 Alan Breier, M.D.
Exhibit 5 John Lechleiter, Ph.D

Page 234

Dr. Casey about that?
A. I do not recall any conversations about that specific study with Dr. Casey.
Q. Was it a matter of concern to you that he had found that 18 percent of the people with normal blood sugar developed diabetic levels of glucose?
MR. SEE: Object to the form.
A. There are certainly a lot of things I could say about this, I would characterize as a report by Dr. Casey. But it was obviously one of the pieces of information that increased our interest and our view of the importance of continuing to analyze -- well, controlled data in this area.
Q. Okay. Well, you never warned doctors in your Zyprexa labeling of Dr. Casey's finding that 18 percent of people who had used Zyprexa for at least four months had fasting glucose levels that met the ADA criteria for diabetes, correct?
A. Well, this is -- this, again,

Page 235

is a retrospective chart. The answer to your question is no.
Q. Thank you.
THE WITNESS: But if I may.
MR. SUGGS: You can say whatever you want, I'm just going to move to strike it.
THE WITNESS: Okay. This was not considered to be, by any stretch, a study. It was something that warranted systematic investigation.
MR. SUGGS: Move to strike as nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. And, sir, your company never warned in your labeling that in your analysis in February of 2000 you had found that the incidence of treatment-emergent hyperglycemia in patients treated with Zyprexa was 3.6 percent as compared to the placebo group where the incidence was 1.05 percent, correct?
MR. SEE: Object to the form.

Page 236

A. No, but we did place the finalized numbers in the package insert.
MR. SUGGS: Move to strike that portion of your answer which is nonresponsive.
Q. In fact, the label change that ultimately came about within months after your proposal here in February, asserted that there was, essentially, no change in glucose levels between patients who used Zyprexa and those who were on placebo, correct?
MR. SEE: Object to the form.
A. My recollection is that we did report something close to 3.6 percent for olanzapine.
MR. ALLEN: Objection, nonresponsive.
A. And that the number for placebo was slightly less but not substantially less than olanzapine. And I don't recall the specific numbers.
MR. SUGGS: Again, move to strike as nonresponsive.

Page 237

Sir, maybe you don't remember what your labeling, actually, said, so let me show that to you. I'm going to hand you what's been previously marked as Plaintiff's Exhibit 4858.
(Whereupon, Deposition Exhibit(s) 4858 previously marked, was presented to the witness.)
MR. SUGGS: For the record this is a May 9, 2000, letter to FDA from Gregory T. Brophy with several attachments.
THE WITNESS: I've looked at the document.
QUESTIONS BY MR. SUGGS:
Q. And have you seen it before, sir?
A. Yes, I have.
Q. How recently?
A. I believe in the last week to two weeks.
Q. And had you seen the document

on the record. This is the beginning of tape four of the deposition of Dr. Charles Beasley.

QUESTIONS BY MR. SUGGS:

Q. Dr. Beasley, the second -- could I get you to direct your attention to the first page of this Exhibit 4858?

A. Yes.

Q. The second numbered item in this letter refers to the change that was, actually, made regarding hyperglycemia, am I correct?

A. It's with reference to the laboratory findings of hyperglycemia.

Q. Okay. And that's the same type of laboratory findings that you were referring to in your proposed label, correct, was to discuss what the incidences were and with respect to laboratory findings?

A. Actually, I believe, in the original proposal there was no suggestion that we included any specific incidences or numbers.

Q. Okay.

A. I should --

Q. But the basis -- I'm sorry.

A. I should add other than to indicate that the frequency for olanzapine was between one and 10 percent.

Q. Okay. And that was in the common or frequent category, correct?

A. That's correct.

Q. Okay. There is nothing in the labeling language that was, actually, implemented in May which refers to hyperglycemia as being common or frequent, correct?

A. From my perspective that is not --

Q. Sir, I need to have you answer my question. And my question is, just with respect to the language that was used in the label change, did you tell doctors that the incidence of hyperglycemia was common or frequent? Did you use those words?

A. We did not use those words.

Q. Very good.

A. We provided the numbers.

Q. In fact, sir, you said in one of your earlier answers, if I can find it here. I have a rough transcript of the -- of your testimony here on my computer and you said quote, "My recollection is that we did report something close to 3.6 for olanzapine," referring to 3.6 percent of hyperglycemia.

A. That's correct.

Q. Can you point to me any language in the text that was, actually, used that uses the figure 3.6 percent?

A. No. You add the numbers together for the two --

Q. Okay.

A. -- treatments.

Q. Can you -- would you read for the jury the language that is used?

A. Yes. "In the olanzapine clinical trial database, as of September 30, 1999, 4,577 olanzapine-treated patients begin paren, representing, approximately, 2,255 patient-years exposure," end paren, "and 445 placebo-treated patients who had no history

of diabetes mellitus and whose baseline random plasma glucose levels were 140 milligrams per deciliter or lower were identified. Persistent random glucose levels greater than or equal to 200 milligrams per deciliter," paren, "suggestive of possible diabetes," end paren, "were observed in 0.8 percent of olanzapine treated patients," paren, "placebo 0.7 percent," end paren". Transient," paren, "i.e., resolved while the patients remained on treatment," end paren, "random glucose levels greater than or equal to 200 milligrams per deciliter were found in 0.3 percent of olanzapine treated patients," again, paren, "placebo, 0.2 percent, end paren. Persistent random glucose levels greater than 160"-- excuse me -- "greater than or equal to 160 milligrams per deciliter observed in 1.0 percent of olanzapine treated patients," begin paren", placebo, 1.1 percent," end paren. "Transient random glucose levels greater than or equal to 160 milligrams per deciliter but less than 200 milligram per deciliter were found in

Page 246

1.0 percent of olanzapine treated patients," paren, "placebo, 0.4 percent," end paren.

Q. And that's the final language that went into the labeling, correct?

A. That's correct.

Q. And this is the language that came out of the end process that began with you and Kenneth Kwong suggesting a label change because your review of random glucose level of patients revealed an incidence of treatment-emergent hyperglycemia in the Zyprexa group of 3.6 percent as compared to 1.05 percent in the placebo group, correct?

A. And again, I believe what I have testified to is that the numbers that you have just quoted were, in fact, the result of the initial preliminary data analysis.

Q. And after you tortured the data for some period of time you came up with this language which, essentially, shows no difference between Zyprexa users and placebo users in terms of hyperglycemia, correct?

MR. SEE: Object to the form.

Page 247

A. And again, I would disagree with your characterization of tortured. I would again refer to checking and double checking. There is a numerical deference with more on olanzapine but the numbers are certainly closer together.

Q. Is it your testimony that the change here that we see, from what was in the rationale for original proposal versus what came out of the end of the process, is because you checked your arithmetic and you found the numbers were wrong?

A. Well, it would not be appropriate to characterize it as arithmetic. It's the process of checking the computer programs that result in finding the results that you have.

Q. Well -- sir, in fact --

MR. SEE: I'm sorry. You can finish your answer, Dr. Beasley, if you weren't finished.

A. There are --

MR. ALLEN: Under that criteria we'll be here all day

Page 248

because he never finishes.

MR. SEE: As I said, Dr. Beasley, you can finish your answer if you haven't.

A. These were complex studies that had to be combined in appropriate fashion, and my understanding is that the final numbers represented here were after multiple rechecking of the computer programs that obtain the numbers.

Q. Who was it that finally crunched the numbers, was it you or someone else?

A. It was not me. I am not a statistician a -- or versed in either the systems or the statistical programs that provide these numbers.

Q. My question was who was it that crunched the numbers, do you know?

A. I think, probably, Mr. Paul Berg would have been involved. Whether he was the only statistician or systems person I would not know.

Q. Earlier when we were talking

Page 249

about your original proposal which found a rate of hyperglycemia --

MR. SUGGS: Strike that.

QUESTIONS BY MR. SUGGS:

Q. Earlier when we were talking about your analysis, that you and Dr. Kwong had done, which found a rate of hyperglycemia in Zyprexa users about three and-a-half times higher than placebo users, I think, you referred to that as the first successful run of the analysis, am I correct?

A. That's correct.

Q. Who ran the numbers when you did that?

A. Okay. I believe that, again, Mr. Burg was the statistician who would have overseen or, actually, performed all of the -- all the analysis.

Q. So is it your testimony that this was just some computer error that takes the difference between Zyprexa and placebo users from three and-a-half times to virtually nothing?

MR. SEE: Object to the form.

Exhibit 1, Page 14 of 18
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006292

Exhibit 6 David Noesges | Exhibit 2 Charles Beasley Jr. M.D | Exhibit 3 Alan Breier, M.D. | Exhibit 4 Alan Breier, M.D. | Exhibit 5 John Lechleiter, Ph.D

Page 250

A. And, again, I've characterized there continuing to be a slight numerical difference between drug and placebo with more on drug. And that is my understanding. The process of running these programs, as I understand it, is quite complex.

Q. Well, sir, do you recall that you did later analyses in which you concluded that, "our continuous analyses showed that olanzapine does result in statistically significant mean increases in random glucose relative to placebo and haloperidol?"

A. I don't recall that specific set of analyses.

Q. Okay, well, we'll talk about that in just a minute. Let's finish up with this label change that you guys did in May of 2000. What happened, five months later, was that FDA came back and made you take it out -- made you take that language out of the label; is that correct?

A. That's correct.

MR. SUGGS: Okay. Let me

Page 251

show you what's been previously marked as Plaintiff's Exhibit 195.

(Whereupon, Deposition Exhibit(s) 195 previously marked, was presented to the witness.)

MR. SUGGS: Which for the record is an October 11, 2000, letter from Russell Katz, the director of the Division of Neuropharmacological Drug Products at FDA to Gregory Brophy.

QUESTIONS BY MR. SUGGS:

Q. Have you seen this document before?

A. I believe I have.

Q. And have you -- how recently have you seen it?

A. I believe during the last few weeks.

Q. And did you see it before then?

A. I don't recall whether I would have seen this specific letter. I was

Page 252

certainly made aware of its contents.

Q. And who made you aware of the contents?

A. I don't know the specific person. It would have likely been one of the regulatory people for the compound.

Q. And if we just cut to the chase here, what happened was FDA five months after you made that label change on your own without prior FDA approval, FDA came back on October 11, 2000, and said you have to take that language out, correct?

A. That's correct.

Q. And the reason why they made you take it out is because the FDA said, this is on the second page of the document, "The descriptive data that is provided expresses a certain level of implied safety with respect to treatment emergent hyperglycemia." Do you see that language, sir?

A. Yes, I do.

Q. And in fact, that that was the case. The data that you reported in there, the statements that you had in the

Page 253

labeling showed that there was, essentially, no difference between hyperglycemia in Zyprexa users versus placebo patients. And the FDA concluded that that expresses a certain level of implied safety; is that correct?

MR. SEE: Object to the form.

A. I think you've asked me two questions. With respect to the FDA's impression, that is correct. I view these data, quite frankly, as not reassuring, although not ominous, not reassuring because of the difference.

Q. Let me ask you this --

A. I clearly felt it was important to report these incidences.

Q. When you did the analysis for your proposed label change in February of 2000, and we've talked about it several times before, the 3.6 percent for the Zyprexa users versus the 1.05 percent for placebo users, did you do any tests of statistically significant to determine whether that finding was statistically significant?

know who the statisticians were that were working with her.
Q. Okay. I want to make sure I understand the time frame here. In February of 2000, a year before this e-mail, you and Kenneth Kwong do an analysis which finds an incidence of treatment-emergent hyperglycemia three and-a-half times higher in Zyprexa users versus placebo users, correct?
MR. SEE: Object to the form.
A. And again you've characterized that, I believe, as a final finding.
Q. I'm not characterizing as final, partial, whatever. You did an analysis that you thought was important enough and you felt confident enough in to submit to the Global Product Labeling Committee which said that the incidence of treatment-emergent hyperglycemia was three and-a-half times higher in Zyprexa users as compared to placebo users, correct?
A. That is correct and I'm trying to provide the context.

MR. SUGGS: Move to strike the nonresponsive portions.
Q. Three months later, you and others jen-up language that goes into the labeling under the special supplement changes being effected, which shows, essentially, no difference between the incidence of hyperglycemia in Zyprexa users versus placebo users. And five months after that, FDA makes you take out that language because they say it's -- it gives an implied sense of safety, correct?
MR. SEE: Object to the form.
A. And I would agree with you --
Q. You need to answer the question, first, sir.
MR. SEE: I think he's answering your question.
A. I agree with you with respect to the action of the FDA. In your question you characterized our actions in a certain fashion that I would disagree with.
Q. And then five months after the FDA makes you take out that language,

which they said was expressing a certain level of implied safety with respect to treatment-emergent hyperglycemia, you do another analysis which finds a statistically significant mean increase in random glucose for Zyprexa relative to placebo and haloperidol, correct?
A. That was my understanding at the time having not been involved in those analyses.
Q. And, sir, if I could direct your attention to the remaining language in that paragraph, you go on to state, "These increases are occurring as early as week one," correct?
A. Yes.
Q. That would be week one after beginning use of the drug?
A. That's correct.
Q. And you say "These changes are accounted for, in part but not entirely, by weight increase," correct?
A. I think you have excluded a parenthetical in the -- in this but -- that

states, "may not represent a true deterioration in glycemic metabolism but simply an increase in food intake since these are random and not fasting glucoses."
Q. And then you go on to say, "These changes are accounted for, in part but not entirely, by weight increase," correct?
A. That's correct.
Q. And then you say: Categorical analyses to values above a set of thresholds, 126, 140, 160, 200 milligrams per deciliter, do not reveal significant findings, but trends are there, except for the comparison of clozapine to olanzapine to the lower two thresholds, clozapine more, correct?
A. That's correct.
Q. And so, when you do categorical analyses like that, you are splitting the data up into different chunks, correct?
A. That's correct. We have been talking -- most of what we've been talking about so far has been categorical analysis.

Page 270

Q. Okay. And we know that on October 11, the FDA comes out and says you've got to take that label language out, right?
A. Correct.
Q. Okay. So within days after you meet with the outside experts, FDA tells you to take the label out, right?
A. Yes.
Q. Dr. Baker in Exhibit 6998, goes on in his e-mail to say, "They kindly allotted two hours for discussion of olanzapine's potential hyperglycemia risks and Charles Beasley, Chris Bomba, Patrizia Cavazzoni, Suni Keeling and I attended. Unfortunately, this consultation reinforced my impression that hyperglycemia remains quite a threat for olanzapine and may merit increasing even further medical attention and marketing focus on the topic." Did I see that?
A. Yes, that's correct.
Q. Okay. In the second paragraph he goes on to state, "They were, however, concerned by our spontaneous AE

Page 271

reports." That's referring to adverse event reports, correct?
A. That's correct.
Q. "And quite impressed by the magnitude of weight gain on olanzapine and implications for glucose. Much of their input for helpful steps came back to addressing weight gain."
Did I read that correctly?
A. That's correct.
Q. And you had been warned about the weight gain problem by another panel of outside experts as we said -- as we talked about right at the beginning of your deposition back in December of 1995, correct?
A. That's correct. And this was something that we described and from my perspective, given Dr. Breier's efforts, we were attending to.
Q. And continuing on in his e-mail Dr. Baker said, "Citing methodological questions, at least the vocal members were not reassured adequately by our analyses, such that the finding that relative risk was

Page 272

not higher than comparative drugs. Disconcertingly, one member compared our approach to Warner-Lambert's reported argument that Rezulin did not cause more hepatic problems than other drugs in its class." Do you see that language, sir?
A. Yes, I do.
Q. Were you familiar with what Warner-Lambert was doing with respect to Rezulin?
A. No. I was familiar with the drug and I was familiar with the fact that it was, ultimately, withdrawn from the market.
Q. Because of safety problems, correct?
A. Because of the perception that it had a risk of hepatic dysfunction.
Q. And these outside experts were making comparisons between what you guys were doing, with respect to Zyprexa, and what Warner-Lambert was arguing in connection with their drug Rezulin, correct?
MR. SEE: Object to the form.
A. That is not consistent with,

Page 273

at least, my recollection of the meeting. My recollection is that they were advising us not to take the approach, whatever that was, that Warner-Lambert took. They wanted to see that we maintained an image of being a company of high integrity, which they presumably felt, or at least the individual who expressed this, Warner-Lambert had lost.
Q. And you must have had a different impression than Dr. Baker then, because in the last sentence in that paragraph he said quote, "Disconcertingly, one member compared our approach to Warner-Lambert's argument that Rezulin did not cause more hepatic problems than other drugs in its class," correct?
A. And again, my recollection is that the emphasis that was being placed was on not evolving to a point where we produced a negative image for ourselves.
Q. Okay. As I said, it appears your recollection is different than Dr. Baker's, correct? It least according to this e-mail?

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Exhibit 1, Page 17 of 18
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI
006295

Exhibit 6 David Noesges
Exhibit 2 Charles Beasley Jr. M.D
Exhibit 3 Alan Breier, M.D.
Exhibit 4 Alan Breier, M.D.
Exhibit 5 John Lechleiter, Ph.D

exhibit. October 10, 2000, this is your words. "These guys were really concerned about the weight gain. Not only because of diabetes risk but all the other potential health risks." Those would be some of the risks we discussed in All About Diabetes, right?

A. That's correct.

Q. So the doctors in Atlanta, who talked about why they were concerned about weight gain were concerned because weight gain can lead to hyperglycemia, which is prediabetes, and diabetes can occur and all those risks such as peripheral neuropathy, amputations, and blindness are concerns, right?

MR. SEE: Object to the form of the question.

A. Those would be consequences or adverse outcomes of diabetes.

Q. Right. And these -- and that's exactly what these doctors were concerned about?

A. I think my reference here is

to the other potential health risks such as cardiac disease and those things.

Q. Very good. And I'm glad you corrected me. I very much apologize. They were also concerned that the weight gain could lead to cardiovascular disease and high triglycerides and things of that nature?

MR. SEE: Object to the form of the question.

A. Again, I think, triglycerides being a marker, that wouldn't be necessarily something they would have expressed concern about. And again, I don't recall them directly expressing concern about "X" or "Y" or "Z". Clearly, the sentiment was that their focus was on weight gain. That, because this had been best established with the molecule.

Q. Thank you, sir. Let's go on. They initially thought it might simply be a response to improvement in schizophrenia with a few outliers. And you put this parenthetically, parens, "a rather naive view but they ain't shrinks."

A. See, I'm just a good old boy.

Q. Yes, you are. You know what, I'll tell you something, I read your e-mails, you've got a good sense of humor. At some point in one of these e-mails you talk about it being, this weight gain issue, being a weighty problem. Do you recall that?

A. I think I saw that in --

Q. Right.

A. -- the message today.

Q. Right. So you were just using normal sense of humor as a pun, weren't you?

MR. SEE: Object to the form of the question.

A. It was certainly a matter that was important to us and another way of characterizing that was that it was weighty.

Q. Right, sir. I'm just asking. You're speaking like a regular person right now, right?

A. Correct.

MR. SEE: Object to the form of the question.

Q. Let's go back and continue to look at what you said on that day internally at your company. You said, "They were naive to think" -- by the way when you said it was a rather naive view you were saying the reason weight gain was occurring wasn't because people were getting better on schizophrenia, that's what you're saying here, right?

MR. SEE: Object to the form of the question.

A. Well, it was the issue with their belief -- and I'm not sure how they got this impression -- that it was a few outliers, that would influence the mean change.

Q. And you thought that was a rather naive view, correct?

A. That's correct.

Q. When they understood this is seen in nonpsychotic normals, which you told Mr. Suggs, we see weight gain in individuals who are not schizophrenic and psychotic, correct?

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK
IN RE: MDL-1596
ZYPREXA PRODUCTS
LIABILITY LITIGATION
THIS DOCUMENT RELATES TO:
ALL CASES

C O N F I D E N T I A L

- - -

July 27, 2006

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Videotape deposition of
CHARLES BEASLEY, JR., M.D.
VOLUME 2

- - -

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Page 445

right?
A. And my understanding at the time is that in some of the analysis there had been found to be a correlation.
Q. Well, your answer is a little more clear than that. It says weight accounts for some but not all increase in glucose?
A. That's correct. In statistical models we discuss whether a number of variables can account for an observation.
Q. And by the way, you said the weight accounts for some. What accounted for the rest of the increase?
A. I don't recall at this time anything other than baseline glucose in those analysis that were done.
Q. Okay, sir. And that is in February of 2001, when you say weight accounts for some, right?
A. That's correct.
Q. And it was February of 2001 when you had sent the e-mail saying "our

Page 446

continuous analysis shows there's a statistically significant difference in blood glucose levels comparing Zyprexa to placebo and Haldol?"
A. That's correct.
Q. And then shortly after that you're sent to Cialis, aren't you?
A. I was transitioned to Cialis in 2001, in the middle of 2001.
Q. In the middle of 2001. You're transitioned to Cialis after you've been working on Zyprexa since 1991.
A. And I think for, for some very good reasons for Cialis.
MR. ALLEN: Objection. Nonresponsive.
A. I moved to that team as medical director, yes, sir.
Q. I haven't even asked a question. But you're anticipating my question.
Now I'm going to put this back to where we were because I'm lost. In 2001, after you wrote the memos we've just

Page 447

gone over concerning weight gain and hyperglycemia and continuous analysis you're sent to Cialis; is that correct?
A. I was sent to Cialis.
Q. Is that in the Central Nervous System department?
A. No, it is not.
Q. And you had spent your entire career since you started at Eli Lilly in the CNS department?
A. That's correct.
Q. And you are the man that's being asked the questions about the continuous analysis, you give your answers, and the next thing you know what department do you ship to?
A. As I've stated, my responsibilities were changed to Cialis.
Q. Who changed your responsibilities?
A. I believe it would have been Mike McDonald, who was the head of medical at that time.
Q. Okay. How were you informed?

Page 448

A. I was asked to take on that responsibility by Dr. McDonald.
Q. Right. You didn't request a change, the company requested you to change?
A. That's correct.
MR. ALLEN: Thank you. Okay, sir, we're on my last document, I believe. It's 6128.
THE WITNESS: I'm sorry, I have not given my --
MR. ALLEN: Well, I think he had a copy of this already. That's a different one. Okay.
Isn't that it?
MR. SEE: 6128.
MR. ALLEN: Can you give it to him? I don't think he has it.
I thought you had that already. I apologize, Mr. See, I thought you all used that yesterday.
MR. SEE: We're going to look and see if we have it.
MR. ALLEN: Sure. It's this one, the ludicrous, it could be

Exhibit 2, Page 2 of 2
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006298

Exhibit 6 David Noesges
Exhibit 7 Sidney Taurel
Exhibit 3 Alan Breier, M.D.
Exhibit 4 Alan Breier, M.D.
Exhibit 5 John Lechleiter, Ph.D

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK
IN RE: MDL-1596
ZYPREXA PRODUCTS
LIABILITY LITIGATION
THIS DOCUMENT RELATES TO:
ALL CASES

CONFIDENTIAL

- - -

January 11, 2007

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Videotape deposition of
ALAN BREIER, M.D.

- - -

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Page 26

Q. And what's his position?
A. He is president of Lilly Research Laboratories.
Q. And to whom does he report?
A. He reports to Sydney Taurel.
Q. And Sydney Taurel is the Chief Executive Officer and Chairman of the Board of the company; is that correct?
A. Yes.
Q. Could you briefly describe your duties and responsibilities in the positions of Vice-president and Chief Medical Officer?
A. My responsibilities are to lead the medical organization.
Q. How many people are in the medical organization?
A. We have, approximately, I'm going to say, 2,000 people in the medical organization.
Q. Okay. I'm going to be asking a lot of questions about your activities regarding Zyprexa, but before I do that, I'd like to find out more about your background.

Page 27

Am I correct that your received a Bachelor of Arts degree from the University of Toledo in Ohio in 1975?
A. That's correct.
Q. And you received a Doctor of Medicine degree in 1980 from the University of Cincinnati School of Medicine?
A. Correct.
Q. And then you were a resident in psychiatry from 1980 to 1984 at Yale University School of Medicine; is that correct?
A. Yes.
Q. And I know that you completed your residency in 1984, and that before you joined Lilly in 1997, you were at the University of Maryland and at the National Institute of Mental Health, sometimes referred to as NIMH, but I'm unclear as to what you were doing in that 13-year time period. Could you flesh it up?
A. Sure. When I left residency training at Yale, I joined the intramural program of NIMH. That was, primarily, for

Page 28

further research training. I focused at that time on primarily schizophrenia research.
After completing a three-year research fellowship, I then assumed a position at the University of Maryland in the Department of Psychiatry and was an associate research professor there.
After completing that position, I returned to the NIMH in a more senior position, and I was there for, I believe, about four years, and then joined Eli Lilly and Company in 1997.
Q. Okay. So you started off at NIMH to do a three-year fellowship after your residency, then you were at University of Maryland as an associate research professor for again how long was it?
A. I believe that was about six years.
Q. And were you tenured?
A. Yes.
Q. And then you went back to NIMH for, it would have been, what, four more years?

Page 29

A. Yes. And I just want to be absolutely precise. When I originally started at the University of Maryland, there were not tenure tracks, as I recall, for research professors, and I'm recalling that through that period of time that professors were then tenured.
Q. Okay. And were you tenured at the time you left University of Maryland to go to NIMH?
A. I believe so.
Q. Okay. And before joining Lilly, did you have any particular training or expertise in the diagnose and treatment of diabetes other than what is generally provided in medical school?
A. I did not.
Q. Okay. Am I correct that you had not conducted any research regarding diabetes before joining Lilly?
A. No, I did not.
Q. And you had not published any scientific articles regarding diabetes before joining Lilly; is that correct?

analysis and then the needs, the clinical needs of an individual patient. The data is accessed by physicians in multiple different ways.

Q. But one of the ways is from the label that they get from the drug company, correct?

A. That's one.

Q. Okay. And, sir, when you were head of the Zyprexa Product Team, were you aware that FDA regulations require that the labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug and that a causal relationship need not have been proved? Were you aware of that, sir?

THE WITNESS: Could you repeat your question?

MR. SUGGS: Sure.

QUESTIONS BY MR. SUGGS:

Q. Were you aware, sir, back when you were the head of the Zyprexa Product Team that FDA regulations require that the

labeling shall be revised to include a warning as soon as there's reasonable evidence of an association of a serious hazard with a drug and that a causal relationship need not have been proved?

THE WITNESS: Let me just understand. Are you describing criteria that would be used in order to determine where information would go in the label?

MR. SUGGS: No, sir. Well, in part. I'll represent to you, sir, that the FDA regulations do state that and require that the labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug, a causal relationship need not have been proved. I'll represent to you that's what the regulation states.

THE WITNESS: Um-hum.

QUESTIONS BY MR. SUGGS:

Q. My question to you is, were you aware of that when you were head of the Zyprexa Product Team?

A. Yes.

Q. Okay. And in that context of that FDA regulation requirement, what did the term "association" mean to you when you were head of the Zyprexa Product Team?

MR. BOISE: Object to the form of the question.

A. Well, there's a number of different types of association. There's a temporal association, there's causal association. If we're talking about association that relates to labeling one must consider things like the consistency of the data, the strength of the data, the quality of the data.

So all of those factors are taken into account when determining information that should go into the label and then where in the label it belongs.

Q. Okay. You may have been responsive to this, but I'm not sure, so I want

to probe this further.

A. Okay.

Q. In the context of that FDA regulation that I just talked about where the FDA does require the labeling shall be revised to include a warning as soon as there is, in the FDA regulations terms phrase, reasonable evidence of an association of a serious hazard, that's what the regulation says, what did "association" mean to you in that context?

MR. BOISE: Object to the form of the question.

THE WITNESS: And are we specifically talking about a warning? Is that what your question is?

MR. SUGGS: Yes.

A. Again, that would be -- a few of the things that would be very, very important would be the strength of the association, the quality of the data, the consistency of the data, if there is a causal relationship that would be important, the

Page 98

type of event we're talking about in terms of its gravity and seriousness.
So, again, multiple factors are considered when determining where one proposed to put something in the label.
Q. Okay. Would you agree, sir, that reasonable evidence of an association could include a statistically significant finding in a clinical study that an adverse reaction occurs more frequently with a particular drug as compared to placebo or some other control group?
MR. BOISE: Object to the form of the question.
Q. That that could constitute reasonable evidence of association?
MR. BOISE: Object to the form.
A. You, again, would kind of need to look at the exact phenomenon you're talking about, and one would look for quality, consistency, validity of the signal. It's a little difficult to talk about this in the abstract, but typically one study and one

Page 99

finding, if there's other data available that is perhaps contrary to that, one study would not suffice.
So one would need to look at the totality of the information in order to make their ultimate decisions.
Q. But you would agree that a finding of a statistically significant increased incidence of an adverse reaction in a clinical trial could constitute part of the evidence that would be assessed in making a determination as to whether there was reasonable evidence of an association, correct?
A. I can't agree with that statement as you just articulated because one would need to look at that particular clinical trial, the strength of the trial, the methodology, other data that might be available, mechanistic issues.
In other words, what I'm trying to indicate is that labeling is a very serious business. One needs to consider all of the relevant information, methodology,

Page 100

other data, et cetera, before one can make an informed labeling decision.
Q. Would you agree, sir, that results of a controlled clinical trial is often regarded as the gold standard of scientific evidence?
A. I would not agree with that statement as you articulated because each clinical trial is subject to its own strengths and weaknesses. And there are some clinical trials that provide certain sorts of proof or evidence, and other sort of clinical trials that don't.
So one would have to actually look at the clinical trial in question. We call it kind of looking under the hood, really understanding the methodology, the patient characteristics, all of those factors before one could make an informed decision on results from that trial.
MR. SUGGS: Okay. Let me show you what's been previously marked as Plaintiff's Exhibit 8562.
(Whereupon, Plaintiff's

Page 101

Exhibit(s) 8562, previously marked, was presented to the witness.)
MR. SUGGS: For the record this is a two-page -- take it back -- three-page document. It has a title at the top that says Zyprexa Business Processes.
QUESTIONS BY MR. SUGGS:
Q. Do you recognize this document, sir?
A. Let me take a moment to review it.
Q. Sure.
A. Okay.
Q. My question was, do you recognize the document?
A. I don't recognize this. Don't recall this specific document.
Q. Okay. I should note for the record also that when these documents are produced to us, Lilly also produces a computer database, and in some instances it shows a date, and in this particular instance, the

Exhibit 6 David Noesges
Exhibit 7 Sidney Taurel
Gary Tollefson
Exhibit 4 Alan Breier, M.D.
Exhibit 5 John Lechleiter, Ph.D

Lilly-produced database shows that this document was dated August 27, 2001.
Sir, below that centered heading there's a side heading entitled "Zyprexa Key Decision Team." Do you see that?
A. Yes.
Q. Was there, in fact, a Zyprexa Key Decision Team in 2001 as noted in this document?
A. Yes.
Q. Okay. And does the document accurately describe the voting members of that key decision team?
A. I'm refreshing my memory from this document, but I must say that I don't recall specifically the voting members of this committee, but I accept what is on this piece of paper.
Q. Do you recall when the Zyprexa Key Decision Team was formed?
A. No.
Q. Do you know whether it was in place when you took over as head of the Zyprexa Product Team?

A. I don't believe so.
Q. Okay. Did the Zyprexa product -- pardon me. Did the Zyprexa Key Decision Team exist within the Zyprexa Product Team during your tenure, pardon me, through August 2003 when you then moved on to be chief medical officer?
A. I don't recall.
Q. Okay. So the Zyprexa Key Decision Team did exist for some period of time within the Zyprexa Product Team, but you can't remember for sure exactly when it got started or how long it lasted; is that fair to say?
MR. BOISE: Object to the form.
A. That's correct.
Q. Okay. And the stated purpose, at least in this document, of the Zyprexa Key Decision Team is for efficient cross-representational critical decision making body for the Zyprexa Product Team. Did I read that correctly?
A. Yes.

Q. And did that accurately state the purpose of the Zyprexa Key Decision Team?
A. My recall of this particular committee is not very sharp. I'm reading this and you're reading it appropriately, but I don't have a good firsthand recall of the intricacies of this particular team.
Q. Let me ask you with respect to the types of decisions. The document lists the types of decisions to be made by the Zyprexa Key Decision Team, and they included, again, according to the document, clinical study priorities, label changes/modifications, publication priorities, key issues management, key marketplace decisions, IPP final submission Zyprexa marketing plan. Did I read that correctly?
A. You did.
Q. And did that accurately describe the types of decisions that were made by the key decision team?
A. I'll have to answer it the same way as I did before: I'm not recalling

this particular committee very sharply, but you're reading the document correctly.
Q. Okay. Do you have any reason to doubt that those were the types of decisions made by the Zyprexa Key Decision Team?
A. Well, I mean, I know how these kinds of decisions ultimately got made, and, I mean, I could speak to that.
Q. Okay. Well, the document indicates that down in the process section, the third paragraph within there, that "Decisions were made on the basis of a group vote. Alan Breier retains the right to make a final decision if he's opposed to the group vote."
Did that accurately reflect how decisions were made within that team?
A. I don't recall. It's very possible that this was a relatively short-lived committee and that could be why I'm not recalling it, but I don't have a recollection.

Page 110

the determination as to whether or not a label change or modification would be proposed or recommended by the Zyprexa Product Team?

MR. BOISE: Object to the form.

A. Again, that would be a cross-functional group of scientists who were working with the data. If the analysis of the data indicated that this was something that warranted a label change and would change what we call our core label, we would then take that information to GPLC, the group we talked about earlier. GPLC would look at it, determine, yes, this should be added to core or no it shouldn't.

Q. Okay. Maybe I'm not being clear here or maybe I just need to explore this further.

Who within your Zyprexa Product Team made the decision as to whether or not a proposal would be made to the Global Product Labeling Committee to change or modify a label?

Page 111

MR. BOISE: Object to the form.

A. We generally made those decisions in a fairly cross-functional format. We had safety physicians on the team, we had other experts on the team who would be working with other scientists. They would then analyze data. If they felt this was something that should go to the team, I would be brought into the discussion. We would analyze and look at the data carefully, and then we would make a determination, yes, this is something that needs to go to GPLC, let's get on the GPLC agenda.

Q. Let me ask the question this way. You know how Harry Truman had a sign on his desk that said "The buck stops here?"

A. Yes.

Q. With respect to labeling decisions within the Zyprexa Product Team and whether a labeling change should be taken to the Global Product Labeling Committee for review, where did the buck stop in the Zyprexa Product Team for that type of decision?

Page 112

MR. BOISE: Object to the form.

A. On the Zyprexa Product Team, the buck would stop with me. That determination, again, would be predicated on a cross-functional group of scientists, content experts working on the data, and determining on the strength of the data we would then make a determination to go to GPLC.

Q. And would it be fair to say that while you were president -- pardon me -- while you were team leader of the Zyprexa Product Team, that you would have been aware of any proposal made by the product team to the Global Product Labeling Committee with respect to a label change?

A. Definitely.

Q. Okay. Would it also be fair to say that if a proposal was made by the product team to the Global Product Labeling Committee to change the Zyprexa label, not only would you have been aware of that proposal, but you would, in fact, have signed

Page 113

off on that proposal going to the Global Product Labeling Committee, correct?

A. I would be knowledgeable about it and I would endorse it going forward.

Q. Okay. And would it be fair to say that if something was taken to the Global Product Labeling Committee by your team, you would have wanted to make sure, in your own mind, that before that was done that the proposal was appropriate?

A. We would strive to get it right.

Q. Okay. And you would want to make sure that the basis for that proposal was well thought out and well analyzed before it was taken to the Global Product Labeling Committee, correct?

A. Ideally that is absolutely correct.

Q. Can you think of any -- As you sit here today, can you think of any instance where that did not occur?

MR. BOISE: What didn't

Page 122

Q. Okay. How -- and why is it that you were presuming that?
A. We're a very science-driven team. We looked at data a lot. We looked at signals. We had a process of continual iteration of data where a signal would pop up, we would reanalyze, we would look for better data. We would continually strive to understand what the studies were telling us. We did that with J, as well as other trials.
So I'm, again, I'm presuming that in the course of my activities, we probably reviewed this. And then as I was indicating before, went on to try to determine is this real or not, and through careful analysis determined that we did not feel this was a signal.
MR. SUGGS: Move to strike the nonresponsive portion.
QUESTIONS BY MR. SUGGS:
Q. When you referred in your answer to "J" did you mean that to be the HGAJ study?
A. Yes.

Page 123

Q. Do you also presume that the other members of the?
MR. SUGGS: Strike that.
QUESTIONS BY MR. SUGGS:
Q. Do you also presume that the other medical members of the Zyprexa Product Team would have been familiar with the data from the HGAJ study, and in particular, this finding in June of 1995 that there was a statistically significant increased incidence of high glucose in the Zyprexa users?
MR. BOISE: 1999? The time period for that?
MR. SUGGS: Yes.
A. I can't speak for every physician or scientist on the team in terms of their knowledge of this particular finding because we had people working on, you know, vastly different themes. I would expect that scientists working, specifically, on this theme or on this particular trial would have been aware of it.
Q. Okay. Well, Dr. Beasley's already testified that he was aware of this

Page 124

information. Would you have expected other physicians, such as Dr. Baker and Dr. Kinon, to have been aware of it as well?
MR. BOISE: Object to the form of the question.
A. I can't speak for Kinon or Baker, they were not on the Zyprexa Product Team.
Q. Okay. Would you have expected Mauricio Tohen to have been aware of that?
MR. BOISE: In 1999?
MR. SUGGS: Well, whenever he came on the Zyprexa Product Team.
A. I, again, I can't speak for Mauricio Tohen. He was our bipolar expert. He tended to work and spend most of his focus on our bipolar program. I'm not sure.
Q. Okay. By November of 1999, were you also aware that there had been hundreds of adverse reaction reports relating to elevated blood glucose and diabetes-related events?
MR. BOISE: Object to the

Page 125

form of the question. Foundation.
A. I don't recall at that time the precise number, but I was aware that there were spontaneous adverse events of high glucose.
Q. And a large number of such reports?
MR. BOISE: Object to the form. Vague.
Q. Well, let me ask this. If, in fact, the evidence shows that as of September 1998 there were 200 adverse event reports tallied by Lilly relating to blood glucose elevations, would you have been aware of that?
A. Again, I'm not recalling the exact number. I was clearly aware that there were adverse events reported in the database, I just don't recall the number.
Q. And adverse events relating to blood glucose and diabetes?
A. Yes.
Q. Okay. And I'm assuming that you were aware in November of 1999 that Lilly

for the scope of future activities;" is that correct?
A. You read it correctly.
Q. And did the members of that executive steering committee that are listed there, which is composed of yourself and a number of others, did they stay involved in this process?
A. Yes. We had been working with a number of them before this and had a number of activities, scientific activities, going on.
The purpose of the steering committee was to update a broader group of what we were doing, get their input, and then suggestions for future directions. Because we had already had cross-functional interactions with some of the key people, we decided that we would continue on as we had before; in other words, I would take responsibility for bringing in key people at appropriate times as opposed to, say, having a biweekly meeting or something like that with these people on a formal basis.

So the spirit of that was continued on, but not as a regular meeting of those key individuals, although I took, again, responsibility to keep them informed and to continue to get their input.
Q. And when you described this situation at the beginning of your e-mail where "olanzapine-associated weight gain and possible hyperglycemia is a major threat to the long-term success of this greatly important molecule," for how long had that been regarded as a major threat within the company?
MR. BOISE: Object to the form of the question.
A. Well, the data on weight gain was in awareness from day one, so there was no question about that. As we went into the marketplace, it was very clear that this was a molecule that was having a very, very positive impact on this devastating illness, schizophrenia/bipolar.
There were at this time clinicians in the field asking more questions about potential interventions for weight gain, et cetera. We reasoned if we were better able to understand it from a scientific perspective, offer more interventions, that would then allow more patients to take the medicine than were not being given the medicine because of the concerns around weight gain.
MR. SUGGS: Move to strike the nonresponsive portion.
QUESTIONS BY MR. SUGGS:
Q. For how long had weight gain and possible hyperglycemia been regarded by Lilly as a major threat to Zyprexa?
MR. BOISE: Object to the form of the question.
A. I'm going to have to answer it the same way I did before. We were very cognizant of weight gain from day one. It was very well described at that time, and those characteristics of weight gain did not change.
Q. Did you regard weight gain as a major threat to Zyprexa from day one?

MR. BOISE: Object to the form.
A. We acknowledged that weight gain was for some patients, particularly excessive weight gain, was an undesirable attribute of the drug.
Q. That's not my question. You used -- in your e-mail you describe olanzapine-associated weight gain and possible hyperglycemia as a major threat to the success of Zyprexa. My question is: For how long had you regarded that as a major threat?
A. And again, I'm putting the word "threat" into context, explaining it as those individuals who gained weight to an excessive amount, was a clear side effect of the drug.
MR. SUGGS: That's not my question, sir.
MR. BOISE: Just let him finish and then you can answer it.
QUESTIONS BY MR. SUGGS:
Q. You characterized that issue,

Page 162

either decreasing it or increasing it or whatever, but that they couldn't adjust the dose to deal with olanzapine weight change? Is that a fair restatement?

A. Yes.

Q. Okay. And then in parentheses you say, "Fact: OWC is not dose dependent." Correct?

A. You've read that correctly.

Q. So the fact was the same as the perception, correct?

A. Yes.

Q. Okay. Then you also note that physicians, in the following bullet point that "Physicians want more data." I'm assuming that was based on market research, correct?

A. Yes. Each one of the bullets under this section of market research would have been data brought into the company through surveys of physicians from the market research department.

Q. Okay. And then in your next bullet point you say, "Blanket detailing will

Page 163

be damaging since many physicians do not see OWC as an issue."

Did I read that correctly?

A. You did.

Q. We need some more translation there. Blanket detailing refers to going out and having your sales reps -- well, let me back up for a second.

We need to talk about detailing. In the pharmaceutical business, the process of a sales representative calling on physicians and discussing the product with the physician is often referred to as detailing, correct?

A. That's correct.

Q. Okay. In fact, sales representatives used to be referred to as detailmen, correct?

A. I'm not familiar with that term, but that's consistent with what you said.

Q. Okay. So when you're talking about blanket detailing here, what you're talking about, that phrase would mean having

Page 164

sales representatives from Lilly go out and talk to all physicians about a particular issue, correct?

MR. BOISE: Object to the form.

A. No. What this phrase means is having a unidimensional message. In other words, as opposed to presenting all relevant data or important relevant data would be to have a single isolated message.

Q. And what you say here is blanket detailing will be damaging since many physicians do not see olanzapine weight change as an issue, correct?

A. That's what it says.

Q. Okay. And how was it determined that many physicians do not see olanzapine weight change as an issue, do you know?

A. Well, again, this is market research, this isn't Lilly's opinion. This is the information coming into the company from prescribing physicians. What I interpret this to mean is to say that

Page 165

physicians that were in the survey, some of them were saying I'm interested in different information in a detail call. I'm not seeing weight gain as a problem in my patients, but I've got questions about other things. So don't give me a single message detail, but give me the information that's important to me.

I think each physician has, at various times, different questions and different needs for data, and that's what I interpret this bullet point to be referring to.

Q. Okay.

MR. SUGGS: I've been told that we have about five minutes left on this tape and it's now 12:30. You want to break for lunch?

MR. BOISE: Yeah.

THE VIDEOGRAPHER: Marks the end of tape two of the deposition of Alan Breier. We're off the record at 12:27.

(A lunch recess was taken by the

Page 186

phrase "treatment emergent" mean?
A. "Treatment emergent" is a term that's used for an event that crosses a certain threshold. It doesn't refer to what the baseline was or the starting point.
Q. Well, doesn't the phrase "treatment emergent" indicate that the situation emerged during treatment?
A. Yes. But the reality of glucose, particularly random glucoses, is there's a lot of up and down. It's very possible that someone could have a high level at one point, say, a baseline, a low level later, a high level later on. So there's quite a bit of fluctuation with glucose.
So if you crossed a certain threshold at a certain point in time in a clinical trial, that would be considered a treatment-emergent event.
Q. Well, doesn't, in fact, the new statement that was proposed indicate that these were people whose random glucose was higher after they were treated than before they were treated?

Page 187

A. Well, what this -- in this particular instance, what it indicates was that the random glucoses at baseline were, say, 140, and then the event was captured at some point around 160.
Q. So their baseline blood glucose level was lower at the beginning than it was after they took the drug, correct?
A. On this one measure. But what I was trying to convey with random glucose --
Q. I'm sorry, what one measure?
A. With this one blood measure at baseline that would indicate that they were below 140 but the day before they could have been at 160.
So what I'm saying and trying to indicate is that particularly with random glucoses, there's a tremendous amount of variability. And I don't think that the baseline starting point for a definition of a treatment-emergent event is necessarily the critical component.
Q. Well, apparently, though,

Page 188

your product team and pharmacovigilance group thought this finding of treatment-emergent hyperglycemia in the olanzapine group warranted a revision to the label, correct?
A. I don't know all or who was involved in this particular analysis because, as I noted before, I don't have recollection of it, but whoever put this table together suggested that it go into the label.
Q. Well, we know that at least according to the first page of the document this was the proposal of the product team, correct?
A. That's what it says, and Pharmacovigilance.
Q. And Pharmacovigilance.
Now, when they refer to the treatment-emergent hyperglycemia in the olanzapine group being 3.6 percent and that the incidence of a placebo group was 1.05 percent, the rate of treatment-emergent hyperglycemia in the Zyprexa group was three and-a-half times higher than in the placebo group, correct?

Page 189

A. I would agree that 3.6 percent is three and-a-half times greater than 1.05 percent.
Q. And it's your testimony that you have no recollection of this submission being made to the Global Product Labeling Committee?
MR. BOISE: Objection. Asked and answered.
A. During the 2000 time frame, I do not have a recollection of this analysis or this document.
Q. Sir, in your November -- by the way, this label change was never made with this language, was it, sir?
A. I can attest that these data did not go into the label because we learned that these data were not reflective of the random glucose situation of this dataset.
MR. SUGGS: Objection, nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Your labeling never advised physicians of the proposal that was made

Page 190

here, correct? Yes or no?
A. We did not advise clinicians of this particular finding because additional analyses were conducted that were more valid and clinically meaningful than these analyses, and it was the correct analyses that we submitted to the FDA and shared with clinicians.
MR. SUGGS: Sir, you're giving me spin which I'm going to move to strike as nonresponsive. I need a yes or no answer.
MR. BOISE: I object to your characterization, sir.
MR. SUGGS: I need a yes or no answer.
QUESTIONS BY MR. SUGGS:
Q. Did your company advise prescribing physicians with the language that was proposed there, yes or no?
MR. BOISE: Object to the form of the question. Asked and answered.
THE WITNESS: I want to be

Page 191

very clear --
MR. SUGGS: Then say yes or no, sir.
THE WITNESS: I am not spinning any data during this proceedings nor have I at any other point.
QUESTIONS BY MR. SUGGS:
Q. Sir, can you give me a yes or no answer? Did the company tell doctors what was proposed in this label change or not? It's a simple yes or no question.
MR. BOISE: And he's answered your question.
MR. SUGGS: No, he has not. He has not.
I want a simple yes or no answer.
MR. BOISE: The record will reflect that he has answered it.
A. We don't share inaccurate data with clinicians.
Q. Sir, did you or did you not tell physicians of that label change that was

Page 192

proposed there by the product team and pharmacovigilance, yes or no?
MR. BOISE: Objection, asked and answered.
A. We do not share inaccurate data with clinicians.
MR. SUGGS: Move to strike the nonresponsive portion.
QUESTIONS BY MR. SUGGS:
Q. Sir, did you tell physicians at any time that analysis of clinical trial data from Lilly's own studies showed that the existence of treatment-emergent hyperglycemia was three and-a-half times higher than in the placebo group?
MR. BOISE: Object to the form of the question.
Q. Yes or no?
A. We did not.
Q. Thank you.
By the way, these clinical trials that are referred to there in that middle section where it says "a recent review of random glucose levels of patients in

Page 193

olanzapine clinical trials revealed that the incidence of treatment-emergent hyperglycemia was three and-a-half times higher than in the placebo group," what clinical trials were those, do you know?
MR. BOISE: Object to the form.
A. Again, I don't recall this specific analysis. My presumption would be that it would have well likely come from the integrated clinical trial dataset, which is a compilation of multiple trials.
Q. And do you know who did the analysis?
A. No.
Q. Do you know when they did the analysis?
A. This particular analysis?
Q. Yes.
A. Presumably the analysis were done prior to 2/21/2000.
Q. Do you know how they did the analysis?

Q. Okay. That seminar that's referred to there at Lilly at the end of 1999, did you attend that seminar?
A. Yes.
Q. Okay. And I assume Dr. Casey was, must have been invited to come and give a presentation, correct?
A. I invited him.
Q. Okay. And at that seminar, according to this document, "He," referring to Dr. Casey, "performed chart review of 136 veteran patients who had been exposed to olanzapine therapy for at least four months, average of 1.4 year. Of the 39 patients who had normal fasting glucose levels before olanzapine therapy, seven, or 18 percent, had fasting glucose levels of 126 milligrams per deciliter or higher during olanzapine therapy." And then in parentheses it says, "threshold that met the 1998 ADA diagnostic criteria for diabetes."
Do you see that language?
A. I do.
Q. And the ADA that's referred

to there is the American Diabetes Association, correct?
A. Yes.
Q. Okay. And so in this review of charts that Dr. Casey did of patients who had normal fasting glucose levels before they started using Zyprexa, 18 percent of them had fasting glucose levels that exceeded the criteria for diabetes after they had used it for at least four months; is that correct?
A. You are reading this correctly.
Q. Okay. Now, did Dr. Casey undertake that chart review on his own or was this part of a study that was being conducted by Lilly?
A. I don't know.
Q. Okay. When Dr. Casey came to Lilly and gave that presentation in which he said that 18 percent of people with normal blood levels had diabetic blood levels after using the drug for four months or more, did that come as a surprise to you at that point, or were you aware of his findings before he

came to give the seminar?
MR. BOISE: Object to the form of the question.
A. I don't recall if he and I talked about the data before he came or not.
Q. Do you recall who else was at that seminar where Dr. Casey said that 18 percent of the people who use Zyprexa after four months had diabetic blood levels?
A. I don't recall, sitting here at this moment, who else was at the seminar.
Q. Okay. The very term "seminar" makes me think, and I could be wrong, that there was a group of people there. Is that a fair assessment?
A. I think that's a fair characterization.
Q. And would you have expected the majority of people from the Zyprexa Product Team to be there?
A. I, again, don't recall who was in attendance. Typically, when we have a seminar with an outside speaker, we advertise it fairly broadly within the company. It's

an open-door policy, so those interested in this particular area were invited.
Q. Okay. And it's fair to say that, also, isn't it, sir, that Lilly never advised prescribing physicians in the labeling of Dr. Casey's findings, did it, sir?
MR. BOISE: Object to the form.
A. No, we didn't, because this gets to a very central point that we've been discussing today, and that gets to quality of data.
Q. Sir --
A. If I could just finish.
These are 39 patients, a retrospective analysis in which there are no controls, no understanding of baseline factors, inadequate amount of data to really understand even a full temporal association.
So these are the very kinds of data that, while it's important to look at all the data, and we were interested in looking at all the data, this is the type of

Page 202

study alone that one cannot draw very many conclusions.

MR. SUGGS: Move to strike the nonresponsive portion of your answer after the word "no."

QUESTIONS BY MR. SUGGS:

Q. Sir, this proposal to change the label that was reviewed by the Global Products Labeling Committee did not go forward in February of 2000, correct?

MR. BOISE: Object to the form.

A. These data were not included in the label.

Q. Now, you did make a label change several months later in May of 2000, correct?

A. That's correct.

Q. And we've seen the document where that was done, Exhibit 4858. If you can find that in the pile. That was the May 9, 2000, letter?

A. Yes.

Q. And this May 9, 2000, letter

Page 203

is from Gregory T. Brophy in the U.S. Regulatory Affairs Department in Eli Lilly to the FDA on May 9, 2000, correct?

A. Yes.

Q. And it informs the FDA that Lilly has already revised the package label for Zyprexa in three respects, correct?

A. Yes.

Q. And Dr. Brophy notes in his letter of May 9, "Effective immediately we will be implementing this change," correct?

It's on the second page, second to the last paragraph, last sentence.

A. Yes.

Q. And so this label change was made without prior FDA approval, correct?

A. That's correct.

Q. Okay. Now, one of the things that this label change did had to do with the neuroleptic malignant syndrome. And that has really nothing to do with the issue of diabetes. Would that be a fair characterization?

A. It's an important safety

Page 204

phenomena. You're correct, it's not related to diabetes.

Q. Okay. And then another change that was made to the labeling was that there was an addition in the adverse reaction section of the labeling, in the post-introduction reports part of the label, inclusion of diabetic coma. So that that section then read, "Adverse events reported since market introduction which were temporally but not necessarily causally related to Zyprexa therapy include the following: Diabetic coma and priapism," correct?

A. Yes.

Q. And priapism is another condition that has nothing to do with diabetes, correct?

A. Correct.

Q. Okay. Priapism is involuntary sustained erection, correct?

A. Correct.

Q. Okay. And then the other change that was made was item No. 2 in the

Page 205

adverse reaction section, there was some additional language added regarding the laboratory changes section and findings of data from the olanzapine clinical trial database with respect to random plasma glucose levels, correct?

A. Yes.

Q. And could you read that into the record, please?

A. The --

MR. BOISE: What, the entire section?

MR. SUGGS: Sure.

MR. BOISE: You can read. I can read.

MR. SUGGS: Well, the jury might want to hear it.

MR. BOISE: Why don't you read it in?

MR. SUGGS: No, I'd rather he read it in. Would you please read it into the record, sir?

MR. BOISE: Is it a question?

MR. SUGGS: It's a request.

Q. You had considerable skepticism expressed about the results of this analysis by other consultants to the company, did you not?

A. I would characterize that most people who saw the data found it very helpful. This was a unique dataset of over 6,000 patients in controlled trials. Just comparing it to the Casey report of a very small, retrospective, poorly-controlled dataset.

It were these kinds of studies, the Casey report, that were in the public domain that were not terribly informative. And we felt that we had a unique set of data, a one-of-a-kind in terms of quality and length, numbers of exposures.

And most of the input I received on this data was quite laudatory and positive. In fact, we not only submitted this data to the FDA, but we submitted it to regulatory bodies worldwide, and it's in the European label today. So those scientists looked at it and found it quite helpful and

meaningful.

MR. SUGGS: Move to strike as nonresponsive.

QUESTIONS BY MR. SUGGS:

Q. Do you recall that outside consultants to the company in a meeting of October 2000 informed the company that they were highly skeptical of these findings?

A. Not quite sure what you're referring to.

Q. All right. We'll come back to that.

If I could direct your attention to the following page. This is comments from another reviewer. And the first numbered comment there the reviewer says, "The authors do not adequately emphasize how crude their method is for finding an effect. Random glucose values represent an insensitive method for assessing glucose tolerance."

Do you see that language, sir?

A. Um-hum.

Q. And, in fact, at some point after this, Lilly switched from random glucose blood testing to fasting blood glucose testing, correct?

A. That's correct.

Q. And that's because, in fact, random glucose values are an insensitive method for assessing glucose tolerance, correct?

MR. BOISE: Object to the form of the question.

A. There are strengths and weaknesses to both approaches.

Q. If I could direct your attention to the second point there it states, "Most of the values were, probably, drawn during the first three months of each trial. It would be helpful to know the number of samples in each condition that were collected during the later stages of the trials."

And, sir, in fact, most of the values, the blood samples were drawn during the first three months of each trial;

isn't that correct?

A. I don't know if that's the case.

Q. If Dr. Kwong has testified that that's correct, would you have any basis to dispute that?

A. I would prefer to rely on my own answer here.

Q. And your own answer is you don't know?

A. I don't recall.

Q. Okay. The third point raised there by this reviewer was, "Many of the early studies of olanzapine were biased toward low doses of the drug. Since there's a consensus that most patients require 10-milligram or more of olanzapine, it would be helpful to know if there is a dosage effect on glucose tolerance."

Do you see that language?

A. Yes.

Q. And, in fact, many of the early studies of olanzapine did use low doses of the drug; is that correct?

Page 290

MR. SUGGS: Move to strike the nonresponsive portion.
QUESTIONS BY MR. SUGGS:
Q. You talked to Dr. Tollefson about this information you received, correct?
A. We talked nearly daily when we were both in the office. I can't recall sitting down with Dr. Tollefson and having an exact conversation about this topic. I assume we did because these are the kinds of things we talked about in our frequent communications.
Q. Okay. Directing your attention to the e-mail preceding the one from Mr. Baker, pardon me, the one from Mr. Brodie, the one at the bottom of Page 3 which starts off by saying, "FYI: My take was that this board of academic endocrinologists was impressed enough by the magnitude of weight gain and number of reports in the spontaneous adverse event database, that they were predisposed towards skepticism to any analysis that did not find higher hyperglycemia rates on olanzapine than

Page 291

comparators."
I read that correctly, right?
A. Yes.
Q. And that's, essentially, the same kind of concern or lack of belief that was expressed by one of the reviewers of your paper. Do you recall that?
A. I recall that. But I again want to reiterate that we follow the data. If the data were there and demonstrated important relationships then we would communicate that information, we would follow the data.
I, just on this point alone, I'm recalling a letter to the editor by the neuropharm division of the FDA who analyzed data, not only from us but other sponsors, and came to the exact same conclusion, that there is not support from clinical trials of the kinds of associations that we're talking about here. So although it might be surprising, at the end of the day the data has to speak for itself.

Page 292

MR. SUGGS: Move to strike everything in your answer after your first sentence "I recall that."
QUESTIONS BY MR. SUGGS:
Q. In fact, one of the reviewers said that the authors present a highly curious?
MR. SUGGS: Strike that.
QUESTIONS BY MR. SUGGS:
Q. One of the reviewers of your paper for publication that we looked at earlier, Exhibit 1440, said that "The authors present a highly curious dataset. Since their own work has shown that olanzapine is associated with a clinically and statistically pertinent increase in weight compared to both haloperidol and placebo, they seem to be suggesting that olanzapine exerts a sizable antidiabetic power."
That's what he said, correct?
A. That's what that one reviewer said.

Page 293

Q. And your consultants in the meeting in October of 2000 were skeptical of your results as well, correct?
MR. BOISE: Object to the form. Go ahead.
A. Again, what I got from the consultant was, okay, those categorical analyses are interesting, let's keep looking at the data, and they were suggesting additional analyses.
It's not unusual in science to have surprising findings, to have findings that maybe are not predicted, but the scientific process is to continue to do the experiments, look at the data, analyze the data, and let the science lead the way. And that's precisely what we did on this topic.
Q. Can I direct your attention to Page 2. This is an e-mail in the same chain from Dr. Beasley to you with copies to Robert Baker, Paul Berg, Scott Clark, John Holcombe, Roland Powell, Alvin Rampey and Roy Tamura, correct?
A. Yes.

Page 302

Q. Sir, let me try for the fourth time, and I'd appreciate just a simple yes or no answer to what I think is a simple question.

Did Lilly tell physicians that weight gain with Zyprexa was manageable for most patients?

MR. BOISE: Object to the form of the question.

A. I don't recall that exact phrase.

Q. Okay. In other words, you don't know?

A. I know what we did in terms of communicating weight gain.

Q. If I could direct your attention back to Dr. Beasley's e-mail. Three lines up from the bottom he says, "There does not seem much to say about scientific analyses of weight gain. We know it's a weighty problem. When you translate 1 to 2 percent gain of 40 plus kilos into the absolute number based on 5 million patients, the number is 50 to 100,000. 100,000 people

Page 303

putting on 90 pounds of weight is a lot."

Were you aware of that type of calculation before Dr. Beasley mentioned it in this e-mail to you?

A. I knew there was a distribution of weight gain. And knew, again we talked about the tails of a bell-shaped curve.

Q. And you recall this morning I asked you whether you were aware that Dr. Beasley had done calculations indicating that there were some people who gained 80 to 90 pounds of weight and you said you didn't recall that?

MR. BOISE: Object to the form.

A. I'd need to refresh that transcript.

Q. Okay. Well, does this refresh your recollection that Dr. Beasley, had, in fact, calculated on the order of 50 to 100,000 people gaining 90 pounds of weight while using Zyprexa?

A. I don't doubt the statistics.

Page 304

It's again a 1 to 2 percent. And those would be the tails of that bell-shaped distribution.

And the Kinon publication, I think we presented the data quite clearly on not only the more likely weight gain but also extremes at both ends.

MR. SUGGS: Move to strike the nonresponsive portion.

QUESTIONS BY MR. SUGGS:

Q. Sir, if I could direct your attention to the following page. At the top of Page 3, Dr. Beasley writes, "On the diabetes side, the concern was about the use of categorical analyses."

Do you see that language?

A. Yes.

Q. And who was it that decided to do categorical analyses?

MR. BOISE: Object to the form of the question.

A. I don't know that I know who decided initially. For approaches to data of this nature, we would typically do it in a

Page 305

cross-functional framework. We would consult endocrinologists in and outside the company, bring in our best people from stats and from neuroscience and create a delineated plan.

Q. Would that have originated within the Zyprexa Product Team, a decision to conduct categorical analyses of blood glucose?

A. I'm sure that Charles was involved in, Dr. Beasley were involved in those discussions.

Q. Okay. And back at this time in October of 2000 -- well, this analysis actually began in -- at least by February of 2000, as we saw earlier, correct?

MR. BOISE: Object to the form of the question.

A. Yes.

Q. Okay. And at that point in time there was nobody on the Zyprexa Product Team who was an expert in the field of diabetes, correct?

MR. BOISE: Object to the form.

Page 350

hyperglycemia, et cetera.
QUESTIONS BY MR. SUGGS:
Q. Do you recall receiving this e-mail from Dr. Beasley back in February of 2001?
A. I do.
Q. And when was the last time you reviewed this document?
A. Um, I believe within the last month.
Q. And in this e-mail Dr. Beasley wrote starting in the third sentence, "Our continuous analyses show that olanzapine does result in statistically significant mean increases in random glucoses relative to placebo and haloperidol. No significant difference relative to Risperidone but power is small. Clozapine is associated with a larger olanzapine versus haloperidol and a significant increase compared to haloperidol. These increases are occurring as early as week one. May not represent a true deterioration in glycemic metabolism but

Page 351

simply an increase in food intake since these are random and not fasting glucoses. These changes are accounted for in part but not entirely by weight increase."
Do you see that language, sir?
A. Yes.
Q. And, sir, does that refresh your recollection that Dr. Beasley told you that the glucose elevations that they were seeing were partially accounted for by weight gain?
A. Again, we've looked at this very carefully and --
Q. Sir, my question is whether that refreshes your recollection that that's what Dr. Beasley told you?
A. You've read this e-mail correctly. He and I have had multiple different conversations on this topic.
Q. And that's my question, is whether he told you about that, whether this refreshes your recollection that he told you? And does it now refresh your recollection?

Page 352

MR. BOISE: Objection. He never said he -- object to the form.
A. You've read the e-mail correctly. The key point I think in this e-mail is the problem with continuous measures of random samples.
Q. Sir, let's get back for a second. Remember before I showed you that document, I asked you do you recall Dr. Beasley telling you that increases in glucose with Zyprexa users were accounted for in part but not entirely by weight increase and you said no. So I showed you the document. And now I've shown you that language.
And my question is: Does this now refresh your recollection that Dr. Beasley told you that? That's my question.
A. And I would say yes at this one point in time, but in order to give you fuller context to the question --
Q. Sir, I'm just asking for a direct answer to my question, and you have

Page 353

answered it, yes, this does refresh your recollection that Dr. Beasley told you that, correct?
A. To that narrow question yes.
Q. That's my question.
A. I do think, though, it's important to appreciate that what he points out here is very, very important in interpreting the continuous data, and that is the food effect of random samples, and that alone makes it nearly impossible to draw the conclusions around weight.
THE WITNESS: Move to strike your answer as not responsive.
QUESTIONS BY MR. SUGGS:
Q. Sir, can we get back to Exhibit 1111? That's the one in your left hand.
A. Yes.
Q. At the bottom of Page 4 is another heading that states "What We Don't Know." We already talked about part of that, the part that said you didn't know how to effectively deal with weight gain associated

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK
IN RE: MDL-1596
ZYPREXA PRODUCTS
LIABILITY LITIGATION
THIS DOCUMENT RELATES TO:
ALL CASES

C O N F I D E N T I A L

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January 12, 2007

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Videotape deposition of
ALAN BREIER, M.D.
VOLUME 2

- - -

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Page 427

referred to by metabolic issues is weight gain because it's under a section called Weight Gain and the available data on these newer drugs was, primarily, related to weight gain.
Q. Okay, those drugs also, though, have less reported adverse effects such as hyperglycemia and diabetes than Zyprexa or Clozaril or Risperdal or Seroquel; is that correct, sir?
MR. BOISE: Objection to the question.
MS. JOBES: Objection to the form, foundation.
MR. BOISE: Also compound.
A. That's incorrect.
Q. Okay. Lilly never informed physicians in the Zyprexa label that Zyprexa's weight gain is roughly twice that of Risperdal, did it?
MR. BOISE: Object to the form of the question.
A. The weight gain described in the label related to Zyprexa is very

Page 428

extensive. It's provided in a number of places in the label in great detail. The convention of labeling for weight gain and most side effects -- in fact, I can't think of an exception for any side effect -- would not include the safety information from another sponsor's drug. So, it would have been inappropriate to add safety information on another sponsor's drug in most instances.
Q. Sir, I'm not asking you for your opinion, I'm asking for fact. The Zyprexa label did not inform physicians that Zyprexa weight gain was roughly twice that of Risperdal, correct?
MR. BOISE: Object to the form of the question.
A. Again, the Zyprexa weight gain sections are quite extensive, they were so from day one. It would have not been appropriate to include weight gain from another atypical antipsychotic drug. And so as regarding to the label, you are correct.
I think if there is something related to your question about

Page 429

communication of weight gain, there are appropriate venues where you can communicate not only one's own weight gain data on their own drug but weight gain associated with other drugs that might be important to prescribers in making a prescribing decision such as medical letters, publications, and those appropriate vehicles were used.
MR. SUGGS: Move to strike the nonresponsive portion which is everything other than "you are correct."
QUESTIONS BY MR. SUGGS:
Q. If I could direct your attention to the next section in this document that pertains to diabetes. And there are a number of bullet points below that heading. And in particular, I direct your attention to the third bullet point. You see where I'm indicating, sir?
A. Yes.
Q. Okay. And the first sentence there states, "Results of two Lilly epidemiology studies, analysis of AdvancePCS

Page 430

and GPRD databases, indicate that the risk of DM is increased in patients treated with antipsychotics including Zyprexa."
And the DM that's referred to there is diabetes mellitus, correct?
A. That is correct.
Q. Okay. So Lilly had conducted two epidemiological studies which showed that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa, correct?
A. You've read that sentence correctly.
Q. And Lilly did not include in the warning section or the precaution section of its labeling any language informing physicians of that fact --
MR. BOISE: Object to the form of the question.
Q. -- correct?
MR. BOISE: I'm sorry. Objection. Foundation.
A. Again, we need to go back to appropriate --

Page 431

Q. Sir, I need to have you answer my question as a matter of fact. I'm not asking for your opinion. I'm not asking for your spin. I just want you to confirm for the jury on this record that your labeling did not inform physicians that results of two Lilly epidemiological studies indicate that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa. It's a simple yes or no question. Did Lilly tell that to doctors or did they not?

MR. BOISE: Object to the form of the question. Compound. You've asked about four questions there. What is the simple question?

Q. My simple question, sir, is: It is true, is it not, that Lilly's label did not inform physicians in the precautions or warnings section in 2002 that "Results of two Lilly epidemiological studies indicate that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa"?

Page 432

A. I first want to take umbrage with your comment about spinning. And I assure you that I'm not spinning any answers, I'm answering as forthrightly as I possibly can.

Q. Then can you please give me a yes or no answer to that question, sir?

A. Yes.

The approach to labeling requires that you take into account the totality of the data --

MR. SUGGS: Excuse me, sir. Can you please answer the question simply and directly yes or no, and then after answering directly, if you feel the need to expand on your answer then by all means you can say whatever you want. I'm not going to try to cut you off at all. But please, sir, would you answer the question directly and then give whatever other verbiage you feel is appropriate. Okay? Let me restate the question.

Page 433

QUESTIONS BY MR. SUGGS:

Q. It is true, is it not, that Lilly's label in 2002 did not inform physicians in the warnings or the precautions section that results of two Lilly epidemiological studies showed that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa? Yes or no?

A. The answer is no. And the reason for that is because it would have been inappropriate to include such language based on the data that was available in 2002. These studies did not change the appropriateness of the label as of 2002.

They are used in labeling because we take a totality of all of the information when we examine our label. So these two studies did inform our thinking but reassured us that we were appropriately labeled in 2002.

MR. SUGGS: Move to strike the nonresponsive portion.

MR. BOISE: Okay, let's take

Page 434

five. Take a break.

MR. SUGGS: Okay.

THE VIDEOGRAPHER: Marks the end of tape No. 1 of the deposition of Dr. Breier. We're off the record at 10:45.

(At this time, there was a brief recess taken, after which the following proceedings were had:)

THE VIDEOGRAPHER: We are back on the record. This is the beginning of tape No. 2 of the deposition of Dr. Breier; it's 11:03.

QUESTIONS BY MR. SUGGS:

Q. Dr. Breier, I'd like to direct your attention back to Exhibit 4051. In the bullet point just below the one we were talking about it states "FDA FOI Database of reports of DM cases: Clozaril 542, Zyprexa 434, Risperdal 244, Seroquel 57."

We need to do some

Page 451

correct?
A. Yes.
Q. Okay. So it was your expectation that if your sales force went out and promoted the use of Zyprexa within the new Japanese label and told physicians "don't give this to patients with diabetes, test people's blood glucose, and explain this issue sufficiently to the patient and family members," that that would, by design, dramatically reduce the number of adverse events, correct?
MR. BOISE: Object to the form.
A. That is correct. And the reason why is a very important point --
MR. SUGGS: Sir, I didn't ask for your opinion.
A. -- and that is because the data that we had at the time, including the TED analysis, indicated that the majority of cases or many of the cases that occur were, actually, latent diabetics at baseline prior to assignment or active diabetics

Page 452

undiagnosed, and they then were emerging on treatment.
So because of the high rate of diabetes in this population and the fact that patients were going on to treatment already with either prediabetes or diabetes, then for many of these cases it was a matter of time, irrespective of what drug they were on, that their diabetes then would be diagnosed.
So with the contraindication at baseline, those cases that were now going into the different treatment arms would now be going to other agents, and here again, irrespective of drug, would be emerging as cases of diabetes. So I think this puts things into an important context.
MR. ALLEN: I object to everything after "that is correct" as nonresponsive.
MR. SUGGS: I was going to make the same objection.
QUESTIONS BY MR. SUGGS:
Q. You recall being informed --

Page 453

MR. SUGGS: Well, let me back up for a second.
Let me show you what's been previously marked as Plaintiff's Exhibit 3211.
(Whereupon, Plaintiff's Exhibit(s) 3211, previously marked, was presented to the witness.)
MR. SUGGS: For the record, this is an e-mail from Vicki Poole Hoffmann to Kristine Healey with a copy to Robert Baker.
QUESTIONS BY MR. SUGGS:
Q. Do you know those individuals?
A. I have no recollection of Kristine Healey. I do know who Robert Baker is, and I'm not recalling who Vicki Poole Hoffmann is.
Q. Okay. In the first paragraph of Ms. Hoffman's e-mail, she states, "We are not sure that Zyprexa 'causes' hyperglycemia, because

Page 454

of the high background rate in schizophrenics, and we have not yet said, specifically, that Zyprexa is or is not associated with hyperglycemia. Our strategy has been to say that if these agents are associated with hyperglycemia then all agents are associated with it at comparable rates."
Do you see that language, sir?
A. Yes.
Q. And that was, indeed, the Lilly strategy, was it not?
MR. BOISE: Object to the form of the question. Foundation.
A. I would disagree with the statement as worded. Again, Vicki Poole Hoffmann, I don't know who that is. I don't believe this is a person with medical background, certainly is not a physician, and that would not be a precise articulation of our understanding of the data.
Q. Sir, was it your understanding that Vicki Poole Hoffmann was in the Issues Management Department?

Page 455

A. I'm just not recalling who that is.
Q. Do you recall being informed in June of 2002 that a clinical study by Lilly indicated that high nonfasting glucose in Zyprexa users was probably causally related?
MR. BOISE: Object to the form. Foundation.
THE WITNESS: I'm not understanding the question. Could you repeat it?
MR. SUGGS: Let me show you what's been previously marked as Plaintiff's Exhibit 7802.
(Whereupon, Plaintiff's Exhibit(s) 7802, previously marked, was presented to the witness.)
MR. SUGGS: Which, for the record, is a one-page document Listing of Treatment Emergent Abnormal Lab Findings in Olanzapine-Treated Patients. This

Page 456

is from study HGFU.
QUESTIONS BY MR. SUGGS:
Q. Are you familiar with study HGFU?
A. I'm recalling that to be a bipolar trial that looked at olanzapine plus mood stabilizers.
Q. And if you could direct your attention to the laboratory value for glucose nonfasting. It shows that 2.2 percent of the people who got olanzapine had high glucose and 0 percent had, of the placebo group, had high glucose; isn't that correct?
A. Yes. What I'm reading is 185 patients on olanzapine plus mood stabilizer, of the 185, four, or 2.2 percent, is on the glucose nonfasting high line. And that then looks like it's being contrasted with 97 patients with mood stabilizer plus placebo with zero cases or 0 percent.
Q. Um-hum. And to the right on that line there's some letters, A -- you see those letters A?
A. I do.

Page 457

Q. And if you could drop down to the bottom of the page there's a little legend describing what those letters mean. Could you read what it says for letter A aloud?
A. "Category: A equals event probably causally related."
Q. And did anyone inform you of that conclusion with respect to study HGFU?
MR. BOISE: Object to the form of the question. Foundation.
A. No. And I was, actually, quite aware of the data coming out of the FU trial, both efficacy and safety.
I'm not familiar with categorizations of this nature. I don't know who produced this single page. It was not the position that the data would be reflected as described in this particular table.
The data that I see on the page certainly would not support it if it were valid, and I don't know if it is or not.
So I must say I'm -- I can't comment too strongly to this particular

Page 458

one-pager, given I don't know who authored it, I don't know where it came from, I don't know if it was, for example, a rough draft or an early draft or produced by someone who was not fully cognizant of the data.
If we thought there was a new signal in FU, we all would have been working on it, we would have understood it, we would have communicated it to the FDA and we would have taken appropriate action.
MR. ALLEN: Object to everything after "no" as nonresponsive.
MR. SUGGS: Beat me to it.
QUESTIONS BY MR. SUGGS:
Q. Did you know a Dr. Simeon Taylor?
A. I have a recollection of that individual.
Q. And what's your recollection of that individual?
A. My recollection is that he was an endocrinologist who joined Lilly. Worked at Lilly, I'm recalling, for a

Page 479

Zyprexa, and other typical agents. Our message." And then there are seven items listed there, correct?
A. Yes.
Q. And at the core of your message was the position that the "Data do not support a causal link between Zyprexa and diabetes, and while the scientific literature is mixed there does not appear to be consistent differences among atypicals."
That would be item No. 4, correct?
MR. BOISE: Object to the form of the question.
A. You read item No. 4 correctly. That is reflective of the scientific information. You used the word "core." I don't know precisely what you meant by that. But this statement is here --
Q. Well, let me restate it. If you have a problem with that, let me state it this way: Included in your message was the Point No. 4 that "Data do not support a causal link between Zyprexa and diabetes;

Page 480

while the scientific literature is mixed there does not a appear to be significant differences among atypicals." Correct?
A. You read that correctly, and that is the best reflection of the totality of scientific information.
MR. SUGGS: Move to strike the nonresponsive portion.
QUESTIONS BY MR. SUGGS:
Q. When you stated there that there does not appear to be consistent differences among atypicals, that was referring to differences in rates of hyperglycemia and diabetes, correct?
MR. BOISE: Object to the form of the question.
A. That's my reading of that item.
Q. And on the second page under the heading Corporate Response Letter it states, "On July 11 customers will begin to receive the corporate response letter, Attachment 1, a letter targeted to clinicians, delivered by their Lilly sales

Page 481

representative. The letter is written on behalf of Lilly and signed by Doctor Alan Breier. Market research on the letter was conducted July 2-3 and was very positive."
And my question to you, sir, is Exhibit 9201 a copy of that letter that was referred to in Exhibit 995?
THE WITNESS: Take a look at this.
A. It appears to be the case.
Q. Okay. And to your understanding -- oh, by the way, this letter that is Exhibit 9201, is that something that was actually prepared by you or did someone else draft it?
MR. BOISE: Object to the form of the question.
A. I take accountability for the content of this letter. I've signed it. This was a communication that had input from others.
Q. Who? Which others?
A. I'm not recalling who, specifically, may have contributed. It's not

Page 482

unusual when we have a document that we circulate it for input and comments, and I'm quite certain that we did that with this.
Q. Did anyone from the marketing department review and comment?
A. Certainly we would have circulated it to members of marketing, particularly given the fact that it was going to be going to the sales force and then to physicians. But I'm not recalling precisely, precisely who.
Q. Would Cassandra Mehlman have reviewed this?
A. I'm not recalling that name. I have no idea.
Q. How about Jack Jordan or Mike Bandick?
A. I would assume that both of them would have reviewed it, again, given the fact that it was going to be going to the sales force to then to be circulated through that particular channel.
Q. Okay. How about Denice Torres?

Exhibit 6 David Noesges | Exhibit 7 Sidney Taurel | Gary Tollefson | Exhibit 5 John Lechleiter, Ph.D

A. Dr. Lechleiter was in charge of the product teams.
Q. And, in fact, I guess the best way to say it, since he's the one that appointed you to be the head of the Zyprexa Product Team, he was your boss?
A. I reported to Mr. van den Bergh, and Mr. van den Bergh reported to Dr. Lechleiter.
Q. And just for the record, Dr. Lechleiter is now the chief operating officer of the entire Lilly company?
A. That's correct.
Q. And I know without a doubt, because in my job, in any job, and the jury will understand, that when you're reporting to your superior concerning a trip to Japan, you're going to try to be as accurate and as truthful as you possibly can be so your superior will have true and accurate information upon which to make his or her decision that needs to be made, right?
MR. BOISE: Objection. Asked and answered.

A. We would convey our impressions as accurately as possible.
Q. And you told us at least one of the reasons you went to Japan was to assess how the affiliate was doing in Japan after the label change, right?
MR. BOISE: Objection. Asked and answered.
A. That's correct. We wanted to assess their implementation of the guidelines.
Q. Yes, sir. And if you look at Paragraph 1, and I will read it into evidence so it will be easier than making you read it. Here's the first paragraph of what you tell Dr. Lechleiter and Mr. Mayr, the head of global sales and marketing. You say this: "This is a summary of issues and proposed actions in follow-up to our previous update on Japan. It is clear that the impact of the label change in Japan has had a" very profound. We concluded, we, keep going on, you left out -- what word should have come after profound?

MR. BOISE: You left out a word before very.
MR. ALLEN: Yes, I did. Let me read it again.
QUESTIONS BY MR. ALLEN:
Q. "It is clear that the impact of the label change in Japan has been very profound. We concluded we have lost substantial ground and trust in our relationship with the MHLW."
That's the Japanese equivalent of the FDA, correct? Sir?
A. Yes.
Q. "Market research shows we have also lost quite a bit of credibility with prescribers and opinion leaders. Basically, because they felt left in the dark with what they perceived as the late sharing of safety information. As a result, there has been a 75 percent drop in new patients who are being put on the drug and a continuing fairly high drop-out rate. That's going to lead to a significant performance impact. Probably, over and above the

10 percent assumed on the sales line in the short term. Although we think we will be able to stem the tide and turn this around."
Did I read that correctly?
A. Yes.
Q. So you knew as a fact that a label change concerning diabetes, a warning concerning diabetes, as a fact, would have an impact on sales, correct?
MR. BOISE: Object to the form of the question.
A. What was, I think, a bit surprising was first the number of patients who were not put on the drug initially which, correct, had an impact on sales, but what's not conveyed in this e-mail was how rapidly the sales performance returned to normal and then actually went quite a bit beyond normal.
So our history is that it's very difficult to predict an impact of a label change and Japan is a good case in point.
MR. FIBICH: Objection. Nonresponsive.

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: MDL-1596

ZYPREXA PRODUCTS
LIABILITY LITIGATION
THIS DOCUMENT RELATES TO:
ALL CASES

SHAFIQA WARDAK : LOS ANGELES
: COUNTY,
V. : CALIFORNIA
ELI LILLY, et al. : BC348211

JOEL ALGARIO : LOS ANGELES
: COUNTY,
V. : CALIFORNIA
ELI LILLY, et al. : BC347855

PATRICIA GODLEY, : LOS ANGELES
et al. : COUNTY,
V. : CALIFORNIA
ELI LILLY, et al. : BC347856

- - -

March 28, 2007

- - -

C O N F I D E N T I A L

- - -

Videotape deposition of JOHN C. LECHLEITER, Ph.D.

- - -

GOLKOW TECHNOLOGIES, INC.
1880 John F. Kennedy Boulevard
Suite 760
Philadelphia, Pennsylvania 19103

Page 90

way related. I'm limited to time to four hours. His answers are taking way too long, and I'm asking for us to have yes or no answers to yes or no questions.
MR. LEHNER: That was not a yes or no question.
MR. ALLEN: Well, I'm going to object. His answer is nonresponsive.
BY MR. ALLEN:
Q. My question was, was it approved or not?
MR. LEHNER: That wasn't your question.
MR. ALLEN: Well, whether he agreed --
MR. LEHNER: You want to ask him a new question, go ahead.
MR. ALLEN: Let's go ahead.
BY MR. ALLEN:
Q. Sir, I'll short-circuit all of this. Zyprexa is not and has never been approved by the FDA for anxiety, has

Page 91

it, sir?
A. I don't believe Zyprexa has been approved for anxiety, you're correct.
Q. You actually know it's not been approved?
A. Right. It's not currently in the approved label.
Q. You know for a fact that Zyprexa is not and has never been approved for depression, correct?
A. Zyprexa is not currently approved for depression.
Q. And has never been?
A. I want to make a caveat here. Zyprexa, the active ingredient in Zyprexa, which is called olanzapine, in combination with Prozac, this is a product that we have approved and registered at the FDA, it's called Symbyax, that fixed combination, one of the ingredients of which is olanzapine or Zyprexa, is approved for the treatment of bipolar depression, which is a form of

Page 92

depression.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. The product, pharmaceutical product Zyprexa has been approved by the FDA?
A. It's approved by the FDA.
Q. That product has never been approved for depression; is that correct?
A. That product itself has never been approved for depression.
Q. Either depression or bipolar depression?
A. That product itself has not been approved for bipolar depression. I do want to note that that product in combination with fluoxetine or Prozac is approved for bipolar depression.
MR. SUGGS: Objection.
BY MR. ALLEN:
Q. Zyprexa has never been and is currently not -- or never been approved for dementia, correct?

Page 93

A. Zyprexa has not been approved for dementia.
Q. And it's never been?
A. Zyprexa has never had an indication for dementia or the treatment of the psychosis associated with dementia nor for dementia.
Q. The FDA has never approved Zyprexa for Alzheimer's disease; correct?
A. The FDA has not approved Zyprexa for Alzheimer's disease.
Q. And it never has?
A. That's correct.
Q. Zyprexa has never been approved for autism, correct?
A. Correct.
Q. Is has never been approved for obsessive compulsive disorder or attention deficit disorder, correct?
A. Correct.
Q. Zyprexa is not indicated for and has never been approved by the FDA for sleep disturbances, correct?
A. Correct.

Exhibit 6 David Noesges | Exhibit 7 Sidney Taurel | Exhibit 8 Gary Tollefson

marked for identification.)

- - -

BY MR. ALLEN:

Q. Sir, I've handed you what's been marked as Deposition Exhibit Number 6. This is an on line document I got from the Wall Street Journal's web page concerning stock prices. Particularly I was looking at the stock price of Eli Lilly in the year 2000 from August 1st to October 10th. On August the 1st, Eli Lilly's stock price was somewhere near $110 per share. And before the end of August, it had dropped to $75 a share in August of 2000. What happened --

MR. LEHNER: Object to the form.

BY MR. ALLEN:

Q. -- to cause this stock price fall?

A. Stock price is generally responsive to -- can be responsive to external events. In this case, we were surprised to receive, I believe, in early

August, at about the time that you point to this stock price decline, word that was quite unexpected that a three-judge panel had reversed an earlier court's decision about the validity of our Prozac patent.

Q. Yes. And, in fact, Prozac had been the number one selling drug product for Eli Lilly up until August of 2000, had it not?

A. I'm not certain about that. It's possible that Zyprexa sales were larger than Prozac sales at that time. I'm not certain.

Q. Nevertheless, you know if you take the number of share prices or the share price, that Eli Lilly stock after Prozac lost its patent rights in August of 2000 lost $36 billion worth of equity. Did you know that?

MR. LEHNER: Object to the form.

THE WITNESS: Sir, it's not unusual when a company receives

this kind of news that tells investors that a key patent may be jeopardized or may be revoked sooner than the market had anticipated for the market to react this way based on their estimate of revenues, in this case, Prozac revenues, that would not be incurred.

MR. SUGGS: Objection, nonresponsive.

BY MR. ALLEN:

Q. My only question to you was, sir, the stock capitalization of Eli Lilly lost $36 billion in August of 2000 when this -- when your stock fell. Is that correct?

A. I don't have a basis for saying that. This simply shows me that the stock fell. I don't know what the valuation numbers were at that time.

- - -

(Whereupon, Deposition Exhibit Lechleiter-7 (Zyprexa MDL

Plaintiff's Exhibit No. 09070) "Eli Lilly & Company: Part A" (Gulati) 2002 ZY202166113 - ZY202166126, was marked for identification.)

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BY MR. ALLEN:

Q. I'm going to hand you what I marked as Exhibit Number 7. Particularly I'm going to point to Page 7 and part of Page 8, I've highlighted it for you, so we can know what we're going to talk about. I've given this to your lawyer before the deposition.

This is a report that was contained in Kellogg Graduate School of Management, Northwestern's University's graduate school, contained in your files and produced in this litigation. If we turn to Page 7, the highlighted language.

MR. SUGGS: Excuse me, can you also point out this is also Zyprexa MDL Plaintiff's Exhibit 9070.

You're familiar with this, are you not, sir, this consensus statement? You know exactly what this is, don't you?

A. Yes, I've seen this document before.

Q. Sir, we obviously -- and you've read it before, have you not?

A. Yes, I have.

Q. I want to read certain selected portions and talk about it. It's on the board also if you need to, sir, you have it in front of you.

This consensus statement, by the way, was put out by the American Diabetes Association, the American Psychiatric Association, the American of Clinical Endocrinologists, and the North American Association for the Study of Obesity, correct?

A. That's what I read here, yes.

Q. Yes, sir.

Also you know that they had

a panel of experts and Eli Lilly made presentations before this panel before this consensus statement was published, correct?

A. I believe that's correct.

Q. You also know that your company was given drafts of this consensus statement prior to the time of its publication, do you not?

A. I do recall that we saw a draft.

Q. Right.

In fact, your company was given the opportunity to make comments upon the draft before this consensus statement was published, correct?

A. I don't recall that specifically.

Q. Anyhow, so the jury knows, this consensus statement is something that you, Dr. Lechleiter, are personally intimately familiar with, correct?

MR. LEHNER: Object to the form.

THE WITNESS: Sir, I'm familiar with the development of this document. I was familiar with the fact that there was a consensus conference. I was familiar with the fact that this represents -- this publication represented the outcome of that meeting. That's what I'm familiar with.

BY MR. ALLEN:

Q. And once this thing was published, the consensus statement, once it was published, you considered it a corporate crisis for Eli Lilly, correct?

A. I considered the conclusions reached in this consensus statement to be dead wrong.

Q. Yes, sir. Of course you're not an expert in diabetes, are you?

A. I'm not an expert in diabetes, but I think if you --

Q. You're not an expert in obesity, are you?

A. I'd like to finish the answer to my question.

What you don't have attached here are some subsequent letters to the editor that appeared, and I think the comment I made about the conclusions we drew about this consensus recommendation or consensus conclusion were supported by other experts in the field who were expert in diabetes, including the FDA, the group at FDA that oversees the regulation of Zyprexa.

MR. ALLEN: Objection, nonresponsive.

BY MR. ALLEN:

Q. Sir, you understand the American Diabetes Association, the American Psychiatric Association and the American Association of Clinical Endocrinologists and the North American Association for the Study of Obesity is made up of individuals who do not manufacture nor sell antipsychotic medications. You understand that?

A. I believe it would be Mr. Brodie.
Q. Mr. Brodie from the diabetes care side of the company says, "Subject: Re: Meeting with endocrinologic consultants." I'm sorry if I mangled that word.
He says, "Robert," he sent it to Robert Baker. The jury will know who Dr. Baker is. "Robert...clearly this group of Endocrinologists (who spoke up and I would rate those who did speak up as the leaders of the pack) are very concerned with the approach Lilly is taking towards the issue that Zyprexa leads to diabetes. I can only hope that you and all of the team who attended the North American Diabetes Advisory Board," that's NADAB, is it not?
A. I believe it is, yes.
Q. -- board "meeting are gaining the ear of senior leadership and articulating this finding. Although the board's recommendation is probably not

the way Lilly typically does business, I do believe they made a very strong point that unless we come clean on this, it could get much more serious than we might anticipate."
Did I read that correctly?
A. You read that correctly.
Q. Now, you were senior leadership, were you not?
A. This was in 2000. Yes.
Q. And Tom Brodie says, the people who attended this meeting need to get the "ear of senior leadership." No one ever came to you and told you about what the endocrinologists said in 2000?
A. Sir, I wasn't the only member of senior leadership. We had a very talented, bright group of Lilly people, including physicians, who attended that meeting. Their job would have been to summarize and take appropriate notes on what was said at that meeting, to take that information to other people in the organization, to

consider that information, and to put that in context, and this is the important point, with all of the other information we gathered. We cannot draw conclusions made from a presentation of data to a group of endocrinologists for a two-hour period and even suggest that that is the only view or the only evaluation we would take of the product, nor of any conclusions that we might draw about the product.
MR. SUGGS: Objection, nonresponsive.
BY MR. ALLEN:
Q. Sir, you didn't even come close to answering my question.
MR. LEHNER: Object to the characterization.
BY MR. ALLEN:
Q. You told me you were in senior leadership. We saw where Mr. Brodie recommended that the ear of senior leadership be gained based on this meeting. Isn't that what Mr. Brodie

said?
A. Mr. Brodie had that opinion.
Q. Yes, sir.
And my only question to you was, did anybody ever come to you and report on the October 2000 meeting with endocrinologists? Yes, no or you don't know?
A. I believe your question was, did anyone ever report to senior leadership?
Q. Well, my question is now, sir, did anybody come and report on the meeting to you?
MR. LEHNER: Asked and answered.
THE WITNESS: Asked and answered.
BY MR. ALLEN:
Q. What's the answer?
A. No one reported specifically on the outcome of this meeting to me --
Q. At any time?
A. -- but I believe other

Page 278

this report. It says, "in the following order (most to least)." Clozaril is the most, Zyprexa is next, Zyprexa is more than Seroquel, and Seroquel is more than Risperdal. Do you see that?
A. I see what's written here.
Q. That's in the policy committee meeting. That's very similar to Table 2 of the consensus statement published in January of 2004, is it not, sir?
A. I don't think it's similar to Table 2. Table 2 doesn't have the same order shown here.
Q. We'll let others be the judge of that.
All right. The next bullet point. "Zyprexa weight gain is roughly twice that of Risperdal. (Average 7 kilograms versus 3-and-a-half kilograms)."
Did I read that correctly?
A. You've read what's here correctly.

Page 279

Q. All right.
And then it says, "Pfizer's Geodon and BMS's aripiprazole" -- now, that's Abilify, is it not?
A. I believe that's the product name.
Q. You know it's the product name, do you not, sir?
A. Aripiprazole, I think that is Abilify. Is that what you said?
Q. Don't you know it's Abilify?
A. Yes. I'm very sure of that.
Q. Okay.
"Pfizer's Geodon and BMS's" Abilify "appear to have less metabolic issues than other atypicals."
Did I read that correctly?
A. That's what's written there.
Q. So, internally at Eli Lilly in April of 2002, the policy committee was told that Zyprexa has more weight gain than Seroquel and Risperdal, that Zyprexa weight gain is twice that of Risperdal, and that the other products on the market, Abilify and Geodon, have less metabolic issues than the other atypicals, correct?

Page 280

MR. LEHNER: Object. Mischaracterizes the document.
THE WITNESS: This is a set of statements made in this document. I don't know what the basis was for this. I don't know how they were developed. What I can say is that in our product label, we reported that in a long-term use of Zyprexa in controlled clinical trials, patients who gained weight averaged a weight gain of seven kilos, so, I do recognize that directly from our product label.
MR. SUGGS: Objection, nonresponsive.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. Now, in these Zyprexa safety

Page 281

product overviews, skipping down, under "Diabetes (DM)," the second bullet point. "A recent Zyprexa clinical trial analysis indicates patients with baseline diabetes risk factors (obesity" -- let me stop there.
Is obesity a diabetes risk factor?
A. It's listed as such in this document.
Q. So, therefore, a product that causes obesity increases the risk of diabetes, true?
A. I'm not a diabetes expert. It lists obesity here as a risk factor for diabetes in this document.
Q. So, Zyprexa, assume with me, using your common sense as a Harvard graduate and as president and COO of Eli Lilly, assuming Zyprexa causes a patient to become obese, it would increase that patient's risk for diabetes, true?
A. That's not necessarily true.
Q. Okay, sir.

Exhibit 5, Page 6 of 9
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006328

Exhibit 6
David Noesges

Exhibit 7
Sidney Taurel

Exhibit 8
Gary Tollefson

Q. Right.
"Results of two...epidemiological studies (analysis of AdvancePCS" -- what's AdvancePCS stand for, sir?
A. AdvancePCS is a pharmaceutical benefit manager that handles prescription execution for customers.
Q. So, you got their database. "(Analysis of AdvancePCS and GPRD," what's that?
A. I don't know what that refers to.
Q. "(Analysis of AdvancePCS and GPRD databases) indicate that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa." Did I read that correctly?
A. That's what that sentence states, and that was information that would have been gleaned from that particular type of an analysis, but it takes, I think, a composite of different

analyses to draw any conclusions, if you're trying to do that here.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. Sir, as of the time this policy committee on Zyprexa Safety Overview is written on April the 12th, 2002, when it is reflected --
MR. ALLEN: Tom, please.
Tom, please.
BY MR. ALLEN:
Q. -- when it is reflected that results of two epidemiologic studies indicate that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa, your package insert or label on Zyprexa contained no warning on diabetes or hyperglycemia, did it, sir?
A. Sir, we continuously monitored the occurrence through our drug event reporting system of any reports of hyperglycemia or diabetes. We analyze

that data. We promptly submitted that data to the FDA. It was made very clear to us in advance of a label change that, in fact, impacted all of the products in this category in September 2003 that FDA was considering a composite of all kinds of data, including epidemiology studies, but also primary clinical trials.
We did a lot of work in this period to understand both weight gain and hyperglycemia, and I think this document in total, not just the sections you're citing, represent our good faith effort to understand this and to make sure that we were adequately communicating appropriate safety information to prescribing professionals.
MR. ALLEN: Objection, nonresponsive.
MR. SUGGS: Objection, nonresponsive.
BY MR. ALLEN:
Q. Just for the record, sir, just so we can get a clear, concise

record, remember you took an oath to say the truth, the whole truth and nothing but the truth? Remember that?
A. Yes, sir.
Q. You're a pharmaceutical manufacturer senior executive and their president and COO, correct?
A. Yes, I am.
Q. You know what short, concise and to the point means, do you not, sir?
A. Sir, I'm trying to give the shortest --
Q. Again, my question to you is, do you know what short, concise and to the point is?
A. Sir, I'm trying to give an answer that is responsive to your question that is as brief as possible.
Q. Let's look at this date. And as brief as possible, April the 12th, 2002, do you have that date in your head, sir?
A. Yes.
Q. Okay.

As of that date, there was no warning in the Zyprexa label on diabetes and hyperglycemia, was there, sir?

MR. LEHNER: Object to form.

THE WITNESS: Hyperglycemia and diabetes were both in the label as adverse events from the day we launched the product.

MR. SUGGS: Objection, nonresponsive.

MR. ALLEN: Objection, nonresponsive.

BY MR. ALLEN:

Q. Sir, the FDA certainly differentiates between adverse reactions and warnings, does it not, sir?

A. Those are different sections within the label.

Q. Yes, sir. Right. And listen to my question.

As of April the 12th, 2002, the time of this policy committee meeting Zyprexa safety overview, there was no warning in the Zyprexa label on hyperglycemia and diabetes, was there, sir?

MR. LEHNER: Object to the form.

Go ahead. You can answer.

THE WITNESS: The Zyprexa product label fairly represented what we believed to be the best knowledge we have of the product and what FDA felt was the information most appropriate to communicate in the label.

MR. ALLEN: Objection, nonresponsive.

MR. SUGGS: Objection, nonresponsive.

BY MR. ALLEN:

Q. Sir, as of April the 12th, 2002, the policy committee meeting Zyprexa safety overview, there was no warning in the Zyprexa label as defined by the FDA, was there, sir?

A. I don't recall. I don't have the label in front of me. I do know that later in September, I believe, of 2003, there was a warning introduced in all manufacturers' labels that spoke specifically to the occurrence of diabetes and hyperglycemia and the fact that the FDA could not determine whether that was causally related to these products or not.

MR. SUGGS: Objection, nonresponsive.

BY MR. ALLEN:

Q. Is that the best answer you can give a jury?

A. I don't have the label. If you want to show me the label from --

Q. The jury will see the label. And I'm asking you --

A. I believe the first warning that was introduced was the warning introduced in September 2003.

Q. Okay.

So, now, let's go back to my question. As of April the 12th, 2002,

there was no warning in the Zyprexa product label, as that term is defined by the FDA, concerning hyperglycemia and diabetes, correct?

A. There was nothing of that nature in the section under warnings, but certainly diabetes and hyperglycemia were listed in the label and had been listed in the label as adverse events since the time we introduced the product.

MR. ALLEN: Objection, nonresponsive.

MR. SUGGS: Objection, nonresponsive.

BY MR. ALLEN:

Q. Sir, honestly, under oath to a jury and to a judge, you understand there's a difference between a warning under the FDA's definition and an adverse reaction, correct?

A. Yes, I do.

Q. You understand that differentiation is defined by law, correct?

Page 298

the increased reporting of diabetes related to Zyprexa was the issue of weight gain, correct?
A. No. I would not concede that. I would say that individuals, whoever it was that prepared this report, looking at sheer raw numbers, that's what these 542, 434 are, just raw numbers, are speculating about why these numbers may be different. I can cite other reasons, and there are other reasons why they might be different, in addition to the ones cited, which include weight gain, illness severity and reporting bias.
Q. Go down under "Diabetic Ketoacidosis." You know what that is under C? Do you know what that is, diabetic ketoacidosis?
A. I know what that is.
Q. That's a deadly condition, is it not, related to diabetes?
MR. LEHNER: Object to the form.
THE WITNESS: DKA is a

Page 299

potential serious complication of uncontrolled diabetes.
BY MR. ALLEN:
Q. You had a lot of information about DKA back in April of 2002. You were looking into that, weren't you, you, personally?
MR. LEHNER: Objection to the form.
THE WITNESS: Sir, I don't agree with your conclusion that we had a lot of information.
BY MR. ALLEN:
Q. Okay. Thank you. Diabetic --
A. And I don't -- I'm sorry. I want to answer the question. And no, I was not looking into this personally.
Q. Okay. Diabetic ketoacidosis, second bullet point. "FDA Freedom of Information Database cases of DKA (cases) and "total exposures):" Clozaril, 103 cases, total exposure not available; Zyprexa 132 cases, 3.7 million exposures. Did I read that correctly?
A. That's what's written here.
Q. And of the gross number of cases of diabetic ketoacidosis as reported to the Zyprexa policy committee -- I mean, excuse me, Lilly's policy committee, Zyprexa had the most cases; is that correct?
A. Numerically, as it is shown here, Zyprexa had the most cases. It also is another situation where the absolute number that you cite cannot be taken without some additional context. There are many reasons and many explanations for why these numbers are different, and I think in looking at this information, as the FDA certainly did, and as Lilly did, I don't think one can draw clear conclusions.
MR. SUGGS: Objection to the nonresponsive portion.
BY MR. ALLEN:

Page 301

Q. Of course, sir, I'm going to hand you -- April of 2002 was a busy month for your company, was it not? Wasn't it a busy month for your company --
MR. LEHNER: Object to the form.
BY MR. ALLEN:
Q. -- regarding Zyprexa?
MR. LEHNER: Object to the form.
THE WITNESS: I don't recall. That was five years ago.
- - -
(Whereupon, Deposition Exhibit Lechleiter-21 (Zyprexa MDL Plaintiffs' Exhibit No. 00320), "Appendix 6: Japanese Dear Doctor Letter" ZY 4051 1633 - ZY 4051 1638, was marked for identification.)
- - -
BY MR. ALLEN:
Q. Let me show you this. What

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA	)	
	)	
Plaintiff,	)	
	)	
vs.	)	CASE NO.
	)	3AN-06-5630 CIV
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	

The videotaped deposition upon oral examination of DAVID THOMAS NOESGES, a witness produced and sworn before me, Carolyn L. Smith, CSR, RPR, Notary Public, in and for the County of Hamilton, State of Indiana, taken on behalf of Plaintiff, at the offices of Ice Miller, One American Square, Suite 3100, Indianapolis, Indiana, on January 11, 2008, at 9:31 a.m., pursuant to all applicable rules.

said it's a definition.
MR. SUGGS: It's a medical dictionary. I can't remember which one.
Q Would you accept that definition that indication is something that points to or suggests the proper treatment of a disease?
A I think you are clearly outside of my area of expertise. I would consult with --
Q Okay.
A -- my medical colleagues. If it was a clinical question, with my regulatory colleagues. If you are asking is that the FDA definition of indication, which is what's relevant for our package label, I don't know the answer to that.
Q Would you agree, sir, as someone in charge of marketing and sales that doctors look to the indication section of the label to see if the drug is appropriate to use for the proper treatment of the disease?
A Yes, I believe that's one source doctors may use to make that decision.
Q Okay. And the diseases for which the drug is indicated or appropriate to treat are listed in the indication section of the label, correct?
A The indication section of the label indicates --

those disease states are indication for which the drug has received FDA approval for promotion.
Q And Zyprexa was originally -- well, strike that.
As someone in charge of the marketing of Zyprexa and also responsible for sales of Zyprexa, you and the people who worked under you needed to be familiar with, conversant with what was contained in the label, correct?
A Yes.
Q And in 1996 -- well, let me put it this way:
Before 2000, Zyprexa was indicated for the management of psychotic disorders, correct?
MR. BOISE: Object to the form.
QUESTIONS BY MR. SUGGS:
Q Do you recall that?
MR. BOISE: Almost right.
THE WITNESS: I don't believe that is the exact indication. I would have to look at the package label to tell you what the exact indication was prior to that time frame.
QUESTIONS BY MR. SUGGS:
Q Okay. Do you recall that in 2000 the indication section of the label was changed to say that Zyprexa is indicated for the treatment of schizophrenia and Zyprexa is indicated for the

short-term treatment of acute manic episodes associated with Bipolar I disorder?
A Yes, I do.
Q Okay. You recall that in 2004 the indications were expanded to include treatment for the short-term treatment of acute mixed or manic episodes associated with Bipolar Disorder I and as maintenance treatment in bipolar disorder?
MR. BOISE: Object to the form, foundation.
THE WITNESS: Yes, I'm aware of the label change, but I would have to read from the label to know whether that's the exact language of the label in that time frame.
QUESTIONS BY MR. SUGGS:
Q Okay. You know, sir, that Zyprexa was never approved for the treatment of anxiety, correct?
A Yes, that's correct.
Q It was never approved for the treatment of irritability, correct?
A Zyprexa never had an indication for the treatment of irritability -- irritability, no.
Q Zyprexa was never approved for the treatment of disruptive sleep, correct?
A Zyprexa never had an indication for the treatment of disruptive sleep.

Q Zyprexa was never approved for the treatment of mood swings, correct?
A Zyprexa never had an indication for the treatment of mood swings, but certainly mood swings are an element of the symptoms of bipolar disorder.
Q Zyprexa never -- was never approved for the treatment of complicated mood symptoms?
A Again, we never had a specific indication for complicated mood symptoms, but those are symptoms consistent with -- with certainly the bipolar disorder indications for Zyprexa.
Q Move to strike the nonresponsive information.
Zyprexa was never approved for dementia associated with Alzheimer's, correct?
A No, sir, it was not.
Q I'm going to hand you what's been previously as Plaintiffs' Exhibit 4121.
For the record this exhibit is entitled "ZYPREXA - Primary Care Strategy and Implementation Overview."
The first section is entitled "Background." It states, Following several months of study by the LillyUSA Zyprexa Brand Team, the affiliate approved the recommendation that Lilly actively promote Zyprexa to selected current primary care prescriber

Exhibit 7
Sidney Taurel

Exhibit 8
Gary Tollefson

Page 170

2000.
What was the Sigma sales force, do you know?
A Sigma was a primary care sales force that among their responsibilities included Zyprexa promotion to primary care physicians.
Q It goes on to state, "It has gained over 12 share points since that time. As the current market leader in primary care, ZYPREXA will continue to revolutionize the way complicated mood disorders are treated by primary care physicians."
Do you see that language, sir?
A Yes, sir, I do.
Q And as we have talked about before, Zyprexa was not indicated for complicated mood disorders, was it, sir?
MR. BOISE: Object to the form of the question, mischaracterizes his prior testimony.
THE WITNESS: Zyprexa was indicated for schizophrenia and bipolar disorder.
QUESTIONS BY MR. SUGGS:
Q If I could direct your attention to page 5. And this is basically walking the sales rep through the use of a brochure, correct?
A Yes. This is a message example for sales representatives to use to help them in terms of how

Page 171

they communicate to physicians.
Q What we see here on this page in the upper right-hand corner and on the succeeding pages is an image of the brochure that was being used, correct?
A Yes.
Q And then the rest of the text on the page is a description provided by Lilly's marketing folks as to how to use that brochure, correct?
A Yes.
Q For example, on page 5 here, they show the front cover of the brochure -- and by the way, do you recall what this particular brochure was called?
A I don't know that it had a name.
Q Okay. But anyway we see the picture of the doctor and the patient on the first page. It looks like the patient is fording a river by stepping on various stones, correct? And the doctor is there to hold her hand as she gets over there, right?
A Yes, that appears to be what -- what the diagram depicts.
Q They have a suggested call opener there, correct?
A Yes.
MR. BOISE: Object to form.
THE WITNESS: Yes.

Page 172

QUESTIONS BY MR. SUGGS:
Q And what's a "call opener"?
A In this context the call opener is simply an introductory statement for the sales representative to make during the call to the doctor.
Q And the sales rep was to say, "Doctor, you treat patients who present with complicated mood symptoms. Many of these patients are struggling to gain control of symptoms like anxiety, irritability, disruptive sleep, and mood swings. I would like to talk about how ZYPREXA can help you help your patients gain control of these complicated mood symptoms," correct?
A Yes, sir, that's correct.
Q No mention of schizophrenia or the acute manic phase of Bipolar I disorder?
MR. BOISE: Object to the form of the question. Object to the form of the question.
THE WITNESS: There's no mention of that in this specific sentence, no.
QUESTIONS BY MR. SUGGS:
Q And Zyprexa was not approved for any of the symptoms that are listed in that call opener, was it, sir?
MR. BOISE: Object to the form of the

Page 173

question.
THE WITNESS: These symptoms are consistent with the symptoms of bipolar disorder as I read them.
QUESTIONS BY MR. SUGGS:
Q Sir, Zyprexa was not approved for the treatment of any of the symptoms that are listed in that call opener; isn't that correct, sir?
MR. BOISE: Object to the form of the question.
THE WITNESS: Zyprexa is indicated for schizophrenia and bipolar disorder.
QUESTIONS BY MR. SUGGS:
Q Not anxiety, irritability, disruptive sleep, or mood swings or complicated mood symptoms. It was indicated for schizophrenia and bipolar, correct?
MR. BOISE: Object to the form of the question.
THE WITNESS: Zyprexa is indicated for bipolar disorder whose symptoms include the symptoms that are described here in this call opener.
QUESTIONS BY MR. SUGGS:
Q Sir, one of the things that Lilly did was to have what they call "patient profiles."
Do you remember that?

Page 194

sales support personnel in LillyUSA and all sales activities that take place in the United States or with US Healthcare Professionals," correct?
A Yes, sir, that's correct.
Q And the policy statement was that, quote, It is the policy of LillyUSA that all sales personnel appropriately document sales calls with Healthcare Professionals in the call tracking system; is that correct?
A Yes, that's what it says.
Q What was the call tracking system?
A This is referring to basically the sales representatives' computer database that was available to them in this time frame, which would have been effective June 1st, is what this document is referring to -- to put their -- to document calls they were making on healthcare providers.
MR. BOISE: just so the record is clear it's June 1st, 2004.
Q And, in fact, this call system existed before 2004, correct?
A Yes, it did.
Q Okay. Can you describe for us, generally, what is involved in this call system or call note system?
A Depends on the time frame. While that system has been in place, the process of gathering call notes has changed over time.
Q Okay. Well, is it fair to say that the sales rep is expected to -- shortly after his calling on a particular physician is expected to go to a computer database and enter information about the particular sales call that he had?
A Yes, that's correct.
Q And all of that information is to go into a centralized database, correct?
A The sales representative inputs the data into their computer laptop which then is stored centrally, but I don't know the details of how -- how that information gets stored.
Q Okay. Again, I'm not asking for the details; but it's fair to say that there is a database of call notes that describes the -- or that lists the -- who the sales rep was, the doctors that they called on, the products that they discussed and what was said during the sales call, correct, or what information was presented at the sales call?
MR. BOISE: Object to the form of the question, compound.
THE WITNESS: No. It's important to note two things: One, it depends on the time frame, what

Page 195

Page 196

got documented and, secondly, the call notes are not a comprehensive description. It won't describe everything that happened on the call or everything that was said on the call. To the contrary, it's more of a summary and notes taking process for the sales representatives to use for themselves.
QUESTIONS BY MR. SUGGS:
Q Understood; but -- and management can access the database quite easily, correct?
A Certainly the sales representative, sales managers can access their call notes.
Q If, for example, you wanted to go to get all of the call notes with respect to a particular sales representative, that could be easily retrieved from the call note system, correct?
MR. BOISE: Object to the form of the question.
THE WITNESS: I would have to work with our IT folks to get that, but I certainly could pull data from the call notes. Now, what I don't know is how far back the data goes at any time.
QUESTIONS BY MR. SUGGS:
Q I understand. There's a limitation on anything.
But I mean since whatever system is present now, you could certainly go to -- go to that database and make a query to pull up all of the call notes from Representative Harry Jones, for example?
A I'm assuming I would be able to. It's not something I have done in management. We don't routinely pull together data from the call notes.
Q Okay. And similarly if you wanted to get all of the call notes with respect to a particular doctor, the call note database would permit you do so, correct?
MR. BOISE: Object to the form.
THE WITNESS: Again, you are outside of my expertise in exactly what we can retrieve from the database.
QUESTIONS BY MR. SUGGS:
Q Okay. Directing your attention back to Exhibit 9.
A Yes.
Q There is a Definitions section there and sales call is defined as a face-to-face discussion about Lilly products between a healthcare professional and a Lilly sales representative, correct?
A Yes, it is.
Q And a call note is defined as a business record documented within a call system that accurately reflects all aspects of the sales call, correct?

Page 197

Exhibit 7
Sidney Taurel

Exhibit 8
Gary Tollefson

Page 206

around Zyprexa's usefulness in elderly patients.
QUESTIONS BY MR. SUGGS:
Q And, sir, Zyprexa was never approved for the treatment of hostility in elderly patients, was it, sir?
MR. BOISE: Object to the form.
THE WITNESS: Zyprexa does not have an indication for hostility in elderly patients.
QUESTIONS BY MR. SUGGS:
Q And Zyprexa was never indicated for the treatment of agitation in elderly patients, correct?
MR. BOISE: Object to the form, foundation.
THE WITNESS: Zyprexa does not have a specific indication for agitation in elderly patients.
QUESTIONS BY MR. SUGGS:
Q And, in fact, Zyprexa was never indicated or approved for the treatment of cognition or for improving cognition, correct?
MR. BOISE: Object to the form.
THE WITNESS: Improvement of cognition is certainly a symptom of schizophrenia as can be hostility and agitation, but there is not a specific indication for cognition.
QUESTIONS BY MR. SUGGS:
Q And, in fact, nowadays, at least since 2004,

Page 207

there's been a black box warning against using Zyprexa for patients with dementia and Alzheimer's, correct?
MR. BOISE: Object to the form, foundation.
THE WITNESS: Your language is not in the specific label language that we currently have.
QUESTIONS BY MR. SUGGS:
Q I did not represent that it was.
There has been a black box warning in the Zyprexa label since 2004 with respect to the elderly, correct?
A Yes, that's correct.
Q That did not exist in 2002 when this call note was made, correct?
MR. BOISE: Object to the form, foundation.
THE WITNESS: No, I do not believe it did.
QUESTIONS BY MR. SUGGS:
Q Was Zyprexa indicated for the treatment of patients whose symptoms were aggravated by a SSRI?
MR. BOISE: Object to the form.
THE WITNESS: Zyprexa's indication, as we have discussed before, was for schizophrenia and bipolar disorder.
QUESTIONS BY MR. SUGGS:
Q Didn't sales reps in Alaska, in fact, promote

Page 208

Zyprexa as being especially good for patients whose symptoms were aggravated by an SSRI?
MR. BOISE: Object to the form of the question, foundation.
THE WITNESS: Sir, what I can describe to you, as I have before, is what our marketing messages were on a given time frame, but I would have to know what time frame you were describing and then I could indicate to you what the company approved message was.
QUESTIONS BY MR. SUGGS:
Q Let me show you another set of call notes, which I'll mark as Exhibit 12.
(Deposition Exhibit 12 marked for identification.)
MR. SUGGS: Did I give you a copy?
MR. BOISE: Not yet.
MR. SUGGS: Sorry.
MR. BOISE: While you are shuffling, this has been marked as Exhibit 12, is a grouping of seven pages of call notes.
MR. SUGGS: Yes.
Q If I could direct your attention to the first call notes -- the first call note on the first page, these appear to be call notes from Margaret

Page 209

Williams, dated May 17, 2002, with respect to a meeting with Dr. Kathryn Flores in Soldotna, Alaska, text which says in part, "Also got in a decent ZYP recap, reminded doc that ZYP is a great mood stabilizer, especially for patients whose symptoms were aggravated by an SSRI."
Do you see that language, sir?
A Yes, sir, I do.
Q Now, there were drugs that were approved as being mood stabilizers, correct?
A I would have to check the specific indications of Lithium and Depakote to know what the label language is around their indication.
Q Well, Depakote was a mood stabilizer.
Zyprexa was not indicated as a mood stabilizer, was it, sir?
MR. BOISE: Object to the form, foundation.
THE WITNESS: Again, I'm not a clinical expert, but my understanding of the term "mood stabilizer" refers to medicines that are indicated for treating bipolar disorder.
QUESTIONS BY MR. SUGGS:
Q Well, sir, as we have talked about before, in 2002 Zyprexa was only indicated for schizophrenia and the acute manic phase of Bipolar I disorder.

SUPERIOR COURT FOR THE
STATE OF ALASKA
THIRD JUDICIAL DISTRICT OF ANCHORAGE

STATE OF ALASKA : Case Number
v. :
ELI LILLY & COMPANY : 3 AN 065630 CIV

- - -

C O N F I D E N T I A L

- - -

September 19, 2007

- - -

Videotape deposition of SIDNEY TAUREL, held in the offices of Ice Miller, One American Square, Indianapolis, Indiana 46282-0200, commencing at 8:34 a.m., on the above date, before Linda L. Golkow, a Federally-Approved Registered Diplomate Reporter and Certified Shorthand Reporter.

- - -

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Exhibit 7, Page 1 of 28
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006337

Exhibit 6
Gary Tollefson

(Whereupon, Deposition Exhibit Taurel-2, "Eli Lilly Said to Play Down Risk of Top Pill," (Berenson) New York Times, December 17, 2006 (4 pages), was marked for identification.)

- - -

BY MR. SUGGS:

Q. The headline states, "Eli Lilly Said to Play Down Risk of Top Pill."

The first two paragraphs of this article state, "The drug maker Eli Lilly has engaged in a decade-long effort to play down the health risks of Zyprexa, its best-selling medication for schizophrenia, according to hundreds of internal Lilly documents and e-mail messages among top company managers.

"The documents, given to The Times by a lawyer representing mentally ill patients, show that Lilly executives kept important information from doctors about Zyprexa's links to obesity and its

tendency to raise blood sugar - both known risk factors for diabetes."

Do you see that language, sir?

THE WITNESS: I see it, yes.

BY MR. SUGGS:

Q. And did --

I'm assuming that when that article was published, it was probably noticed by the members of the board of directors, correct?

MS. GUSSACK: Objection, no foundation.

BY MR. SUGGS:

Q. You may answer.

A. I believe that they paid attention to it. It was a very important article obviously.

Q. Okay.

Did the board of directors or its public policy and compliance committee investigate those allegations that I just read?

MS. GUSSACK: Objection.

THE WITNESS: Could you repeat the question.

MR. SUGGS: Sure. Could you read it back to him.

- - -

(Whereupon, the requested portion of the notes of testimony was read by the court reporter.)

- - -

THE WITNESS: We informed immediately the board of our response to this -- to these allegations. As we informed them, those allegations are based on a select small number of documents and do not reflect the conduct of the company.

BY MR. SUGGS:

Q. That really, I don't think, was responsive to my question.

My question was, did the board of directors or its public policy and compliance committee investigate those allegations?

MS. GUSSACK: Objection.

THE WITNESS: No, they did not do an investigation because they trust and they rely on the report that -- and the compliance systems that we have in place and have been following this issue for a long time. And we're satisfied that all of the information that we have had over the years on Zyprexa has been appropriately reflected in our label and shared with doctors.

BY MR. SUGGS:

Q. Did you provide members of the board or its public policy and compliance committee copies of any of the documents that were referenced in this article?

MS. GUSSACK: Objection.

THE WITNESS: This article did not specify specific documents. So, we couldn't share those.

Q. Those 2,000 additional sales reps, part of their function was to promote Zyprexa, correct?
MS. GUSSACK: Objection.
THE WITNESS: Not necessarily. Many of those, I believe, were outside of the United States, and I'm not sure in 2000 -- I know that in 2000, the product was not yet available in every country. So, some of these sales reps would have been promoting Zyprexa, but I don't know how many.
BY MR. SUGGS:
Q. But clearly you invested in the years before 2000 in the marketing capability of Zyprexa, correct?
A. We invested in both our R&D and marketing capabilities in general to handle both existing and products to come. With eight new products especially in some new therapeutic areas for us, it was important for us to increase the

number of sales representatives. For example, in 2000, we launched a product called Xigris. That was in a totally new area for us, so, we needed a completely discrete, separate sales force for that product, which we created in several countries around the world.
Q. If I can direct your attention back to the previous page in the right-hand column, the second paragraph under the heading "Strong product line fuels growth."
In particular, the last three or four lines of that paragraph, it states, "In 2000, our sales of Zyprexa were $2.3 billion, a 25 percent increase. During the fourth quarter, this neuroscience blockbuster surpassed Prozac as our top-selling product." Do you see that language?
A. Uh-huh.
Q. That is an accurate statement, is it not?
A. Yes.

Q. So, at least by -- by the way, this 2000 Annual Report would have actually been issued sometime in 2001, correct?
A. Correct.
Q. So, by 2001, clearly, Zyprexa was your biggest selling product and had sales in excess of $2 billion a year, correct?
MS. GUSSACK: Objection.
THE WITNESS: You said in 2000?
BY MR. SUGGS:
Q. Yes.
A. The answer is no. Prozac was still bigger.
Q. Well, your 2000 -- the report that we just read here said, "In 2000, our sales of Zyprexa were $2.3 billion, a 25 percent increase. During the fourth quarter" --
A. Ah.
Q. -- "this neuroscience blockbuster surpassed Prozac as our

top-selling product."
A. You said during the year 2000. I think for the full year, Prozac was still bigger.
Q. Okay.
From that point forward, was Zyprexa your top-selling product?
MS. GUSSACK: Objection.
THE WITNESS: I don't know the answer to that, but certainly after 2001, as the sales of Prozac came down, it also lost its flagship position in our product portfolio.
BY MR. SUGGS:
Q. Okay.
It's fair to say that by around this time, 2000/2001, Lilly was counting heavily on Zyprexa to help it bridge the gap in the shortfall of corporate revenue that would be created by generic competition for Prozac, correct?
MS. GUSSACK: Objection.

Exhibit 6
Gary Tollefson

Page 78

THE WITNESS: Zyprexa was one of the very many action -- drivers of growth that we had and, again, the response to the Prozac patent expiration was -- included both the launch of new products, which we were just starting to put on the market, and development of new indications and line extensions for existing products. We also took under license a couple of products such as Actos and Cialis, which have since then been launched.

BY MR. SUGGS:

Q. But of all those different products that you were talking about, just Zyprexa was the one that was producing the most revenue, correct, of all of them?

MS. GUSSACK: Objection.

THE WITNESS: Several products that I've just quoted were not yet launched, but they were a very important part of how our investors were looking at Lilly. What's important is not just make up for the revenue of a lost -- of a product which had just lost its patent, it's also to have a very promising pipeline of new compounds to be launched.

BY MR. SUGGS:

Q. Sir, I don't think your answer was responsive to my question. I'm going to ask the court reporter to please read my prior question back.

- - -

(Whereupon, the requested portion of the notes of testimony was read by the court reporter.)

- - -

THE WITNESS: I think I was responsive in that I told you that some of these products were not launched. So, evidently the sales of Zyprexa, even if it had been $1, would have been higher than the sale of the product which had not been launched.

BY MR. SUGGS:

Q. Well, and of all the products that the company had on the market, in 2001, Zyprexa was bringing in more revenue than anyone else, correct?

MS. GUSSACK: Objection.

THE WITNESS: I think I've answered.

BY MR. SUGGS:

Q. The answer to that is yes, correct?

MS. GUSSACK: Objection.

THE WITNESS: Zyprexa in 2000 was our second product. In 2001, after the patent expiration of Prozac, became the number one product.

BY MR. SUGGS:

Q. Okay.

When did you personally first become aware that hyperglycemia and diabetes were potential safety problems associated with Zyprexa?

MS. GUSSACK: Objection.

THE WITNESS: I knew from the time we launched Zyprexa that there were incidences of weight gain which are associated with Zyprexa and that adverse events had been observed in some patients taking Zyprexa, adverse events including hyperglycemia and very, very few cases of diabetes. All of these were reflected in our label when we launched the product.

MR. ALLEN: Objection, nonresponsive.

MR. SUGGS: I join in the objection.

BY MR. SUGGS:

Q. Who was it that brought you information about the safety of Zyprexa back at the time it was launched?

MS. GUSSACK: Objection.

THE WITNESS: Before a

product is launched, we have -- even before we submit for registration, we have a review of all of the information on the product.
BY MR. SUGGS:
Q. My question is really more specific than that. I'm asking what individual or individuals did you rely on back in 1996, in that era, to give you information about the safety of Zyprexa?
A. I would rely on the person who had the overall responsibility for Zyprexa. In that time, I believe it was Dr. Tollefson, to give me all of the information regarding Zyprexa on both its efficacy and safety.
Q. For how long did you continue to rely on Dr. Tollefson to provide you that information?
A. For however long he was in the job. I don't remember exactly when he switched to a different job.
MS. GUSSACK: David, I'm

sorry, before we move on, can we take a break now or in a few minutes?
MR. SUGGS: Sure.
MS. GUSSACK: We've been going for about an hour. Is this a good time?
MR. SUGGS: Sure.
THE VIDEOTAPE TECHNICIAN: Off the record at 9:35.
- - -
(Whereupon, a recess was taken from 9:35 a.m. until 9:53 a.m.)
- - -
THE VIDEOTAPE TECHNICIAN: Back on the record. This is the beginning of Videotape Number 2, the deposition of Sidney Taurel. It is 9:53.
BY MR. SUGGS:
Q. Mr. Taurel, when did -- well, strike that.
Did Dr. Tollefson tell you

that in December of 1995, before Zyprexa even went on the market, that an advisory board of outside consultants hired by Lilly had told him and Dr. Beasley that the weight gain associated with the use of Zyprexa might result in increased risks of hyperglycemia and diabetes?
MS. GUSSACK: Objection, no foundation.
BY MR. SUGGS:
Q. Did Dr. Tollefson tell you about that?
A. I do not recall.
Q. Okay.
Were you informed by Dr. Tollefson or anyone else that in the summer of 1995, before Lilly even submitted its NDA to FDA for review, that computer analyses of some of Lilly's clinical trials showed an increased incidence of high blood glucose in Zyprexa users?
MS. GUSSACK: Objection.
BY MR. SUGGS:

Q. Were you informed of that?
A. I was not informed of the specifics of individual trials or data. What I was informed of was the overall clinical safety and efficacy profile of Zyprexa before we submitted, as I mentioned earlier.
Q. Were you informed by Dr. Tollefson or others that beginning in 1998, articles were published in the medical literature by independent researchers noting that patients using Zyprexa were developing hyperglycemia and diabetes?
MS. GUSSACK: Objection.
THE WITNESS: I have been kept informed through regular briefings of new important data as it came out. I do not recall a specific briefing on any specific data by Dr. Tollefson.
BY MR. SUGGS:
Q. If you had been informed that scientific articles were appearing

beginning in 1998 linking Zyprexa with hyperglycemia and diabetes, is that the type of information that you would have passed on to the board of directors or not?

MS. GUSSACK: Objection.

THE WITNESS: I think you're making a hypothetical case here. What I do do and ask is to rely on the internal processes that we have to ensure that we take into account all of the data, the totality of the body of data that we have at any point in time on our products, and reflect those in both our communications with regulatory bodies, including the FDA, and as appropriate, communications to physicians.

BY MR. SUGGS:

Q. Sir, that wasn't the thrust of my question. My question is what information you provided to the board of directors. And my question specifically

was, if it was brought to your attention in December of 1998 that there were published medical articles showing that patients who use Zyprexa were developing hyperglycemia and diabetes, is that type of information something that would have been provided to Lilly's board of directors?

MS. GUSSACK: Objection. Did you say 1978?

MR. SUGGS: I said 1998.

THE WITNESS: We provide to our board of directors conclusions of analyses done on all of our products, not specific one-off pieces of data. I would not even know about them myself.

BY MR. SUGGS:

Q. So, it's your testimony that you would not have been made aware of articles in the medical literature in 1998 indicating that Zyprexa patients were developing hyperglycemia and diabetes?

MS. GUSSACK: Objection, mischaracterizes --

BY MR. SUGGS:

Q. That was not brought to your attention?

MS. GUSSACK: Objection, mischaracterizes the testimony.

BY MR. SUGGS:

Q. You may answer.

A. I got regular briefings on all of the body of evidence that we had and continue to have on our key products, including Zyprexa. I am not in a position in my job to know every article which is being published.

Q. Who was it that gave you regular briefings on Zyprexa back in the late 1990s/2000 time frame?

A. I do not recall the time at which Dr. Breier replaced Dr. Tollefson. So, it was first Dr. Tollefson and then Dr. Breier.

Q. Okay.

Did you continue to rely on

Dr. Breier to keep you regularly informed of Zyprexa, say, up to the present day?

MS. GUSSACK: Objection.

THE WITNESS: Dr. Breier no longer has responsibility for Zyprexa. So, the answer is no.

BY MR. SUGGS:

Q. Okay.

I believe he was head of the Zyprexa product team until sometime in 1994 or late -- strike that. I misspoke.

I believe that Dr. Breier had -- was head of the Zyprexa product team until sometime in late in 2003 and then became the chief medical officer. Is that accurate?

A. That's his current title. I don't recall exactly at what time he took that job.

Q. Okay.

Was he the one who kept you regularly informed of Zyprexa matters until the time he left his position as head of Zyprexa product team and moved

Exhibit 7, Page 6 of 28
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006342

Exhibit 6
Gary Tollefson

Page 94

There's no such thing as a special warnings section or special precaution. The regulators know -- have a different nomenclature, but that information was passed on to the FDA.

MR. SUGGS: Move to strike the nonresponsive portion of your answer.

BY MR. SUGGS:

Q. By at least the fall of 1999, Zyprexa was facing attacks by competitors who were asserting that Zyprexa had a higher incidence of hyperglycemia and diabetes than other antipsychotic drugs because Zyprexa caused more weight gain; isn't that correct?

MS. GUSSACK: Objection.

THE WITNESS: I cannot speak specifically to the time frame that you are talking about. It is clear that competitors have talked extensively about what they see as

Page 95

the risks associated with Zyprexa and sometimes going beyond -- often going beyond what the data shows.

MR. SUGGS: Move to strike the nonresponsive portion.

BY MR. SUGGS:

Q. Were you aware that in 1999 Lilly formed an executive steering committee to deal with olanzapine-associated weight gain and hyperglycemia?

MS. GUSSACK: Objection.

THE WITNESS: Can you repeat the question.

- - -

(Whereupon, the requested portion of the notes of testimony was read by the court reporter.)

- - -

THE WITNESS: I believe that around the time when we heard from the market that there was concern about the issue of weight gain and

Page 96

potential association with hyperglycemia, we wanted to go to the bottom of that issue and that several people were involved, a cross-functional team was involved in looking at all of the data.

BY MR. SUGGS:

Q. I'm going to hand you what has previously marked as Exhibit 8262. For the record, this is a chain of e-mails. The one I will be asking you questions about is on the bottom of the first page. It's from Alan Breier to more than a dozen people dated November 9, 1999.

A. (Witness reviewing document.)

Q. Have you ever seen this document before, Mr. Taurel?

A. Not at the time, no.

Q. I'm sorry, not at --

A. Not at 1999. I'm not on the list here of recipients.

Q. Have you seen this document

Page 97

since that time?

MS. GUSSACK: Objection, privileged. Instruction not to answer.

MR. SUGGS: My question is simply whether he's seen the document since 1999.

THE WITNESS: I've seen it in the context of privileged information from my lawyer.

BY MR. SUGGS:

Q. Okay.

The author of the e-mail that I directed your attention to is Mr. Alan Breier. We've talked about him before. At the time, he was head of the Zyprexa product team, correct?

A. Again, I do not recall exactly when the switch was made from Dr. Tollefson to Dr. Breier.

Q. Okay.

I notice that Steven Paul is one of the addressees of the e-mail. He was a senior executive within the company

Exhibit 7, Page 7 of 28
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006343

Exhibit 6
Gary Tollefson

Page 118

previously been marked as Exhibit 9281.
For the record, Exhibit 9281 is a February 6, 2004 e-mail from Alan Breier to US Medical. And in particular, sir, I'm going to direct your attention to the language in Dr. Breier's e-mail under the bolded heading "Principles."
A. (Witness reviewing document.)
Q. Have you seen this document before, sir?
A. I've been shown this document by counsel.
Q. Okay.
Did you receive a copy of it back in 2004?
A. No.
Q. In that section that I pointed your attention to regarding principles, Dr. Breier starts off by saying, "Making medicine for people facing illness is a much different and higher calling than making consumer products for other markets. We do not

Page 119

sell soap! It therefore requires a different and higher code for conducting our business."
Do you agree with that, sir?
A. Very much so.
Q. Okay.
If you drop your attention down to about the third line from the bottom, Dr. Breier has a sentence which starts off, "we are particularly challenged." Do you see that?
A. Yes.
Q. It says, "We are particularly challenged when it comes to presenting our data in a completely objective, unbiased manner because of our passion for our molecules and the belief that 'spinning' data is sometimes necessary to gain a competitive advantage. If we do not abandon the 'spinning' mentality, we will not restore confidence in our medical research and rebuild the public trust our industry compromised." Do you see that language?

Page 120

A. I do.
Q. Sir, you don't abandon something that you're not already doing, correct?
MS. GUSSACK: Objection.
THE WITNESS: I'm not Dr. Breier, and therefore, I cannot speak for him and what he meant here. But I do note that he refers in the last part of this sentence to the industry, rebuilding "the public trust our industry has compromised." And I believe that here he's talking to our colleague in medical, bringing her to a higher calling and a higher standard of performance than the industry has the image of having. That's why the principles of medical research were adopted. They are very ethical principles, and they were put in a very strong document.
Secondly, this is why Eli

Page 121

Lilly was the first company to create the registry of clinical trials and be totally transparent as to the medical research that we do. So, I believe that this is what Dr. Breier has in mind here when he's saying this.
MR. SUGGS: Move to strike as nonresponsive. Would you read back my prior question.
- - -
(Whereupon, the requested portion of the notes of testimony was read by the court reporter.)
- - -
MS. GUSSACK: Objection.
THE WITNESS: I think I've responded that I cannot take a word out of context without trying to understand what Dr. Breier here is saying. So, I've given my answer as to my interpretation --
BY MR. SUGGS:
Q. Do you know that the word --

Exhibit 7, Page 8 of 28
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006344

Exhibit 6
Gary Tollefson

Page 122

A. -- of what Dr. Breier is saying.
Q. What does the word "abandon" mean to you, sir?
A. It means to leave behind.
Q. It means to stop doing something that you're already doing, right?
MS. GUSSACK: Objection.
THE WITNESS: Again, in this context, I believe that Dr. Breier is talking about the public trust in the pharmaceutical industry, which is -- which has been damaged over the last decade or so with allegations that the industry is not sufficiently objective in presenting data. And he's calling his colleagues in medical to a higher level of standard that would address that public trust perception.
BY MR. SUGGS:
Q. Dr. Breier, you said the

Page 123

word "abandon" means to leave behind. What Dr. Breier was talking about leaving behind was spinning of data, correct?
MS. GUSSACK: Objection.
BY MR. SUGGS:
Q. Isn't that the subject of his e-mail there?
A. I think I've given my answer that this needs to be interpreted in the context of this whole message. For example, he's saying that the patient should be the raison d'etre. It should be -- "the patient is our primary customer." What is good for patients is good for business. I think he is here reaffirming very strong principles that would ensure that Eli Lilly is at the forefront of transparency and ethics in our industry and help, therefore, address this public image that the industry is suffering from.
MR. SUGGS: Move to strike as nonresponsive.
BY MR. SUGGS:

Page 124

Q. What doctor e-mail -- strike that.
What Dr. Breier was talking about in this e-mail was abandoning or leaving behind the spinning of data in order to gain a competitive advantage. Isn't that the subject of his e-mail there?
MS. GUSSACK: Objection.
THE WITNESS: I do not agree. The subject of his e-mail is to talk to all medical colleagues about the principle -- ethical principle of medical research. And part of his message relates to issues of public trust that the industry is suffering from.
BY MR. SUGGS:
Q. Sir, in fact, Eli Lilly itself was regarded by your customers, by payors and doctors who used your product as spinning the data about Zyprexa. Isn't that true, sir?

Page 125

MS. GUSSACK: Objection.
THE WITNESS: No.
BY MR. SUGGS:
Q. Let me hand you what's been previously marked as Exhibit 3223. For the record, Exhibit 3223 is an e-mail from Jerry Clewell to Virginia Stauffer with copies to a bunch of people, probably, I'm guessing, two dozen people. My first question -- by the way, the e-mail is dated January 14, 2004, and the subject is "Re: Annals of Pharmacotherapy Recent articles of interest 2004."
Sir, do you recognize any of the names of the individuals on that e-mail?
A. (Reviewing document.)
One or two. I do not know who Virginia Stauffer is, and know who Jerry Clewell is, and I don't know most of the people who are cc'd.
Q. Which names do you recognize?
A. There is -- Bruce Kinon is a

Page 166

approximately five percent in normal volunteers, then it would be false to tell doctors that weight gain with Zyprexa was manageable for most patients; isn't that correct?
MS. GUSSACK: Objection.
THE WITNESS: I do not know the exact message which was given to physicians. This program was helpful. It was something that met a need that they had, because for many patients under Zyprexa, they saw weight gain. So, this was helping them deal with the potential issue. And even if that premise is true, it only helps five percent of the patients, it's very important.
BY MR. SUGGS:
Q. But, sir, your company was telling Doctors that Zyprexa weight gain was manageable for most patients; isn't that correct?
MS. GUSSACK: Objection.

Page 167

THE WITNESS: I do not know that.
BY MR. SUGGS:
Q. Isn't that exactly what this document says?
MS. GUSSACK: Objection. Do you want him to review the entire document?
BY MR. SUGGS:
Q. No. I want him to look back at the position section that's on Page 2 that we already talked about before where it states "Our Position." "Weight gain can occur with Zyprexa as with other antipsychotics and mood stabilizers. For most patients, this can be managed allowing them to receive the overwhelming benefits Zyprexa offers." That was your position, wasn't it, sir?
A. Well, this is a planning document, as I see the title. What we said to the doctors in visits to them was in accordance with the label. It is -- all the messages to physicians go through

Page 168

a very involved process of medical, regulatory and legal review. So, there's a distinction between what you see in a planning document and actually what we say to physicians.
Q. Well, sir, we have many other documents that indicate exactly what was told to physicians by sales reps.
MS. GUSSACK: Objection. Is that a question?
BY MR. SUGGS:
Q. Are you familiar with what the sales reps went out and told doctors?
A. No, not in detail.
Q. Are you going to deny that doctors were told that weight gain was manageable for most patients?
MS. GUSSACK: Objection.
THE WITNESS: I have no knowledge of exactly what went on in every detail with doctors. What I do know is that the job of our sales reps is to present

Page 169

objective clinically meaningful information on both efficacy and side effects of our drugs. And I trust that they have done that with Zyprexa, as with every other drug.
MR. SUGGS: Move to strike the nonresponsive portion of your answer.
BY MR. SUGGS:
Q. Were you informed that in early 2002, Lilly's medical department concluded that the incidence of treatment emergent hyperglycemia was about three-and-a-half times higher in Zyprexa users as compared to placebo?
A. No.
Q. I'm going to hand you what's been previously marked as Plaintiff's Exhibit 990.
For the record, this is a document, the first page of which says, "Attachment E," and above that it says, "Confidential, Do Not Forward - To be

Exhibit 7, Page 10 of 28
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006346

Exhibit 6
Gary Tollefson

Page 186

give you as unbiased and straightforward view of the science as they possibly can, correct?

MS. GUSSACK: Objection as to form.

THE WITNESS: We consult with these consultants, with these opinion leaders, to get their views on our data, on new products and other things.

BY MR. SUGGS:

Q. And you expect them to give you the best possible expertise they can, correct?

MS. GUSSACK: Objection as to form.

THE WITNESS: Yes, we expect them to use their knowledge and expertise in their advice to us.

BY MR. SUGGS:

Q. And you don't want them to be tailoring their advice to you based on what they may perceive as the company position, correct?

Page 187

MS. GUSSACK: Objection.

BY MR. SUGGS:

Q. You want their bald, unvarnished truthful assessment of the matter, right? That's why you have them, right?

A. Yes.

Q. Okay.

Did anyone inform you, as Dr. Baker notes here, that they, referring to that advisory board, were concerned by your spontaneous adverse event reports and quite impressed by the magnitude of weight gain on olanzapine and implications for glucose? Did anybody ever tell you that back in 2000?

A. No. As I mentioned, I was not aware of a specific meeting, but I'm not surprised that this meeting took place. I think at that time we were doing everything we could to elucidate the issue of whether there was an association of olanzapine with hyperglycemia, and, therefore, it made

Page 188

sense to get the opinion of specialists in diabetes and not just talk to psychiatrists.

MR. SUGGS: I move to strike the nonresponsive portion of your answer.

BY MR. SUGGS:

Q. Directing your attention to a couple of lines down in Dr. Baker's e-mail, he says, "Citing methodological questions, at least the vocal members were not reassured adequately by our analyses, such as the finding that relative risk was not higher than comparative drugs. Disconcertingly, one member compared our approach to Warner-Lambert's reported argument that Rezulin did not cause more hepatic problems than other drugs in its class." Do you see that language, sir?

A. I do.

Q. Rezulin is an anti-diabetic drug, correct?

A. Yes.

Page 189

Q. You were aware that Warner-Lambert was claiming for a while that Rezulin did not cause more liver problems than other drugs in its class, correct?

MS. GUSSACK: Objection.

THE WITNESS: I do not have specific knowledge of that.

BY MR. SUGGS:

Q. Okay.

Were you ever informed by anyone that this outside group of experts "were not reassured adequately by our analyses"?

A. No. What I see in this message and series of messages, in fact, is scientific exchange where you have data and you have various ways to look at the data, you have suggestions to what other information, what other analyses to do, and I believe that informed our actions.

Q. I direct your attention to the next exhibit, which is Exhibit 1453.

Exhibit 7, Page 11 of 28
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006347

Exhibit 8
Gary Tollefson

Page 202

Q. Were you ever advised of that recommendation of the advisory board?
MS. GUSSACK: Objection.
THE WITNESS: Again, I was not aware there was a meeting of the advisory board and, therefore, I could not be aware of that specific recommendation. But they are referring here to the issue of impaired glucose tolerance, and I believe that we conducted something called clamp studies, don't ask me more details about that because I'm not a physician, but this was geared at understanding whether there was a direct correlation between impaired glucose tolerance and Zyprexa. And those studies were conducted later on and did not show the correlation.
MR. SUGGS: Move to strike as nonresponsive.

Page 203

BY MR. SUGGS:
Q. They were clearly saying, "Don't get too aggressive about denial, blaming it on schizophrenia, or claiming no worse than other agents until we are sure of the facts," correct?
A. That's what it says here.
Q. Now, this meeting occurred in October of 2000 about two months after the Federal Appeals Court had denied your patent in that litigation, correct?
A. Which patent?
Q. The Zyprexa patent.
MR. ALLEN: Prozac.
MS. GUSSACK: Objection.
BY MR. SUGGS:
Q. I'm sorry. I misspoke.
This meeting in October of 2000 occurred several months after the Federal Appeals Court held that the Zy -- pardon me, that the Prozac patent was to expire in 2001, correct?
A. Yes.
Q. Okay.

Page 204

That legal decision had a profound impact on Lilly's financial well-being, didn't it, sir?
MS. GUSSACK: Objection.
THE WITNESS: I think we talked about that earlier. It's a decision for which we had been prepared and which led us to the development of several new products and licensing of others and so on.
BY MR. SUGGS:
Q. Sir, do you recall that the day that that Federal Court ruling was announced publicly that Lilly's stock plunged by almost one-third in a day, wiping out over $36 billion in equity?
A. I sure do. I still have the scar tissue.
Q. I'll bet you do.

MR. SUGGS: I'll show -- have marked as Taurel Exhibit 4 --
MS. GUSSACK: After this

Page 205

exhibit, David, would it be appropriate for a lunch break?
MR. SUGGS: Sure.
- - -
(Whereupon, Deposition Exhibit Taurel-4, Wall Street Journal Online Excerpt (1 page), was marked for identification.)
- - -
BY MR. SUGGS:
Q. I went on Wall Street Journal online and had a chart drawn of Lilly's stock between the dates of August 1, 2000 and August 10, 2000, August 10, 2000 being the date of the outside advisory board meeting that we had referred to in the prior exhibits. And it indicates that there was a quite dramatic drop in the stock price in early August there on the day of the announcement from, it looks like something -- the stock value is something over $105 per share, dropping down to about $75 per share. Is that accurate?

very loose term, global management team. To what are you referring?

MR. SUGGS: I'm going to hand you a document. We actually have to put a sticker on this one. This will be Taurel number 5.

- - -

(Whereupon, Deposition Exhibit Taurel-5, Presentation excerpt ZY206198660, was marked for identification.)

- - -

BY MR. SUGGS:

Q. For the record, this is a document produced by Lilly that bears the Bates Number ZY206198660. It's a one-page document. And the first paragraph says, "Chairman Sidney Taurel presented the company's 2002 priorities to the global management team on December 14, stressing their importance as Lilly works to become 'the pharmaceutical growth company of the decade.'" Does that help at all in --

A. Yes. This refers to all the people who have the title of manager and above inside the company. And typically once a year I would discuss in a video or even a live conference the company's priorities for next year.

Q. Okay.

And I presume this probably would have been given, your presentation, sometime in December of 2001; is that correct?

MS. GUSSACK: Objection.

THE WITNESS: Yes. This says December 14.

BY MR. SUGGS:

Q. The people who would have heard this presentation would have been dozens or hundreds of people?

MS. GUSSACK: Objection to the form.

BY MR. SUGGS:

Q. How big was the global management, the group that you would have presented this to?

A. I believe there are about 5,000 people more or less who are at the management level. Whether all of them listened in to this isn't clear. Typically I make the presentation to a live audience of a few hundred, and then the rest is broadcast in various locations.

Q. Okay.

So, this message -- the message that you delivered there would have been broadly spread throughout the corporation; correct?

A. Yes.

Q. Okay.

According to this document, "Taurel emphasized that to weather Year X," which we've talked about before, "and outgrow its competition, Lilly must," and there's a list of bulleted up items, correct?

A. Yes.

Q. Very first thing is "Maximize sales of Zyprexa" correct?

A. Yes. I note that it is a truncated first bullet point.

Q. I would agree. You'd have to ask your lawyer why that was.

A. I am pretty sure that this would have included other products which had been launched since the mid '90s.

Q. Is that speculation on your part?

A. Oh, I'm pretty sure that would be, because this was very much a part of the Year X strategy which I mentioned earlier. We recognize the other bullet points, strengthen our pipeline, maximizing partnering effectiveness if we could license products, and maximize all of our existing products, Zyprexa, Gemzar, Actos, Humalog --

Q. Since --

A. Evista.

Q. Since that section of the document has been redacted by Lilly's counsel, I'll object to any question --

Exhibit 7, Page 13 of 28
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006349

Exhibit 8
Gary Tollefson

Q. Directing your attention to the text in the first page of this exhibit, it says, "Zyprexa was first launched in late 1996. The estimated R&D spend to first launch was $195 million. Since then, Lilly has spent approximately $750 million plus on R&D for Zyprexa's multiple indications.

"On a cumulative IBT basis, Zyprexa will bring in approximately $16.1 billion in IBT through 2004."

Do you see that language?

A. I do see that language, yes.

Q. Is it your understanding that that would be a correct statement?

A. I have no basis to say yes or no.

Q. Okay.

A. I don't know where this document comes from, who wrote it, and one figure which surprises me a lot is the $195 million R&D spend to first launch. Typically, it costs much more than that to bring products to market.

Q. If you wanted to find out -- well, strike that.

Who would you regard as the most knowledgeable person in the corporation to find out whether these figures are accurate or not?

MS. GUSSACK: Objection.

BY MR. SUGGS:

Q. Who would you rely on?

A. I would have to work through my line management, the people who report directly to me. In this case, that would be the CFO who, in turn, would look to within his organization, I guess the controller, who would, in turn, look to somebody else until they find someone who is really in charge and working with Zyprexa. I have no idea who that might be.

Q. Continuing on in the text of this document, it goes on to state, "Sales and IBT have greatly exceeded the pre- launch PMC valuations for Psychosis and Schizophrenia combined. Through

2004, Sales and IBT will be approximately $14.3 billion and $9.2 billion, respectively, above the initial PMC valuations." Do you see that language?

A. Yes.

Q. Now seeing that phrase "PMC valuations" in that context, does that help you understand what they're referring to there?

A. No.

Q. Very first sentence of the next paragraph starts off by saying, "Zyprexa clearly exceeded all expectations." Do you see that?

A. Yes.

Q. That's a fair statement, is it not?

MS. GUSSACK: Objection.

THE WITNESS: I think the success of Zyprexa, once it was launched and the way it was embraced by physicians, was above our expectations. Indeed, the experience that we heard from

patients and physicians alike were that the product really transformed the lives of patients with schizophrenia.

MR. SUGGS: Move to strike the nonresponsive portion.

BY MR. SUGGS:

Q. If I can direct your attention to the following page. It bears the title at the top, "Zyprexa - Revenue and Cost Summary Estimated 1981 through 2002 and Forecasted 2003 through 2004." And the numbers that are expressed there in that chart are in the millions. And do you see that towards the bottom of the chart, the second to last entry there is the total IBT impact?

A. Yes.

Q. Would that be your understanding that the number there states the income before taxes for that particular year?

A. The income before taxes of what?

Page 234

A. Yes.
Q. Were you informed that that was the instruction that was being given to your sales force?
MS. GUSSACK: Objection. I'm going ask that the witness be allowed to review the document before he answers questions about the document.
MR. SUGGS: I'm only asking about that one piece of language.
MS. GUSSACK: I understand.
BY MR. SUGGS:
Q. Sir, were you informed that the sales force was instructed that diabetes was a highly competitive driven issue and that "Therefore, we will NOT proactively address the diabetes concern, but rather only when it arises from an MD"? Did you or did you not become aware that that instruction was given to your sales force?
MS. GUSSACK: I'm going to object and also ask that the

Page 235

witness be given an opportunity to review the document.
BY MR. SUGGS:
Q. Can you answer that question, Mr. Taurel?
A. Not without reading the document.
Q. It is your testimony to the jury that you have to read this entire document in order to answer the question that I posed to you? Is that correct?
MS. GUSSACK: Objection. Mr. Suggs, you already made an agreement with the witness that if he simply said that he wanted to review the document before he answered your question, you would give him the opportunity.
MR. SUGGS: I'm going to give him that time. I just want the jury to understand --
MS. GUSSACK: So, he's not going to answer any more questions --

Page 236

MR. SUGGS: I want the jury to understand that this witness is telling the jury that he has to read this entire document in order to answer that question.
MS. GUSSACK: He's not going to answer any more questions that you pose until he reviews the document pursuant to an agreement that you offered and he accepted.
MR. SUGGS: Fine. Go ahead. Start reading.
MS. GUSSACK: So, your testimony on the issue isn't really relevant.
MR. SUGGS: Start reading. You are wasting time, Counsel.
(Witness reviewing document.)
THE WITNESS: So, what is your question?
BY MR. SUGGS:
Q. My question, sir, was, were you informed that the sales force was

Page 237

instructed that diabetes was a highly competitive driven issue and, "Therefore, we will NOT proactively address the diabetes concern, but rather only when it arises from an MD"?
A. I was not specifically informed of what is in this document. What I know is the context of how we were discussing with physicians. The context is that there was a lot of noise in the marketplace raised by our competitors alleging that there was a correlation between the use of Zyprexa and diabetes. And our instructions to our sales reps was to put this issue in perspective.
MR. SUGGS: Move to strike as nonresponsive.
BY MR. SUGGS:
Q. Sir, do you recall that the sales force was instructed that "Patients treated with Zyprexa, risperidone, haloperidol, divalproex, and ziprasidone in clinical trials had comparable rates of diabetes and hyperglycemia"?

Exhibit 7, Page 15 of 28
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006351

Exhibit 8
Gary Tollefson

Page 242

Psychiatric Association, the American Association of Clinical Endocrinologists and the North American Association For the Study of Obesity, correct?
A. Yes. I'm aware of the process they use, which was to bring together experts from those groups, and they spent two days discussing the data on Zyprexa.
Q. In fact --
A. I'm sorry, on antipsychotics.
Q. In fact, employees of Lilly attended and made presentations at that conference; correct?
A. I believe that's correct.
Q. Also, outside consultants to Lilly appeared and presented material to that conference, correct?
A. I don't know.
MS. GUSSACK: Objection and no foundation.
BY MR. SUGGS:
Q. Do you know Dr. John Buse?

Page 243

A. I don't.
Q. Do you know Dr. David Allison?
A. No.
Q. Do you know any of the presenters that are listed on the last page in the left-hand column other than the Lilly employees?
MS. GUSSACK: What page are you on, David?
THE WITNESS: Among the presenters?
BY MR. SUGGS:
Q. Yes.
A. No. I just recognize one name here, and it is Patrizia Cavazzoni, who is a Lilly employee. I don't know if there are other Lilly employees or consultants to Lilly.
Q. Sir, this consensus statement by those medical organizations that we talked about before concluded that "Clozapine and olanzapine are associated with the greatest weight gain

Page 244

and highest occurrence of diabetes and dyslipidemia," correct?
MS. GUSSACK: Objection as to form.
THE WITNESS: Can you point me to the --
BY MR. SUGGS:
Q. Sure. The summary section, sir, on Page 5, right-hand column, the second full paragraph, four lines down. "Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia." Did I read that correctly, sir?
A. Yes.
Q. It goes on to state, "Risperidone and quetiapine appear to have intermediate effects." Did I read that correctly?
A. Yes.
Q. And it goes on to say -- I can never pronounce this correctly -- "Arip --
A. Aripiprozole.

Page 245

Q. Thanks. "Aripiprozole and ziprasidone are associated with little or no significant weight gain, diabetes or dyslipidemia, although they have not been used as extensively as the other agents." Did I read that correctly?
A. That's what's written here, yes.
Q. That was the conclusion of those medical organizations, correct?
A. That was the conclusion of the group of people that they gathered during two days on this issue, yes.
Q. Sir, even after that consensus statement came out, Lilly continued to maintain that the data showed that the rates of diabetes were comparable between the various agents, correct?
MS. GUSSACK: Objection.
THE WITNESS: I would point out that after this article was written, a number of letters to the editor were sent by various

Page 246

physicians and also by the FDA reporting on different conclusions based on either their clinical experience in the case of individual physicians or the weight of all the data that the FDA spent months reviewing, which was much more than -- much more time and analysis than was devoted by this group of people.

MR. SUGGS: Move to strike as nonresponsive. Would you read the question back to him, please.

- - -

(Whereupon, the requested portion of the notes of testimony was read by the court reporter.)

- - -

THE WITNESS: We believe -- we believed that the weight of evidence at that time, as confirmed by the decision of the FDA not to differentiate between products was that at that time

Page 247

based on the information available, there was no strong basis for the conclusion of the so-called consensus group.

MR. SUGGS: Move to strike your answer as nonresponsive.

Could you please listen to the question when I have the court reporter read it back and answer the question I have asked.

- - -

(Whereupon, the requested portion of the notes of testimony was read by the court reporter.)

- - -

MR. SUGGS: The answer is either a yes or a no or a you don't know.

MS. GUSSACK: I believe the witness has answered the question already.

THE WITNESS: Lilly continued to take its guidance from the decision of the FDA.

Page 248

MR. SUGGS: Move to strike as nonresponsive.

Sir, could you please just answer this question directly.

BY MR. SUGGS:

Q. Did Lilly continue to maintain that there were comparable rates of diabetes between the various antipsychotics even after the consensus development statement came out? It's a yes, no or you don't know. Which is it?

MS. GUSSACK: Objection, asked and answered. You may answer.

THE WITNESS: I would say again that we are bound in our activities to take our guidance from the FDA. The FDA had access not only to all the data that we have access to, but also the data that was supplied by other manufacturers of antipsychotics, and also the data that they get from spontaneous reporting of

Page 249

events in the marketplace. We believe that this was the broadest database possible to reach conclusions, and, therefore, we relied on that conclusion and not on the conclusion that the group of people who worked for two days on this issue arrived at.

BY MR. SUGGS:

Q. Sir, you still have not answered my question.

MR. ALLEN: Objection, nonresponsive.

THE WITNESS: We have taken our guidance from the FDA.

BY MR. SUGGS:

Q. Sir, I'm asking about the statements that Lilly has continued to make. I'm not asking where it came from or anything else. I'm just asking, isn't it true that even after the consensus statement came out with those conclusions that we stated before, Lilly has consistently maintained that the rates of

Page 258

declined. So, it does not -- the answer to your question is, therefore, no.
Q. Okay.
I want to switch gears for a while to talk about what Lilly was warning foreign doctors about as compared to what was it was telling US doctors about. Would it be fair to say that the U.S. market for Zyprexa was the most profitable market as compared to the rest of the world?
A. The U.S. market is the largest market for pharmaceutical products, that's correct, yes.
Q. Prior to 2003, there was no mention in the U.S. label in the Warnings section regarding hyperglycemia or diabetes, correct?
A. I believe that's correct. Those observations that we had in our clinical trials were elsewhere in the label.
Q. And you do recall that there was mention of hyperglycemia and diabetes

Page 259

in the European label before that time, correct?
MS. GUSSACK: Objection.
THE WITNESS: I don't believe that's correct.
BY MR. SUGGS:
Q. Do you recall that in April of 2002, the Japanese regulatory authority required Lilly to issue a warning about diabetes occurring with Zyprexa?
MS. GUSSACK: Objection as to form.
THE WITNESS: I believe that the Japanese authorities mandated a black box warning or their version thereof mentioning instances of ketoacidosis. This is data that we shared with the FDA and the regulatory authorities in Europe and elsewhere. And they concluded that since the few cases on which this black box warning was based were compounded by other

Page 260

factors, there was no reason to change the label outside of Japan.
MR. SUGGS: Move to strike the nonresponsive portion.
BY MR. SUGGS:
Q. Sir, I'm going to hand you what has been previously marked as Exhibit 320, which I will represent to you is a translation of the Japanese "Dear Doctor" letter. I believe the translation or the document was certainly produced to us by Lilly. Have you seen this document before?
A. No. But I'm aware of the change in label which occurred in '02 in Japan.
Q. According to this document, which is dated April of 2002, there were three major elements to the warning over in Japan, correct?
A. Say that again. I'm sorry.
Q. According to this document and the numbered items in the box that you see there, there were three major

Page 261

elements to the warning in Japan, correct?
A. Yes.
Q. The first was: "Do not administer to patients with diabetes... and those who have a history of diabetes..." correct?
A. Yes.
Q. The second part was "During administration of this product" -- I'm just reading what's written here -- "observe sufficiently with such as measurement of blood glucose." Correct?
A. Right.
Q. Was it your understanding that patients were supposed to have their blood glucose measured while they were on Zyprexa, at least the ones over in Japan?
MS. GUSSACK: Objection.
THE WITNESS: It is not clear from what this translation says.
BY MR. SUGGS:
Q. Okay.

Exhibit 7, Page 18 of 28
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006354

Exhibit 6
Gary Tollefson

Page 290

product within the label, and point out how to specifically address concerns about hyperglycemia and the potential use of the product in patients with diabetes." Do you see that language, sir?
A. Yes.
Q. Were you aware of that?
A. Not specifically.
Q. If I could direct your attention to the very last page. Four lines up from the bottom of the last paragraph there's a sentence that starts off "There appears." Do you see that?
A. I'm sorry, the last paragraph or --
Q. Well, the second to last paragraph, the big one there.
A. Starting with "There is a need"?
Q. Starting with "There appears." Are you on the last page?
A. I'm sorry. Yes.
Q. Okay.

Page 291

Do you see where I'm referring to, "There appears"?
A. Yes.
Q. Dr. Breier and Mr. VanDenBergh state, "There appears to be a decrease of hyperglycemic AEs since the label changes." Were you aware of that, sir?
A. No.
Q. He goes on to state, "Again, we will make every effort through promotional efforts and physician-to-physician and medical communications to ensure that we promote the use of the drug within the label, which would by design dramatically reduce the number of events." Do you see that language, sir?
A. Yes.
Q. Did Dr. Breier or Mr. VanDenBergh or Mr. Mayr or Dr. Lechleiter ever inform you of the conclusion of Dr. Breier, that if they promoted the use of the drug within the label in Japan with

Page 292

the language that was in the label there, that that would by design dramatically reduce the number of adverse events?
A. No. This is the first time I see this document, so I would need to really understand the whole context of what Mr. VanDenBergh and Dr. Breier are saying. But, again, as I mentioned earlier, what I do know is that the acceptance of the product in Japan after a period of negative impact started to improve significantly.
MR. SUGGS: Move to strike as nonresponsive.
BY MR. SUGGS:
Q. It's your testimony that you were not made aware that Dr. Breier had concluded that if the product was promoted in Japan in accordance with the label there, that that would by design dramatically reduce the number of adverse events, correct?
MS. GUSSACK: Objection as to form.

Page 293

THE WITNESS: The --
BY MR. SUGGS:
Q. I think you were starting to answer, that is correct?
A. That is correct. Yes. It's not -- I do not get involved in individual trip reports or individual country and product-specific marketing programs.
Q. Did anyone in Lilly ever recommend that the label in the United States be changed to reflect the same type of warnings that were being given in Japan in 2002?
MS. GUSSACK: Objection as to form and vagueness.
THE WITNESS: I know that we shared the data that had caused the change in the label in Japan. We shared the data with both the FDA and regulatory authorities in Europe. Our conclusion, as well as theirs, was that the few cases on which this decision was made

Page 294

were mostly confounded. I think eight or nine cases, if I'm not mistaken, had a number of factors which could explain the adverse events.

MR. SUGGS: Move to strike as nonresponsive.

BY MR. SUGGS:

Q. Sir, my question is whether any individual within Lilly ever recommended or suggested to the corporation that Lilly change the label in the United States to reflect the warnings that were present on the Japanese label after April of 2002?

MS. GUSSACK: Objection as to form.

BY MR. SUGGS:

Q. It's a simple yes or no or you don't know?

A. I do not know. I would doubt it very much, given the fact that as a company, and in agreement with regulatory authorities outside of Japan,

Page 295

it was pretty clear that this data was not conclusive and did not justify a change in label.

MR. SUGGS: Move to strike the nonresponsive portion.

BY MR. SUGGS:

Q. Sir, do you recall that in March of 2007, the FDA informed the company that it was concerned about the adequacy of the Zyprexa label?

A. I'm aware we received a letter -- an approvable letter for Symbyax from the FDA which had some comments about their concerns on the label.

MR. SUGGS: I'm going to hand you what we'll mark as Taurel Exhibit 9.

- - -

(Whereupon, Deposition Exhibit Taurel-9, Letter 3-28-07 (35 pages), was marked for identification.)

- - -

Page 296

MS. GUSSACK: While you're doing that, Mr. Suggs, I'm going to ask you to allow -- to take these questions slowly so that we can make sure that we are observing the agreement that we have established.

MR. SUGGS: Sure.

MS. GUSSACK: I'm sorry, exhibit number --

MR. SUGGS: 9 --

BY MR. SUGGS:

Q. -- which I'll describe for the record as a letter from FDA to Eli Lilly with attachments. It has several, what appear to be fax imprint dates at the top of the pages, the earliest of which is March 28, 2007. It also bears the date of March 28, 2007 with a stamp for G. Brophy. I don't see any other dates on here. I'll also represent this document does not have a Lilly Bates Number on it.

MR. SUGGS: I believe, Nina,

Page 297

this is a copy that you produced to Judge Weinstein in the MDL, and this is a copy of that.

MS. GUSSACK: Thank you.

BY MR. SUGGS:

Q. Mr. Taurel, is this letter that I've handed you as Exhibit 9 the letter that you were referring to?

A. Yes, approvable letter for Symbyax.

Q. It refers to -- by the way, is Mr. Brophy, is he in the regulatory affairs of Eli Lilly?

A. Yes, Dr. Brophy, yes.

Q. This refers to a supplemental new drug application regarding a drug product called Symbyax, correct?

A. Yes.

Q. Symbyax is a combination of both olanzapine and fluoxetine, correct?

A. Correct.

Q. Olanzapine is the generic name for Zyprexa, and fluoxetine is the

Page 306

A. I do.
Q. So there again, with respect to those people who had borderline to high levels at the outset, their rate or incidence of going above 200 milligrams per deciliter was, again, about ten times higher than those folks who were exposed to placebo, correct?
MS. GUSSACK: Objection as to form.
THE WITNESS: I note the next sentence says, "This latter finding was based on a small number of patients in the OFC program, and for this reason, we would like to see such data for the entire olanzapine program."
So, my understanding is that --
BY MR. SUGGS:
Q. Sir, you need to answer the question first.
MS. GUSSACK: Could you finish your statement first.
THE WITNESS: Could you

Page 307

repeat --
MS. GUSSACK: I'm sorry. Could you finish your statement?
THE WITNESS: And my understanding is that we have engaged since that time with the FDA on addressing some of the suggestions and concerns that they have expressed in this letter.
BY MR. SUGGS:
Q. Mr. Taurel, I need to have you answer the question. And my question is that this letter indicates that there is data showing that people who were exposed to combination drug who had borderline to high levels of blood sugar at the outset of treatment had an incidence of -- 46 percent of those folks went on to have blood levels above 200 as compared to only 5 percent of the placebo-treated patients, correct?
A. That's what this says, yes.
Q. And 46 percent is about ten times higher than 5 percent, correct?

Page 308

MS. GUSSACK: Objection.
THE WITNESS: No. It's incorrect. It is about 9.2 percent times --
BY MR. SUGGS:
Q. That's fine. It is over 9 times higher, correct?
A. Yes. But as the next sentence indicates, this finding is based on a very small number of patients. So, the FDA is telling us this is not significant; however, there's here potentially a signal that we want to investigate.
Q. These studies that had been done, do you know when they were done, what year?
A. No, I don't.
Q. Do you know who was responsible within the corporation for conducting those studies?
MS. GUSSACK: Objection as to form and vagueness. Which study?

Page 309

BY MR. SUGGS:
Q. The studies from which this data comes.
A. This data seems to come from the OFC submission, and the OFC or Symbyax submission would have been put together by the Symbyax team. I don't know exactly who are the people on that team.
Q. The FDA goes on to note: "We were troubled that this important finding was not included in your proposed label." Do you see that language?
A. Yes.
Q. When Mr. Paul or Dr. Paul informed the policy committee of this letter, did he also tell the policy committee that the FDA was troubled that this important finding was not included in your proposed label?
A. As I told you, I do not recall exactly how I came to know about this or I do not recall exactly the words that Dr. Paul used. My understanding is

that following this letter, we had communications with the FDA. In fact, they were suggesting I think in the letter that we should discuss with them how to address their concerns, which we did immediately, and we put a very strong team of people and the resources necessary to address those issues.

MR. SUGGS: Move to strike the answer as nonresponsive.

BY MR. SUGGS:

Q. Directing your attention to -- well, do you see towards the bottom of the page there's a heading entitled "Post Marketing Commitments"?

A. Yes.

Q. In the paragraph just above that, it states, "Our overall goal is to improve labeling with regard to these findings so that clinicians will be better informed on what the risks are for their patients. They cannot make reasonable treatment decisions until they have such information. We do not feel

that current labeling for either Symbyax or Zyprexa provides sufficient information on these risks, and we fully intend to insure that these labels are enhanced with the best available information to characterize these risks."

Do you see that language, sir?

A. Yes.

Q. Did Dr. Paul inform the members of the policy committee of that language at that meeting that you would have had shortly after this letter was received by the company?

A. I will repeat that I do not recall the exact words used by Dr. Paul, but that I know that following the receipt of this letter, we immediately put a team of people together to engage the FDA in responding to their concerns and doing the analysis that they wanted us to do and which we wanted to do.

MR. SUGGS: Move to strike as nonresponsive.

BY MR. SUGGS:

Q. Sir, to this day, Lilly has not warned physicians in the Zyprexa labeling of the findings that were noted there in the second paragraph of FDA's letter, correct?

MS. GUSSACK: Objection, and I'm going to ask Mr. Taurel not to answer that question. And consistent with the agreement between counsel, there have been ongoing discussions with FDA that Mr. Taurel is not going to speak to those communications or --

MR. SUGGS: I'm not talking about discussions. My question is --

MS. GUSSACK: -- actions as a result beyond the ex-approvable letter.

BY MR. SUGGS:

Q. I'm not asking for any communications.

Sir, as we sit here today on September 19, 2007, the Zyprexa label

does not reflect the data that is in the second paragraph of the FDA's letter indicating a ten-fold increased incidence of hyperglycemia in people exposed to that combination drug, correct?

MS. GUSSACK: Objection both as to form and to foundation. If you are asking the specific question, Dave, because I want to make sure that we're being faithful to the agreement -- if you're asking the question does the label that's in existence today include this data, that's a question that he can answer.

MR. SUGGS: That's exactly what my question was.

THE WITNESS: Can you ask the question again.

MS. GUSSACK: If he knows.

BY MR. SUGGS:

Q. As we sit here today on September 19, the Zyprexa label does not warn physicians of the data that's

Page 334

products that you developed in the '90s?
A. Following a decline which we had in 2002 due to the Prozac patent expiration.
Q. Well, in fact, you don't list the drugs in any type of alphabetical order, you introduce -- the first drug you talk about is Zyprexa, right? Is that correct?
A. Yes.
Q. Down here you said, "Introduced as a therapy for schizophrenia in 1996, Zyprexa was approved in the U.S. last year for additional indications of acute mania associated with bipolar disorder and the maintenance of treatment response in schizophrenia." Did I read that correctly?
A. You did.
Q. So, what you're saying is what we just discussed, the two indications, and the only two FDA-approved indications for Zyprexa at

Page 335

the time Prozac went off patent were schizophrenia and bipolar mania, right?
MS. GUSSACK: Objection to the form.
THE WITNESS: Schizophrenia had actually two different indications. It was first schizophrenia short term therapy and then the maintenance of treatment response in schizophrenia.
BY MR. ALLEN:
Q. Right. Two disease states. Two diagnoses, schizophrenia and bipolar mania, right?
MS. GUSSACK: Objection as to form.
THE WITNESS: Again, yes.
BY MR. ALLEN:
Q. Thank you, sir.
It says, "We're exploring broader uses for Zyprexa in schizophrenia and other key segments of the antipsychotic market, including bipolar

Page 336

depression and the psychotic or behavioral disturbances that accompany dementia." Did I read that right?
A. You did.
Q. Now, I know it's clear as a bell and you know you can tell me right now, Zyprexa has never been approved for the treatment of dementia either in the past or as we sit here today, has it?
A. No. But at the time I was writing this, we were doing clinical trials, and we had already, I believe, one first clinical trial which was positive. And, therefore, we're pursuing the clinical development of Zyprexa in various new indications, and I believe that we did get approval for other indications which are referred to here.
MR. ALLEN: I need to object as nonresponsive.
BY MR. ALLEN:
Q. I wasn't quibbling with you. Maybe you misunderstood my question. I only asked about dementia, and I just

Page 337

want you and I to agree that Zyprexa has never been approved for dementia, correct?
A. That is correct.
Q. That's all I was asking. That's all I was asking.
A. All I was saying is that at that time, we were doing the clinical trials to get to the FDA, if those were positive, to get an approval for the treatment of dementia.
Q. Right.
A. And the nature of pharmaceutical R&D is that some hypotheses are sometimes confirmed, and others are not.
Q. Yes, sir. You and I are agreeing on that.
A. Good.
Q. Sometimes things work out, and sometimes things don't work out, right, sir?
A. It is the nature of pharmaceutical R&D, yes.

Page 350

A. No.
Q. Has Zyprexa ever been approved for attention deficit disorder or hyperactivity disorder?
A. No.
Q. Has Zyprexa ever been approved for the management of social phobias?
A. No, there's no indication.
Q. Sir?
A. There's not an indication.
Q. If there's no indication approved by the FDA, a drug company can't promote the drug for that, right?
A. Right.
Q. Thank you. That's all I need to know.
Has Zyprexa ever been approved for sleep or sleep disorders, for the treatment of sleep, insomnia, sleep or sleep disorders?
A. Not for a specific treatment of sleep disorders, but a bipolar patient may have sleep disorders, may have a

Page 351

problem with sleeping, and, therefore, this is one of the symptoms that you would find in the approved indication. And the same about -- I'm not a psychiatrist, but I believe the same applies to many of the symptoms that you just talked about.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. You made a very good point, Mr. Taurel, and I had it in my notes. Just so it's real clear, you are not a doctor?
A. That's right.
Q. You have no medical training?
A. No, I don't.
Q. You are not a scientist. I think in one of your answers to Mr. Suggs earlier today, you made a particular point and said to him, and I'm paraphrasing, you'd have to talk to the science end, not the business end.

Page 352

A. Right. I have a general understanding of the areas of medicine where our products are used because I have been in this business for 36 years.
Q. Yes, sir. I got a general understanding as a lawyer, but it wouldn't qualify me to be a doctor now, would it?
A. No. I don't claim to be qualified to be a doctor.
Q. Right. That's why I'm trying to get to just so you and I are communicating. You're not a doctor, are you?
A. No.
Q. You can't make diagnoses, can you?
A. No.
Q. You can't treat people, can you?
A. No.
Q. You wouldn't claim to be an expert in science or technology, would you?

Page 353

A. No.
Q. In fact, you described yourself on the record to Mr. Suggs as you're on the business end of the company, right?
A. Well, I run the whole company.
Q. Yes, sir, you're the big shot, right?
MS. GUSSACK: Objection as to form.
THE WITNESS: That's not what I'm saying. What I'm saying is I have responsibility to supervise all the functions of the company, including the R&D function.
BY MR. ALLEN:
Q. Right.
Now, back to what my question was. Zyprexa was not indicated --
Have you ever heard of Ambien? Have you ever heard of the drug

Page 354

Ambien?
A. Yes.
Q. And Lunesta, I've seen advertisements on TV. You've seen those advertisements, haven't you?
A. Yes.
Q. Those are called direct-to-consumer advertisements, right?
A. Right.
Q. Which you're only allowed to do in the United States and New Zealand, correct?
MS. GUSSACK: Objection to the form.
BY MR. ALLEN:
Q. I think that's right.
A. I think so, maybe some other countries like Singapore.
Q. United States, New Zealand and Singapore can get direct-to-consumer.
Anyhow, you know there are specific drugs that treat sleep and are approved by the FDA for that, Lunesta, Ambien? You're familiar with that?

Page 355

A. Yes.
Q. My point to you is Zyprexa was not approved for sleep, right?
A. There's a difference. I believe these products are approved for insomnia, seen as a disease. Sleep disturbance as part of a symptom of bipolar mania, for example, is a different matter.
Q. Yes, sir. I'm not quibbling. I just asked you a direct question.
Has Zyprexa been approved by the FDA for sleep disturbances or sleep disorders or insomnia?
MS. GUSSACK: Objection to the form.
BY MR. ALLEN:
Q. Yes or no?
A. It has not been approved for insomnia. It has not approved -- it has been approved for schizophrenia and bipolar mania.
Q. Which are two diagnoses, are

Page 356

they not?
A. They are.
Q. Right. Those are diagnoses that, in fact, are defined, I believe, in a book called a DSM. Are you familiar with that?
A. Not specifically.
Q. That's because you're not a doctor, right?
MS. GUSSACK: Objection as to form.
BY MR. ALLEN:
Q. Right? Are you familiar with the DSM-III or DSM-IV manuals?
A. I thought this was a scale, not a book, but I may be wrong.
Q. You are wrong. That's okay. That's because you're not a doctor. So, you're not familiar with the DSM-III or DSM-IV, right?
MS. GUSSACK: Objection as to form.
BY MR. ALLEN:
Q. Right?

Page 357

A. I'm generally familiar that these are scales that are being used to measure symptoms of psychiatric diseases.
Q. DSM-III and DSM-IV?
A. Yes.
Q. Okay.
Now, let me ask just some general questions. By the way, has Zyprexa ever been approved for complex mood disorder?
A. Zyprexa has been approved for schizophrenia and bipolar mania. Those are complex or psychiatric indications, and they do involve mood disorders, disturbance of the mood.
Q. But you have to have --
The diagnosis has to be made by the doctor, schizophrenia or bipolar mania, right?
MS. GUSSACK: Objection as to form.
THE WITNESS: For what?
BY MR. ALLEN:
Q. I don't know. I'd rather

that's what I said.
Q. I'm not -- I'm just putting this into context, simple questions and simple answers.
MS. GUSSACK: Objection.
THE WITNESS: Yes. But you are putting all the emphasis on only Zyprexa. And as I told you several times, we had five new products that we had launched over the previous five years which were growing the company, and we were working on another eight products that were going to be launched. All of that was part of our answer to the so-called Year X challenge.
MR. ALLEN: I need to object to that as nonresponsive to any pending question, and there's a time that you can give those answers and then I can cross-examine you, but I've only got limited time.
BY MR. ALLEN:

Q. All right. Now, I take it then in October of 2000, when it said "Zyprexa PCP launch meeting," you were aware Zyprexa was being launched to the primary care physicians in October of 2000?
A. Yes.
Q. And this was part of the Zyprexa growth strategy, was it not?
A. Yes.
Q. Just for the record, there was no change in the indications for Zyprexa between August of 2000 and October of 2000, was there?
A. I believe this decision followed the approval of the drug for bipolar mania, which took place earlier. And the decision to go into the primary care market was made, in fact, prior to August, prior to the decision that you mentioned of Prozac. It has nothing to do with it. It was following the earlier approval of the product for the indication of bipolar mania.

MR. ALLEN: I need to object to that as nonresponsive.
BY MR. ALLEN:
Q. My only question was, there had been no change in the indications of Zyprexa between August of 2000 and October of 2000; is that correct? Still indicated for the same thing, schizophrenia and bipolar mania, right?
A. That is correct. The only decision --
Q. Thank you --
A. Excuse me. The decision for us to go into the primary care physician is not a decision that can be implemented in two or three months. We need to hire the sales reps, and it takes time. Therefore, it was not driven by anything happening between August to October, but, rather, by the approval earlier, I think in March or so, of the bipolar mania indication.
Q. Sir, I haven't even made any implication one way or the other. You

are answering something and giving a speech about a question I didn't ask.
MS. GUSSACK: Objection.
BY MR. ALLEN:
Q. With all due respect, I think you're being overly defensive, but let's just move on.
A. In my view, you were making an implication.
MS. GUSSACK: Objection. Given the limited amount of time, Mr. Allen, if we could minimize the commentary and focus on the questions.
MR. ALLEN: I would agree. That's what I'm trying to do, is minimize the commentary and focus on the question.
MS. GUSSACK: I was referring to your commentary. Let's not be confused. What's your question?
MR. ALLEN: I'm focusing on his.

A. That's correct.
Q. Let's see what he said to the sales reps back in Orlando in the fall of 2000. Now, putting this in context again, Mr. Taurel, this was when Zyprexa was representing one of your growth opportunities, right, for your business, correct?
A. Zyprexa was and is an important product for the company.
Q. Well, but, we saw --
You specifically said in the 2000 annual report Zyprexa represented a growth opportunity for your company?
A. That's correct.
Q. Now, we're not going to read everything he says. Let's go down here where he says to the sales reps "Now, why don't we go on and talk about some specifics around Zyprexa, and sort of what the future looks like. And I said that Zyprexa is a very, very special molecule.
"Let's go to the first one:

growing sales in the elderly. How many people, in their own lives and their own families, have been touched by Alzheimer's disease. Parents, grandparents, uncles, aunts, best friends. Yeah, so have I. Is there a more tragic illness? That illness takes what we all consider to be human and begins to erode that, month after month after month in a very progressive way. And the need for better treatment in Alzheimer's and other elderly conditions is so paramount and so key, and what you're going to see, and you'll see it with your own eyes, is that Zyprexa is an optimally suited molecule for this disorder."
Did I read that correctly?
A. That's what's written here.
Q. Was Zyprexa approved for the treatment of the elderly and Alzheimer's in October of 2000 when Dr. Breier was telling the sales reps this?
A. I do not believe that Dr.

Breier is saying it was approved, neither is he telling them to talk about this indication. He was talking about planning for the development of that indication through clinical trials.
Q. Well, no. He told the sales reps, you'll see it with your own eyes. Were the sales reps involved in the clinical trials?
A. No. But he -- he's referring to the fact that doctors on their own are using antipsychotics in psychosis and dementia. There's nothing which is indicated for that disease. And those are very difficult patients, and so doctors are using products off label in that indication.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. Now, Dr. Breier is talking to the sales reps and he says, "Zyprexa is an optimally suited molecule." When something is optimally suited, that means

it's the very best, doesn't it, optimal, the very best?
MS. GUSSACK: Objection as to form.
THE WITNESS: I believe taken in context, which is a large sales meeting where Dr. Breier is conveying his enthusiasm for the product that he's responsible for, he's talking about the characteristics of the molecule which might make it a good agent for Alzheimer's. And indeed we were at that point doing clinical trials to find out whether the characteristic that he's referring to and ideally suited and optimally suited were going to be indeed proven in clinical trials.
BY MR. ALLEN:
Q. Well, does he say anything about it's going to be proven in clinical trials, or is he talking directly to the sales representatives at the time of the

Exhibit 7, Page 27 of 28
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006363

Exhibit 6
Gary Tollefson

Page 406

the rest as well.
Q. Well, we don't have time. We'll just get back to the -- you want to see evidence of whether what the sales reps were being told about the elderly. I think that's what you asked for.
Do you remember a person called Martha? Do you remember a person called Martha, sir? Do you know who that is?
A. No.
Q. Do you know that patient profiles were used by your sales teams to promote Zyprexa?
A. Not at the time.
Q. Have you learned that since then?
A. Yes.
Q. When did you learn that patient profiles were used to promote Zyprexa?
MS. GUSSACK: Objection, privileged.
BY MR. ALLEN:

Page 407

Q. Let me ask it again. Did you learn it --
Did you learn that patient profiles were used to promote Zyprexa by the sales force in September of 2007? Is that when you learned it?
A. Yes.
MS. GUSSACK: Objection. I instruct the witness not to answer because it implicates confidential attorney-client communications.
BY MR. ALLEN:
Q. When he learned it, the month is --
Sir, did you know -- let me ask this.
Did you know --
Prior to September of 2007, did you know that Eli Lilly used patient profiles to promote Zyprexa?
MS. GUSSACK: If that doesn't call for privileged communications with counsel, you may answer.

Page 408

MR. ALLEN: Did he know?
BY MR. ALLEN:
Q. Did you know prior to September of 2007 that Eli Lilly used patient profiles to promote Zyprexa?
MS. GUSSACK: I'm instructing the witness not to answer to the extent that it involves any client --
MR. ALLEN: Communications.
MS. GUSSACK: -- client communications, correct.
MR. ALLEN: I'm not asking.
BY MR. ALLEN:
Q. I'm asking your knowledge.
Let me rephrase the question. I'm taking the deposition on September 19, 2007. As of August 31st, 2007, did you know that Eli Lilly used patient profiles to promote Zyprexa as of August 31st?
MS. GUSSACK: As a general matter? Perhaps that would help clarify.

Page 409

BY MR. ALLEN:
Q. As a general matter.
A. We describe patients with a description of their symptoms, and so it is a normal practice to describe patients and how they present to physicians for Zyprexa and for any of our other products.
MR. ALLEN: That didn't answer my question in any regard, so I object to it as nonresponsive. But I'm going to move on.
BY MR. ALLEN:
Q. The evidence will show that a patient profile y'all used to promote Zyprexa was Martha. Now, here's what Mr. Bandick said. "What's the first thing you notice about Martha? She's old. That does two things. First, it reinforces Zyprexa as a nursing home drug. Our mission is to build" --
A. I'm sorry. Where are you?
Q. Page 13, the bottom. Right

Exhibit 7, Page 28 of 28
SOA Obj to Lilly Page/Line Counter Designations
Case No. 3AN-06-5630 CI

006364

Exhibit 8

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: MDL-1596

ZYPREXA PRODUCTS

LIABILITY LITIGATION

THIS DOCUMENT RELATES TO:

ALL CASES

C O N F I D E N T I A L

- - -

November 6, 2006

- - -

Videotape deposition of
GARY TOLLEFSON, M.D.

- - -

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.05, then it's regarded generally and generally accepted by people in the field that that is statistically significant, correct?
A. Correct.
Q. And in this instance, the P value is less than .05; it was .03, correct?
A. True. But I think as you know with your background of statistics, this has not been subject to multiple comparisons. These are -- I mean you're showing me 12 pages of P values here, and I don't know if the appropriate corrections were done or not. But I concur that it says less than .031 for this particular analysis.
MR. SUGGS: Move to strike the nonresponsive portion of your answer.
(Whereupon, Deposition Exhibit(s) 1604, previously marked, was presented to the witness.)
MR. SUGGS: I'd like to show you another similar exhibit which

has been previously marked Plaintiff's Exhibit 1604.
MR. LEHNER: We've been going about almost an hour, 25. Are you going to spend a long time on this one?
MR. SUGGS: It shouldn't take too long. Why don't we finish this one and then we'll take a break.
THE VIDEOGRAPHER: Five minutes left on the tape.
MR. LEHNER: Five minutes left on the tape.
MR. SUGGS: Pardon me?
MR. ALLEN: You've got five minutes left on the tape.
MR. SUGGS: We'll get done then.
QUESTIONS BY MR. SUGGS:
Q. Exhibit 1604 is dated July 5, 1995, and purports to be a computer printout of Abnormal Lab Values For HGAJ All Phases. Do you recognize this document, sir?
A. It looks familiar for the

formatting, yes.
Q. And does it appear to be, in fact, as I said, a printout of Abnormal Lab Values for the HGAJ Study All Phases?
A. Yes. It looks to be one HGAJ which was one of the studies in the new drug application.
Q. Okay. In fact, HGAJ, as you said before, was the largest study, correct?
A. Slightly over half the patients, yes.
Q. Okay. If I could direct your attention to Page 2, towards the bottom of the page, there is a table on that page that shows what the low limits and high limits are of the various tests that are being done, correct?
A. Correct.
Q. Okay. And at the very bottom, or not the very bottom, but second to last is a listing for nonfasting glucose, correct?
A. Yes.
Q. And it shows in the

international system the low limits and high limits, correct?
A. Correct.
Q. The low limit being 2.4975 millimoles per liter and the high limit being 13.875 millimoles per liter, correct?
A. Yes.
Q. And that can be translated to -- well, that's the system, convention that used over in Europe, correct?
A. I believe it's used internationally but, yes, it's used in Europe.
Q. Okay. But here in the United States people tend to use another measuring system of blood glucose that is advocated by the American Diabetic Association, correct?
A. Right.
Q. And to convert the international system to the ADA system you multiply by 18, correct?
A. I don't have the algorithim so I can't answer that.
Q. If I represent that to you

That might be a difference.
Q. With respect to all the other language that's in there it's saying, essentially, there's not much difference between Zyprexa users and placebo users, correct?
MR. LEHNER: Object to the form.
A. Based on the analysis of the clinical trial database that's what the data said.
Q. Okay. And if, in fact, you had included language in Paragraph 2 that a review of the random glucose levels in patients in olanzapine clinical trials revealed that the incidence of treatment-emergent hyperglycemia in the olanzapine group was three and-a-half times higher than that in the placebo group, prescribing physicians would have been concerned about that, wouldn't they?
MR. LEHNER: Object to the form.
A. Again, it points to the

validity of the data.
Q. Sir, regardless of whether --
MR. LEHNER: Let him finish his answer, please.
MR. SUGGS: Perhaps you didn't understand my question, sir.
THE WITNESS: I did. I think. But please restate and help me clarify.
QUESTIONS BY MR. SUGGS:
Q. I'm not asking whether you think the analysis that's in Exhibit 4858 is correct or whether you think the analysis that was in Exhibit 990 was correct. I'm just talking about the effect of the words, okay.
If, in fact, you had changed the label in May of 2000 to tell doctors that the incidence of treatment-emergent hyperglycemia was three and-a-half times higher in Zyprexa users as compared to placebo users, that would have caused concern on the part of prescribing physicians, would it not?

MR. LEHNER: Object to the form.
A. I don't think I could make that kind of generalization. Hyperglycemia was already in as an adverse event term. Now you could poll physicians, some might say, "Gee, I think that means it's 8 times higher," someone else might say, "I think that means it's only 2 times higher." So I don't think you can make that kind of generalization. You want valid data in the package insert. You don't want erroneous data.
Q. Sir, in the context of what was happening in the marketplace in the spring of 2000, with the attacks that Lilly was facing in the marketplace by competitors who were saying that, "Gee, Zyprexa has all this additional weight gain. It's going to increase the risk of diabetes. It's going to increase the risk of hyperglycemia."
And that was what was being said, wasn't it, by your competitors?
A. That is what was being said by competitors.

Q. Okay. And if in the face of that you had come out and changed the label and said, guess what, the incidence of treatment-emergent hyperglycemia is three and-a-half times higher in Zyprexa users as compared to placebo users, that would have fed right into what your competitors were saying; isn't that right?
MR. LEHNER: Object to the form.
A. To me it's already in there as an adverse event and I don't see it as materially different.
Q. You don't think that would have had -- put you at any sort of competitive disadvantage if you'd told doctors that the incidence of treatment-emergent hyperglycemia was three and-a-half times higher in Zyprexa users as compared to placebo?
MR. LEHNER: Object to the form.
Q. You don't think that would have had any effect on your sales?
MR. LEHNER: Object to the

Page 226

form.
A. Commercial consequence is never a decision in package insert inclusion.
MR. ALLEN: Objection. Nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Sir, do you recall that this label change that Lilly did without prior FDA approval in May of 2000 got struck down by FDA in October of 2000?
MR. LEHNER: Object to the form.
A. I don't know that I would have used the term "struck down."
Q. Well, they told you you couldn't use it, didn't they?
A. My understanding was that the FDA was in the process of doing their own analysis across multiple products and multiple sponsors and they did not want to reach, were not ready to reach a conclusion, and certainly not ready to reach a conclusion that was consistent with what had been

Page 227

proposed by Lilly at that point in time. They were still a work in progress to understand this issue. And, in fact, it took them several years to finally come up with a recommendation to the field.
MR. SUGGS: Move to strike as nonresponsive.
(Whereupon, Deposition Exhibit(s) 195, previously marked, was presented to the witness.)
MR. SUGGS: Sir, I'm going to show you what has been previously marked as Plaintiff's 195. For the record, this is a letter from Russell Katz at FDA to Gregory Brophy at Eli Lilly. It's dated in the upper right-hand corner as October 11, 2000.
QUESTIONS BY MR. SUGGS:
Q. Did you ever see this before, sir?
A. I believe so.
Q. And when did you see it?

Page 228

A. When it came out. Dr. Brophy shared it with me.
Q. Okay. And if I could direct your attention to Item No. 3 in the letter, the FDA said that they have completed the review of the application. That's referring back to the May 9, 2000, submission, correct?
A. I presume.
Q. And they determined that the changes proposed in Items 1 and 3 were approvable, correct?
A. I'm sorry, I'm not finding that spot. May I ask where you are?
Q. It's in Item No. 3, the very first paragraph right below that numbered?
A. Ah, yes, I've got it.
Q. Okay. The FDA said they had completed review of the May 2000 application and had determined that the changes proposed in Items 1 and 3 were approvable, correct?
A. Correct.
Q. It was Item No. 2 that had the hyperglycemia language, correct?
A. Correct.

Page 229

Q. Okay. And they go on to say, "Before this application may be approved, it will be necessary for you to submit final printed labeling revised with the deletion of the following paragraph, paren, changes effected Item 2 above." And then they quote the language of the label change that you guys had made, correct?
A. This is the label change the company submitted.
Q. Correct.
A. Yes.
Q. Okay. And then after quoting that language the FDA then said in the following paragraph, this descriptive data -- pardon me -- "The descriptive data that is provided expresses a certain level of implied safety with respect to treatment-emergent hyperglycemia. This reassuring language is not appropriate for submission under 21CFR314.70, paren, C as a special supplement changes being effected." Do you see that language, sir?
A. I do.

Page 250

Q. Okay. When did you see it?
A. The first time I saw it, I believe, was during review with counsel.
Q. Okay. If I could direct your attention to the first paragraph.
By the way, Robert Baker, did he -- was he part of your product team?
A. No. He was a physician in the U.S. Affiliate organization.
Q. Okay. We have Charles Beasley, though, at this time reported to you, correct, he's one of the recipients?
A. We talked about this earlier. I'm not sure if Charles was reporting to me at this point in time or not. He has before or after this time may have been.
Q. Alan Breier, though, certainly reported to you, correct?
A. Yes, for another couple weeks.
Q. Okay. And in the first paragraph Dr. Baker writes, "FYI, the Lilly diabetes/endocrine group held an academic advisory board meeting this weekend in

Page 251

Atlanta. They kindly allotted two hours for discussion of olanzapine's potential hyperglycemia risks, and Charles Beasley, Chris Bomba, Patrizia Cavazzoni, Suni Keeling and I attended. Unfortunately, this consultation reinforced my impression that hyperglycemia remains quite a threat for olanzapine and may merit increasing even further medical attention and marketing focus on the topic."
Do you see that language, sir?
A. I do.
Q. Were you aware of, that there was such a meeting back in October of 2000?
A. I don't believe so.
Q. Okay. Dr. Baker goes on to say, "On the positive side like other endocrinologists they were not impressed with the Newcomer findings." Do you see that?
A. Yes.
Q. Do you take that to mean a reference to Dr. John Newcomer at Washington University?

Page 252

A. Yes.
Q. The same one that you said we ought to send cousin Guido to go talk to him?
A. Actually, Mr. Dennis West, but, yes, the same John Newcomer.
Q. Okay. They go on to say, "They were, however, concerned by our spontaneous AE reports and quite impressed by the magnitude of weight gain on olanzapine and the implications for glucose."
Do you see that language?
A. I do.
Q. And is it your testimony that you were not apprised of the results of that meeting?
A. I don't remember being informed of the meeting or, specifically, the results of this meeting.
Q. Okay.
A. There's nothing here that's inconsistent with, I think, some of the feedback that the company had been receiving and taking into consideration.
Q. I'm sorry, you said there's

Page 253

nothing here that's inconsistent with, I think, some of the feedback that the company had been receiving?
A. Yeah, from different opinion leaders, prescribers.
Q. And for how long had you been getting that type of feedback? Well, what you're talking about that you're saying is not inconsistent is the concern as reported here about the spontaneous adverse event reports and the magnitude of weight gain on olanzapine and the implications for glucose, correct?
A. No. I was saying, No. 1, not impressed with the Newcomer findings and, 2, the magnitude of the weight gain. I think those are issues that, you know, I had certainly heard about on more than one occasion when it came to prescriber issues.
Q. For how long had you been hearing that concern expressed?
A. At least two years, I would imagine.
Q. So at least 1998?

Page 270

that happened with Zyprexa between 2000 -- strike that.

Between 2000 and 2004, the only label changes that occurred in the Zyprexa label with respect to hyperglycemia were, 1, the label change that you folks did in May of 2000 that we've already discussed that the FDA made you take out later that same year, and the label change that was imposed, mandated, by the FDA in September 2003, correct?

MR. LEHNER: Object to the form.

A. I believe that's correct.

Q. And in that label change there was discussion about hyperglycemia and diabetes in the warning section, correct?

A. There was a class labeling that was issued. But I think the FDA was very clear that they did not rank one drug as greater risk than any other drug, did not see that it was related to weight gain, that relationship had not been established, and wasn't even sure if this was causally related

Page 271

to these drugs. But we're suggesting appropriate medical monitoring per ADA kinds of criteria for patients. That's how I understood it.

MR. SUGGS: Move to strike the nonresponsive portion.

QUESTIONS BY MR. SUGGS:

Q. Sir, in your continued involvement with Zyprexa after 2000, were you ever consulted with respect to whether Lilly should make a label change to warn about hyperglycemia after the Japanese government required such a warning in April of 2002?

A. Not that I know of.

Q. I have one last document I want to show you, sir, if I can find my copy.

MR. ALLEN: What is it?

MR. SUGGS: I'm going to hand you what's been previously marked, -- oops, that isn't it.

MR. ALLEN: Let's go off the record while we're looking for a document.

THE VIDEOGRAPHER: Off the

Page 272

record.

(At this time, the parties went off the record, after which the following proceedings were had:)

THE VIDEOGRAPHER: We're back on the record.

(Whereupon, Deposition Exhibit(s) 8666, previously marked, was presented to the witness.)

MR. SUGGS: I'm handing you Plaintiff's Exhibit 8666. For the record, this is a June 27, 2002, e-mail from Simeon Israel Taylor to Willard Dere, with copies to a number of individuals including Dr. Tollefson.

QUESTIONS BY MR. SUGGS:

Q. Dr. Tollefson, you seem to be chuckling when you saw this e-mail, why is that?

A. No. I was just enjoying your inflection of my name.

Page 273

Q. Did I mispronounce it?

A. No. Dr. Dere you did mispronounce. It's Dr. Dere, Will Dere.

Q. Okay. How did I pronounce it -- Dare?

A. Yeah, I think so.

Q. I guess I'm still missing what was so humorous about my pronunciation of your name. Did I mangle it somehow?

A. No. It's fine.

Q. Okay. Do you recall receiving this e-mail on or about June 27, 2002?

A. I'd have to look at it for a moment.

I don't remember this one, no.

Q. Okay. Would you agree with me that this appears to be some discussion in this e-mail about appointing a panel to look at the issue of hyperglycemia?

A. I'm having a hard time determining what the topic for the panel is.

Q. Well, if I could direct your

Page 274

attention to the third page there's an e-mail from Meng Tan to Willard Dere with copies to other folks including yourself.
A. Um-hum.
Q. And he says, "Will, Thank you for inviting me to the June 25-26 meetings on Zyprexa and hyperglycemia meetings." Do you see that?
A. I do.
Q. And then there's some discussion about five potential candidates to consider for that meeting, correct? All of whom appear to be involved with diabetes issues, correct?
A. Yes.
Q. Okay. And then in the succeeding e-mails, there's discussion about various people who might be appropriate to serve on this outside consultant panel, correct?
A. Yes.
Q. And then finally, the last e-mail in this chain is from Dr. Simeon Israel Taylor, correct, on the first page?

Page 275

A. Yes.
Q. And who's Dr. Taylor?
A. He was a, I believe, sort of a guest researcher at Lilly on sabbatical, who had an interest in a variety of areas of internal medicine but I think inclusive of metabolic concerns.
Q. And do you recall where he was on sabbatical from?
A. I do not. I did not know him well.
Q. Okay. Looking at his e-mail, the last part of his first paragraph -- well, actually starting at three lines or four lines up from the bottom in the middle of the line there he says, "Perhaps we should retain the right to veto panel members, but probably not to choose the members. Clearly, this approach entails some risk that we will be unhappy with the panel's findings. However, I feel that we need to deal with the scientific facts, whatever they are. Ultimately, I am expect that a fair-minded, scholarly evaluation of the available data is

Page 276

likely to support several conclusions." And then he lists what those conclusions are, correct?
A. Yes.
Q. And the first conclusion is "Zyprexa, like other members of the class, causes weight gain."
A. Correct.
Q. And would you agree with Dr. Taylor that Zyprexa causes weight gain?
A. Yes.
Q. Okay. And then he goes on to say in point two, "Like other causes of weight gain, Zyprexa-induced weight gain probably increases the risk of diabetes." Do you see that language?
A. That's what he says.
Q. And did you respond back to Dr. Taylor?
A. I don't recall.
Q. I take it you would disagree that Zyprexa-induced weight gain probably increases the risk of diabetes; is that correct?

Page 277

A. I can only echo the position of the Food and Drug Administration that they didn't see the anticipated connection between the two when they reviewed multiple drugs in this class.
MR. SUGGS: Move to strike as nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Sir, you take the position today that Zyprexa does not increase the risk of diabetes, correct?
A. Whether it does or doesn't I think is unknown.
MR. SUGGS: Okay. I have no further questions at this time.
MR. ALLEN: Dr. Tollefson, Scott Allen from Houston, Texas. How are you doing?
THE WITNESS: Good, Mr. Allen.
MR. ALLEN: I'm going to have some questions that follow up to Mr. Suggs. Just mainly, it's going to be clarification for the record

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,
Plaintiff,
v.
ELI LILLY AND COMPANY,
Defendant.

Case No. 3AN-06-05630 CI

FILED
STATE OF ALASKA
THIRD DISTRICT
08 FEB 11 PM 4:28
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ELI LILLY'S NOTICE OF FILING DEPOSITION DESIGNATIONS UNDER SEAL

Defendant Eli Lilly, by and through counsel of record, files its deposition counter-designations to plaintiff's amended designations with Exhibits A-D, under seal, attached to this notice. Portions of the deposition designations may be confidential.

DATED this 11th day of February, 2008.

See Judge Rindner's order of 6/13/08, page 19, #13
Documents unsealed
Lwade 8/11/08

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Pages 6372B-6412

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT AT ANCHORAGE

Filed in the Trial Courts
STATE OF ALASKA, THIRD DISTRICT
FEB 11 2008
Clerk of the Trial Courts
By _____ Deputy

STATE OF ALASKA,

Plaintiff,

v.

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Defendant.

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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, v. ELI LILLY AND COMPANY, Defendant.	Case No. 3AN-06-05630 CI **ELI LILLY AND COMPANY'S DEPOSITION COUNTER-DESIGNATIONS FOR TRIAL**

Defendant Eli Lilly and Company ("Lilly") counter-designates for trial the following deposition transcript excerpts in response to Plaintiff State of Alaska's Amended Trial Deposition Designations:

I. Deposition of Michael Bandick, designated pages Exhibit A.

Start (Page:Line)	End (Page:Line)
83:5	83:7
166:6	166:7
208:17	208:18
211:6	211:7
245:23	245:23
322:19	322:21
433:19	433:20
455:15	455:18
522:14	523:2

II. Deposition of Jack E. Jordan, designated pages Exhibit B.

Start (Page:Line)	End (Page:Line)
29:20	30:5
51:22	52:11
55:18	55:24
423:7	423:11

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III. Deposition of Bruce Kinon, M.D., designated pages Exhibit C.

Start (Page:Line)	End (Page:Line)
52:9	52:16
65:20	66:7
72:16	72:17
73:17	73:18
75:7	75:17
82:4	82:18
91:22	91:22
92:10	92:15
93:7	93:17
130:18	130:22
237:17	237:24
241:2	241:21
412:14	412:23

IV. Deposition of Denise M. Torres, designated pages Exhibit D.

Start (Page:Line)	End (Page:Line)
244:11	246:10
257:6	257:13
358:19	359:13
401:8	403:4
424:9	424:16
561:6	562:13

Lilly's counter-designations are subject to this Court's rulings on Motions in Limine. Lilly reserves the right to introduce any of the deposition testimony set forth in plaintiff's deposition designations. Lilly further reserves the right to counter-designate any deposition testimony not yet taken in this or any other matter. Lilly further reserves the right to introduce additional deposition testimony not included above, if deemed necessary for the

rebuttal of testimony from witnesses called by plaintiff or exhibits introduced by plaintiff at the trial of this action.

DATED this 11th day of February, 2008.

PEPPER HAMILTON LLP
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and
LANE POWELL LLC
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IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: MDL-1596

ZYPREXA PRODUCTS

LIABILITY LITIGATION

THIS DOCUMENT RELATES TO:

ALL CASES

C O N F I D E N T I A L

- - -

June 9, 2006

- - -

Videotape deposition of

MICHAEL BANDICK

- - -

GOLKOW LITIGATION TECHNOLOGIES
1600 John F. Kennedy Boulevard
Suite 1210
Philadelphia, Pennsylvania 19103
(877) DEPS-USA

A. No.
Q. Do you have any background, education or training in clinical trials?
A. No, I don't.
Q. In medicine?
A. No.
Q. Next question: Did you assist in writing documents that were prepared for the sales force to give to physicians about Zyprexa?
A. Sometimes.
Q. Okay. Do you remember any document in particular, or are there too many to remember, that you wrote in marketing that would be provided to the sales force that you knew would end up in doctors' hands?
MR. FAHEY: Objection to form. You can answer.
A. As I mentioned, I was involved in that activity. There are too many for me to recall any single one for you.
Q. Right. And that's a fair answer. You wrote a lot and lot of documents that you knew would be used by the Zyprexa

marketing department and/or sales force that would be given to doctors concerning Zyprexa.
MR. FAHEY: Objection to form.
A. I was involved in the writing and production of several pieces and played various roles.
Q. For how many years?
A. Approximately, seven.
Q. I want to digress a minute here and we'll come back to it. While my mind's focused on this matter is there a committee at Eli Lilly with the name such as the Copy Clearance Committee?
A. If there is I'm not familiar with it.
Q. Well, in other companies that I have dealt with in other depositions, and I'll give you a description of what I'm talking about and see if it helps you, other pharmaceutical companies have had committees that they have described to me as copy clearance committees. And it was a cross-functional group of the legal

department, the regulatory affairs department, the marketing department, legal regulatory, medical, usually, the clinical affairs department, and they all had to approve the final copy of any document that was going to be released from the drug company providing information on a product.
Does that help you understand the kind of committee I'm talking about?
A. Yes, I think so.
Q. Okay. What's the name of that committee at Eli Lilly?
A. I knew it as MLR or Medical Legal Review.
Q. Medical Legal Review. What departments were represented on the MLR committee?
A. There was a representative from, one or more representatives from medical, typically, a representative from legal, a representative from regulatory, and then one or more representatives from marketing.
Those were the primary ones.

I don't recall if there were any others that were standing members.
Q. Okay. What was the MLR committee's responsibilities?
MR. FAHEY: Just so I can put on the record. I'll let you ask all the questions you want about the process of the MLR team. I'm going to object to the extent that you're going to ask about specific dealings that the MLR committee took or actions they took or decisions they talked about or anything like that. So just with that caveat you can answer.
QUESTIONS BY MR. ALLEN:
MR. ALLEN: Is it Ms. Shinney, is that correct?
THE REPORTER: Swinney.
MR. ALLEN: I very much apologize. I don't know if you can do this but we have time constraints here. So every time Mr. 0 objects or speaks I need, can you record the

Page 166

governed by specific guidelines as to what is and isn't appropriate dissemination of that clinical data.
Q. Where would I find those guidelines?
MR. FAHEY: They have been produced in this case.
Q. Where would I find those guidelines?
A. I don't know exactly where to point you at this point.
Q. And I'm not talking about this case, that's your lawyer over there.
MR. FAHEY: Again, Mr. Allen, this is the third time. I'm not Mr. Bandick's lawyer and if you'd been involved for more than two days you would know that those documents related to GPPs have been produced for over two years in this case.
MR. ALLEN: Is that an objection?
MR. FAHEY: No. I'm just trying to help you. You seem to not

Page 167

know where they are. I'm trying to help you understand where they are.
MR. ALLEN: Well, I appreciate your help, and since you clarified it's not an objection and you were trying to help me I would ask you to do this: I don't need your help nor want your help. So from now on if you have some help you want to offer, just keep your mouth quiet, please, and let me proceed.
QUESTIONS BY MR. ALLEN:
Q. Now, sir, you said there's some guidelines concerning marketing outside the label. You said that, right?
A. I said there was some guidelines for disseminating data outside of the label.
Q. What do you call those guidelines?
A. Well, in general, the guidelines that the company follows are called good promotional practices or GPP.

Page 168

There can be other specific guidelines for that dissemination of data, and I don't, I don't know where to point you to to look those up.
Q. Well, and I appreciate that answer if you just don't remember, but I would assume as the Brand Manager and as the Director of Marketplace Management you would frequently refer to the GPPs, would you not?
A. Yes, I would.
Q. Okay. Were they kept in the marketing department?
A. I had access to a copy of them. I don't know what might have existed in other areas.
Q. Can Lilly under FDA regulations and/or --
THE OPERATOR: Has joined the conference.
A. Welcome back.
Q. Sir? I'm sorry?
A. Okay.
Q. That's okay. What'd you say?
A. Welcome back.

Page 169

Q. Okay. Can Lilly under FDA regulations or the GPP direct the Zyprexa sales force to actively proceed to a physician's office on a routine sales call and promote Zyprexa for the treatment of symptoms?
A. No.
Q. Why not?
A. Company policy is clear on the fact that all promotion will be within the approved label and the indications that follow from that.
Q. So the company policy is clear that all promotion of drug products, including Zyprexa, must be within the approved indications on the product's label, correct?
A. For promotional activities, that's correct.
Q. Okay. What's the difference between promotion and marketing?
A. Well, I was distinguishing between promotional activities and nonpromotional activities. I would say that

MR. ALLEN: Tell you what, so we don't have any confusion you can go yes, yes, yes to every question.
THE WITNESS: Okay.
MR. FAHEY: Why are you going to ask the question if you know the answer?
MR. ALLEN: Because I need his testimony.
MR. FAHEY: Exactly.
MR. ALLEN: Because if you want to take my word for the whole thing we can not have any depositions and I'll award us a lot of money.
MR. FAHEY: That's fine.
MR. ALLEN: Okay.
QUESTIONS BY MR. ALLEN:
Q. Now, doctors receive information concerning Zyprexa from the package insert, correct?
A. Yes.
Q. Doctors receive information concerning the benefits and risks of Zyprexa

from peers and educators?
A. Yes.
Q. Doctors receive information concerning the benefits and risks of Zyprexa from publications?
A. Yes.
Q. Doctors receive information about the benefits and risks of the product from the sales force?
A. From the Lilly sales force, yes.
Q. Doctors receive information about the benefits and risk of the product from marketing materials?
A. Yes.
Q. Doctors receive information about the benefits and risks of Zyprexa from continuing medical education courses?
A. Yes.
Q. And doctors receive information about Zyprexa from medical organizations such as the American Diabetes Association and the American Association of Clinical Oncology -- Endocrinology?

A. As two examples, yes.
Q. Okay. I'm going to show you exhibit -- oh, and by the way, doctors, you knew that doctors would then pass along or could pass along or may pass along that information they learned from those sources to the patient?
A. That's possible.
Q. Right. And, of course, each one of those I talked about, the package insert, peers and educators, publications, sales force, marketing materials, CME and medical organizations were all used as channels and/or tools by the marketing department at Eli Lilly to market Zyprexa, correct?
MR. FAHEY: Differentiating from promotion of Zyprexa? Mr. Allen?
A. I was looking at your exhibit here. Could you repeat your question, please?
(Whereupon, Deposition Exhibit(s) 2 duly received, marked

and made a part of the record.)
QUESTIONS BY MR. ALLEN:
Q. Yes. Exhibit No. 2, we have the doctor. Lilly's on the top, right?
A. On this document, yes.
Q. And then we have various sources, the doctor's right there in the middle and we have the sources we discussed, we have the medical organization, the package insert, the peers and educators, the publications, the sales force, the marketing materials, and the CME, are all places where the doctor gets information, right?
A. Those are all places where doctors get information.
Q. And they're also all tools and channels Eli Lilly used in the marketing of Zyprexa, correct?
MR. FAHEY: Object to the form to the extent -- I'm asking for clarification on what you mean by marketing since we talked about it in three different contexts today.
A. Each of those are channels

through which certain types of information could be provided.
Q. And, in fact, was provided by Eli Lilly?
A. Different types of information would appear in different channels but each of these, in some form, were used by Zyprexa, yes.
Q. Okay. And you said that the doctor would take that information and could or might, convey to the patient, right?
A. It's possible.
Q. Therefore, when Eli Lilly used those tools and channels, such as publications or CME courses, it is important for Eli Lilly to be truthful, accurate, fair, and balanced, and to tell the whole truth, correct?
MR. FAHEY: Objecting to the form to the extent you're talking about CME. He's already said he had no role in the creation of the product that was being discussed at these meetings. All they did was

fund it. If you want to use some other example that's fine but you're mischaracterizing his testimony.
Q. You can answer the question.
A. I was going to say the same thing, Lilly wasn't involved in the content of CME.
For purposes of publications that was clinical trial data. And yes, it would be important to be accurate and truthful about the portrayal of those data.
Q. It's your sworn testimony under oath that Lilly never prepared slides for the use by doctors at CME courses? Is that your sworn testimony?
A. I don't know.
Q. Yeah. Well, so you're not really so positive about what your lawyer just spouted off about over there, are you?
MR. FAHEY: First of all objection, argumentative. Second of all, if you want to take a lunch break now we can.
MR. ALLEN: Why don't we take

the lunch break now.
THE VIDEOGRAPHER: Going off the record, it's 12:29. This is the end of tape three.
(A lunch recess was taken by the parties at this time.)

AFTERNOON SESSION
DIRECT EXAMINATION, (CONTINUING),
THE VIDEOGRAPHER: Back on the record at 1:29, tape 4.
QUESTIONS BY MR. ALLEN:
Q. Mr. Bandick, we're back from lunch, most of us are back from lunch, and we're ready to proceed.
I assume you have a drug product, in this case, Zyprexa, would you like it to have a bigger market or a smaller market?
A. Well, in the case of Zyprexa, the market got bigger as we expanded the label and that was seen as a positive.
Q. You mentioned that several times. So I guess I want to make sure we're communicating. In 1996, when the product was approved, being Zyprexa, it was indicated for schizophrenia, correct?
A. The actual language was a little different. It later was focused on schizophrenia, yes.
Q. So you and I are

Page 242

well, you can tell the jury, you know that you have in your family Lilly stock, right?
A. That's correct.
Q. And Lilly stock options, correct?
A. That's correct.
Q. And the Lilly stock options is somewhere between 5,000 and 8,000 in number, correct?
A. Yes.
Q. Thank you.
Okay. You left your employment with Lilly. How would you characterize you leaving, did you resign or were you fired?
A. I resigned.
Q. Now, we've all seen movies -- let me see. You have children?
A. Yes, I do.
Q. And I have -- you ever ask your kids to clean their room?
A. I have.
Q. So have I. Have they always done it?

Page 243

A. Eventually.
Q. Yeah. Have they never not cleaned their room and then they tried to go out and play or do something they wanted to do?
THE WITNESS: Have they never not?
MR. ALLEN: I'm sorry. I'm sorry, man, I'm just old hat over here.
QUESTIONS BY MR. ALLEN:
Q. When you ask your kids to clean their room have they ever not followed your direction?
MR. FAHEY: I object to the form and the relevance of what his kids did or did not do with respect to their room.
MR. ALLEN: It's going to be relevant here in a second.
MR. FAHEY: I hope so.
QUESTIONS BY MR. ALLEN:
Q. Has it ever happened to you?
A. Yes, it has.

Page 244

Q. Have they ever decided to go out and play when they haven't followed your instructions on what you asked them to do?
A. Yes.
Q. Have you ever told them you can't go outside until you clean up your room?
A. I imagine I have.
Q. Yes. And do they then clean their room?
A. Usually.
Q. And so they could go outside, right?
A. Yes.
Q. They cleaned their room voluntarily, didn't they?
MR. HAMMERLE: Counsel, I object at this stage knowing the time limit we were talking about earlier.
MR. ALLEN: Okay. Well, here, let me make this.
QUESTIONS BY MR. ALLEN:
Q. You said you resigned, right?

Page 245

A. I did.
Q. Did somebody ask you to resign?
A. I was given the choice.
Q. Of resign or be fired?
A. Or -- yes.
Q. Okay. Who gave you the choice of either resigning or being fired?
A. Diedre Connelly and Dan Hasler.
Q. Tell me -- I didn't hear the name?
A. Diedre Connelly and Dan Hasler.
Q. Tell the jury Diedre Connelly's title, please?
A. She was the head of the human resources function. I don't know her exact title.
Q. And who is Dan Hasler?
A. He is VP of Global Marketing.
Q. Why were you fired?
A. I wasn't.
MR. HAMMERLE: Objection, it

Page 322

paragraph: "Pharmaceutical markets serves the following positive purposes for physicians," skipping down, "it provides FDA-regulated information that must be balanced and disclose all risks." Did I read that correctly?

A. You did.

Q. And I think, my copy I highlighted the word "all" and underlined it in red, didn't I?

MR. FAHEY: Objection, what's the relevance of that? Just ask the question.

A. Yes, you did.

Q. Okay. And I want to direct your attention to the word "all." It says "the information must be balanced and disclose all risk." Do you agree with that?

A. There are many mechanisms to provide that and we did follow clear guidelines and policies on how to do that.

MR. ALLEN: Objection. Nonresponsive.

MR. FAHEY: Objection, argumentative.

QUESTIONS BY MR. ALLEN:

Q. My question is: Do you agree that your marketing documents must be balanced and disclose all risk?"

MR. FAHEY: You just changed from marketing documents to promotional documents, which one do you want to ask about?

MR. ALLEN: Let's go with marketing now.

A. Again, because I'm not in the position to be a subject matter expert on those risks or their disclosure, I would say that we followed company policies that were very clear in terms of how to use subject matter experts to address those concerns.

Q. Did your marketing documents that you provided to physicians disclose all risks?

MR. FAHEY: Same objection as to the term marketing. Are you talking about promotional or nonpromotional?

Page 324

MR. ALLEN: I said marketing first. I'm going to go to promotional next.

MR. FAHEY: Well, marketing is promotional and nonpromotional, which he already testified to, which is why I'm asking the question. If you want to make the record confusing you could do that. I'm just trying to clean it up.

MR. ALLEN: Thanks for your help.

MR. FAHEY: You're welcome.

MR. ALLEN: You're welcome.

QUESTIONS BY MR. ALLEN:

Q. In promotional material for Zyprexa did you disclose all of Zyprexa's risks?

A. We provided information that would have disclosed all risks, yes.

Q. All risk?

A. To the best of my knowledge.

Q. And was it fair and balanced? Was it fair and balanced?

Page 325

A. Yes, that was the assessment of the members of our team.

Q. Did it constitute full disclosure as is reflected in Paragraph No. 2?

A. To the best of my knowledge it did.

Q. The last sentence of this entire document Marketing and Promotion of Pharmaceuticals it says: "More importantly it -- well, let me just read the entire last paragraph, two sentences.

"We regard pharmaceutical marketing as an essential part of the research process that brings new products into medical practice. More importantly, it serves a critical educational role in our health care delivery system."

First of all, did I read that correctly?

A. You did.

MR. FAHEY: Actually, you read --

Q. Marketing performs and serves

Page 430

A. Lilly medical had analyzed and made the determination that they felt it was an incorrect decision or an incorrect analysis.

Q. And Lilly got to look at the information and reach its own conclusion, right?

THE WITNESS: Which data?

MR. HAMMERLE: Objection to the form of the question.

THE WITNESS: The cases?

MR. ALLEN: The Japanese action and the reasons for it.

A. Lilly was aware of the data, Lilly was aware of the cases, and, yes, they had a chance to reach their own conclusion.

Q. Don't you think that immediately upon reaching that conclusion that you should have informed the United States doctors and United States consumers, the patients, of the Japanese action and allow the doctors and the patients to reach their own conclusion?

MR. HAMMERLE: Object to the form, counsel.

MR. FAHEY: Asked and answered.

A. That decision would not be mine to make, but I can tell you the policy that Lilly had to provide data that was accurate and truthful was something that we consistently applied before and after the Japanese regulatory change.

MR. ALLEN: Objection, nonresponsive.

QUESTIONS BY MR. ALLEN:

Q. My only question is: Don't you think United States doctors and United States patients should have been told by Lilly about what happened in Japan and allow the doctors and the patients to reach their own conclusion?

MR. HAMMERLE: Objection again. Asked and answered and the form of the question.

A. That was not my decision to make.

Q. Understanding it was not your decision to make. As the Director of Marketplace Management and as the former Brand Manager for Zyprexa who communicates with the audience, including doctors and patients, don't you think that Lilly should have told U.S. doctors and U.S. patients of the Japanese action and allowed the doctors and the patients to reach their own conclusion?

MR. HAMMERLE: Same objections as before.

MR. FAHEY: I join the same objections.

A. Lilly continued to provide data, and I would say that it was consistent before and after the label change. I'm not in a position to answer a should or should not question. I can tell you what we did.

Q. Well, sir, you, for one, certainly if you wanted to, as the director of, and I've all of a sudden blanked out, Director of Marketplace Management for Zyprexa, you certainly could have, on your own initiative, informed the sales force, and asked them to inform the doctors about the Japanese equivalent of a black box. You could have done that had you wanted?

MR. HAMMERLE: Objection as to form.

A. Those decisions don't take place in a vacuum and that's not something that I would have or could have done unilaterally.

Q. Isn't it true, sir, as the Director of Marketplace Management for Zyprexa that's exactly what you can do is you can inform the sales force of a black box warning in a foreign country and ask the sales force to inform the doctors. Isn't that something you can do yourself?

MR. HAMMERLE: Objection.

MR. FAHEY: Objection to form. There was no black box warning in Japan.

MR. HAMMERLE: As to form.

A. What I did in that role was to share content that was carefully reviewed and considered by members of all areas, as

Page 454

presented, we determined that there was significant unmet need in the primary care setting and that we would be able to meet some of those unmet medical needs by promoting the drug in the primary care segment.

Q. Is that a long way of saying you wanted to make more money?

MR. HAMMERLE: I object to the characterization and the form of the question.

MR. FAHEY: I just object to the waste of time.

Q. Sir?

A. It's not a way of saying anything other than what I said. There was unmet medical need. It's where those patients presented and it's where a lot of antipsychotic prescribing was already taking place.

Q. Isn't it true that Zyprexa's success was critical to Lilly's corporate performance during Year X?

MR. HAMMERLE: I object to

Page 455

the form of that remark.

A. What's the context of --

MR. HAMMERLE: I object to the form of the question.

Q. You know what year X is, don't you, sir?

A. I do.

Q. Isn't it true that Zyprexa success was critical to Lilly's corporate performance with the advent of Year X?

MR. HAMMERLE: I object to the form.

MR. FAHEY: Join in the objection.

A. As Zyprexa became a bigger part of Lilly's overall sales, there was a lot of, there was a lot of attention paid to its growth potential.

Q. Well, wasn't it, Year X, the motivating factor to expand the market for Zyprexa?

MR. HAMMERLE: Object to form.

A. No, it wasn't.

Page 456

Q. Okay. Wasn't it true that with the advent of Year X, the loss of the Prozac patent, and the lack of a short term pipeline for new Lilly drugs, you needed to expand your target markets?

MR. HAMMERLE: Again, object as to form.

A. The timetable for the decision to go into primary care was sometime in the spring of 2000. I went into the role in July of 2000 and, I believe, that Prozac last its patent in August of 2000.

MR. ALLEN: Objection. Nonresponsive.

QUESTIONS BY MR. ALLEN:

Q. My only question was isn't it true that with the advent of Year X, the loss of the Prozac patent, and the lack of short term pipeline for new Lilly drugs, you needed to expand your target markets?

MR. HAMMERLE: Again, objection as to form, counsel.

MR. FAHEY: And I object.

A. That's not the way I saw the

Page 457

launch in primary care.

MR. ALLEN: Objection, nonresponsive. I'm not talking about the launch of Zyprexa at this point. You're jumping ahead of me.

Q. I'm asking this question and this question only, isn't it true that with the advent of Year X, the loss of the Prozac patent, and the lack of short term pipeline for new Lilly drugs, you needed to expand your target markets?

MR. HAMMERLE: Same objection as to form.

THE WITNESS: In the context of Zyprexa or broadly?

MR. ALLEN: Yes. In the context of Zyprexa.

A. No, I don't see it that way.

Q. Okay, sir, now let's look at Exhibit No. 12 which this is your document, you did draft it in August of 2000; is that right?

A. Yes.

Q. I'll read the background.

Page 522

third section on this page where it says: "Zyprexa IntraMuscular, olanzapine for injection." You follow me?
A. Yes.
Q. Read out loud what it says right there?
A. "First and only psychotropic indicated for the treatment of agitation associated with dementia."
Q. First of only psychotropic indicated for the treatment of agitation associated with dementia, right?
A. That's what it says.
Q. Was Zyprexa indicated for the treatment of agitation associated with dementia?
A. I'd like to make a comment that on an earlier page, it was Page 7, the last line says "see Pages XX for additional safety information." So this clearly was a draft. There was in the Zyprexa IntraMuscular trials pursuit treat potential agitation indications of which agitation in dementia was one of those indications. If

Page 523

that indication was not approved by FDA, then that would render this draft document moot.
MR. ALLEN: Objection. Nonresponsive.
MR. HAMMERLE: Oh, it's very responsive.
MR. ALLEN: I'm certain that anything you say is good and anything I see say is bad according to you.
THE WITNESS: This is a draft document. I have no, there's no evidence that this was ever shown to a doctor. And it's very common for marketing to prepare materials in anticipation of potential label expansions.
MR. ALLEN: I have one more exhibit for today but we need to go off the record and find it because it's here somewhere and my team can't find it.
THE VIDEOGRAPHER: Off the record.

Page 524

(At this time there was a brief period off the record, after which the following proceedings were had:)
THE VIDEOGRAPHER: Back on the record at 6:35.
MR. GORNICK: As a matter of professional courtesy, I'd like to know if I'm going to be given the opportunity to question the witness tonight or tomorrow, because if you're not going to let me have that chance I'm going to go get my airplane.
Can anybody, can you guys tell me if you're going to give me the chance to question the witness tonight or tomorrow?
MR. HAMMERLE: At this hour when the time's up -- that's a better question, with all due respect, to Mr. Allen, getting together with him ahead of time and measuring your guys' time it seems

Page 525

to me, as I understand the rules.
MR. GORNICK: My question is just simple, when this deposition in five or ten minutes is up in the MDL are you going to let me ask questions?
MR. HAMMERLE: The answer to that is this: Was supposed to be over at 5:30 as a courtesy in the spirit of this we wanted to wait to make sure we got our seven hours in. It's now 25 till seven. And when this time's up with Mr. Allen the time's up and we're going home.
MR. ALLEN: Let me point out since all these self-serving statements are being made. We didn't even start till after ten, and all this other stuff's been going on.
MR. HAMMERLE: That's why we stuck around now. I didn't hold that against you.
MR. ALLEN: People have been

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: MDL-1596

ZYPREXA PRODUCTS

LIABILITY LITIGATION

THIS DOCUMENT RELATES TO:

ALL CASES

C O N F I D E N T I A L

- - -

October 26, 2006

- - -

Videotape deposition of

JACK E. JORDAN

- - -

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Page 26

Q. Okay, good. I wrote that down just in reverse order. What's that mean?
A. That's where you segment the market. Basically, segment, target, and position. So you segment the market, target your customers, and position your product vis-a-vis those customers.
Q. You say you "segment the market," and I'm just trying to use layman's terms, if I was a student in your class -- I took a marketing class probably, in 1978 -- to segment the market, I think what you're saying is for a particular product you may have more than one market segment that you market that product to; is that right?
A. Yes.
Q. For example, let's see, a Ford truck. You could have hayseeds or good deeds or something else. Are you familiar with that kind of example? I think it was in y'all's documents is where I got that. If you don t remember that's all right.
A. I don't remember that.

Page 27

Q. That's fine, we won't talk about hayseeds and good deeds, it was somebody else. But what you're saying is you may have a truck to sell, a Ford.
MR. ALLEN: Let me let your lawyer get through blowing his nose and we'll --
QUESTIONS BY MR. ALLEN:
Q. You have a truck to sell, a Ford truck, is that a good example of a product?
A. I drive a Ford truck, yes.
Q. But -- okay. You may want to sell it to farmers and ranchers, right?
A. Yes.
Q. People that live in the city?
A. Yes.
Q. And maybe mothers of children, potential market?
A. Yes.
Q. Okay. And so while you have one product, you have different segments of the market that you're trying to get to utilize your product?

Page 28

A. Yes.
Q. Okay. And then you said you define the market segments. That's what you do first?
A. Um-hum.
Q. Is that yes?
A. Segment, yes.
Q. Okay. And then you said you target the segment. Is that what I heard you say?
A. Yes.
Q. And tell the jury, please, what you mean by "target the segment?"
A. So, for example, using the Ford truck analogy, you might segment the market into farmers, and use the term. A mother with kids, you, probably, wouldn't focus a pickup truck on the mother with kids, you'd focus it on the farmer.
So you pick your segments, who you're going to really focus on. In that case you target farmers and not the mother with kids.
Q. Okay. But wouldn't you try

Page 29

to engage in communication of your product position and messaging to all the target segments?
A. You may or you may not, depending on your strategy.
MR. FAHEY: Okay. Whoever just joined could they just identify themselves for the record, please?
MR. KUTTLES: Hello. David Kuttles, from Lanier Law Firm.
MR. FAHEY: Okay. You've signed the protective order, right?
MR. KUTTLES: Yes.
MR. FAHEY: Okay. Thanks.
QUESTIONS BY MR. ALLEN:
Q. And you said once you segment the market, define your targets, you position your product?
A. Yes.
Q. Tell the jury what you mean by "position your product?"
A. Positioning is ultimately how you want your customers to think about your product. So, for example, staying with the

Ford truck analogy, it would be that if you drive this truck you're tough, could be a positioning. I'm Ford tough. That's part of what they're trying to have their customers think about their product.

MR. ALLEN: I apologize here, I'm going to get my highlighter that I left.

Sorry, Mr. Jordan.

Mr. Lehner.

MR. LEHNER: How are you, Mr. Allen?

QUESTIONS BY MR. ALLEN:

Q. In product positioning you said you determine how you want your customers to think about your product; is that correct?

A. Yes.

Q. And that is a critical part of marketing, is it not?

A. It is, yes.

Q. Now I'm trying to figure out how you go about getting your customers to think what you want them to think. I'm sure

there's some things you need to do to do that, right?

A. There are, yes.

Q. Can you tell the jury, please, what you teach and what you know about how you get your customers to think what you want them to think?

A. Ultimately, that gets into the marketing mix, which is the next step. And most of that revolves around your promotional activities.

Q. Okay. So you would agree with me as of this juncture, as a person who's in the field of marketing, who worked in the field of marketing at Eli Lilly; is that correct?

A. For part of my time there, yes.

Q. Yes, sir. We're going to take a lot about that today. But we're now just talking about your understanding of marketing and what you teach to your students and so the jury understands what marketing is.

have told
you determ[illegible], once yo[illegible] marketing
environment, you deter[illegible]keting
strategy. We're up the[illegible]

A. Yes.

MR. FAHEY: Objection to form. You can answer.

Q. And after you determine a market -- and part of the determination of a marketing strategy is to position your product such that you want the market -- let me rephrase it again.

As part of your strategy you determine how you want your customers, how you want your customers to think about your product, right?

A. Yes.

Q. Okay. And when you determine how you want your customers to think about the product, you said we go to this next step which is called the marketing mix; is that right?

A. Yes.

Q. And I think you told me, and

I didn't write it down and I got distracted, explain again for this jury, please, as you did previously, what it is, what is a marketing mix?

A. The marketing mix are the four Ps of marketing: Product, what the product is; what the price is for that product; what promotion you're going to do around that product; and then the fourth P is place. Kind of the distribution channel or the place that you're going to sell that product.

Q. And I want to focus on this issue of how you want your customers to think, one of your goals, and you said that deals with the marketing mix. Is there any particular P of the four Ps, or more than one P, of the marketing mix which allows you as a marketer to have your customers think what you want them to think?

A. Well, it ultimately starts with the product. The -- what the product is. And then using promotion to reach your customers, which could be a variety of

Page 50

force gets this information that's synthesized comes from the marketing department, correct?

A. Yeah. It ultimately comes from the medical department but it goes through a process and then marketing rolls it out to sales within Lilly, yes.

Q. Right. So within Eli Lilly this information that would go to the sales force so they can provide, in your words, good and useful information to the customer, goes through the marketing department?

MR. GOLD: That misstates his answer. I think he said it goes to the medical department then it goes through the marketing department.

MR. ALLEN: You can answer my question.

THE WITNESS: Can you repeat it?

MR. ALLEN: Yes.

And I would ask the attorneys, although I know it will do me no good --

Page 51

MR. GOLD: You never know.

MR. ALLEN: I do know. I've been experienced in this for a while.

-- to comply with the protocol.

MR. GOLD: We have been complying with it. And we intend to comply with it. I suggest you do the same.

MR. ALLEN: They don't allow speaking objections. We'll continue.

QUESTIONS BY MR. ALLEN:

Q. Let's retrench for the jury so they understand. We've been interrupted.

We're trying to get the sales force, right, to give good and useful information to the customer. That's our goal, right?

A. It is.

Q. You said the way the sales force gets the good and useful information is they get that information from the company

Page 52

who manufactures and sells the product, right?

A. No.

Q. Okay. Well, tell me where they get it.

A. Some of the data might be studies done by other entities, might be government studies. So the information can come from company studies, external studies. So there's a number of ways to quote/unquote get the information.

Q. Yes, sir. And you said, though, that the marketing department synthesizes this information and passes it on to the sales force, right?

MR. GOLD: I'm not sure he said the marketing department synthesizes any kind of information.

If you have a question just ask it as opposed to trying to restate his testimony, which actually mischaracterizes his testimony, and maybe we can get through this line of questioning.

Page 53

MR. ALLEN: You can answer my question.

A. The process is that the medical group gets the studies, gets the data, analyzes it, and determines, along with the regulatory group, what's medically useful and what's in the context of Lilly's label, and passes that information off to marketing to make materials to communicate with customers through various venues, one of which is the sales force.

Q. Okay. So -- and you used the term, and I'm just trying to find out when you used the term, the record will reflect you used the term "synthesize the data and information." You recall that? Synthesization? Synthesize them?

A. I did use that term and I want to be clear on the process. It's the medical department, along with the regulatory group, that does the analysis, determines what the data's actually saying, and leads the marketing department on what's appropriate to communicate to physicians. So

Page 54

I just want to make sure the process is clear.
Q. Yes, sir. I apologize. And I thank you for your help.
You said the medical and regulatory take the information and give it to the marketing department to determine what's proper to communicate to the physicians?
A. No. There's a whole process that determines what's proper to communicate to physicians. It's called a, it's called, actually, it's a standardized process, it's called the ELMR process, which stands for --ELMR process.
Q. Can you spell that for me?
A. E-L-M-R. It's an acronym for the editor, legal, medical and regulatory.
Q. What's the E stand for, I'm sorry?
A. The editor.
Q. Okay. Go ahead, I'm sorry. Go ahead.
A. Editor, legal, medical and

Page 55

regulatory approve everything that goes out. And then the marketing department takes that approved information for promotional items and communicates it to customers.
Q. And the marketing department also takes this approved information and communicates it to the sales force to help train them so they can appropriately communicate, as you said, good and useful information to the customer?
A. Yes. It goes through the process and is approved and, for promotional activities through the sales force, yes.
Q. You used the term "promotional activities." Is that a term of art?
A. No.
Q. Okay. What do you mean by "promotional activities?"
A. In the pharmaceutical industry there are two communication, ways to communicate with customers: One is promotional, and there are nonpromotional activities.

Page 56

MR. ALLEN: We're going to stop there on that and we'll come back to that in a minute.
QUESTIONS BY MR. ALLEN:
Q. Mr. Jordan, can you tell this jury, please, when were you born?
A. August 7, 1961.
Q. Can you tell the jury, please, a little bit about your educational background and training, please?
A. I can. I graduated from Bremen High School in 1979.
Q. You're a Hoosier born and raised?
A. I am, yes.
Q. Okay.
A. I started at Purdue University, transferred to Liberty University in Virginia. I got a degree in pastoral studies.
Q. Purdue, you started then went to Liberty University?
A. I did, yes.
Q. Okay. And you got a degree

Page 57

in pastoral studies?
A. I did.
Q. And that would be -- is that what I call religion or am I --
A. That would be, yes.
Q. All right. And what year did you get out of Liberty University?
A. 1984.
Q. All right. Following your graduation from Liberty University in 1984, what did you do next education or work-wise?
A. I took two years off.
Q. What did you do those two years?
A. I worked at Bremen Castings Incorporated for most of it.
Q. I'm sorry, sir, it's probably my Texas ears or your Indiana accent, or both, you said you worked where?
A. At Bremen Castings Incorporated.
Q. And I don't know if I asked you this before, how do you spell Bremen?
A. B-R-E-M-E-N.

Page 422

before the sales rep, or before this whole sales piece was prepared, that Zyprexa was approved for schizophrenia and bipolar mania, right?

A. Yeah. It was on Page 2, which I'm assuming is Page 1 of the piece.

Q. My question to you was, there was no doubt that the only approved indications for which Zyprexa could be promoted was schizophrenia and bipolar mania, right?

MR. GOLD: Asked and answered.

A. Yeah. And it's right here in the first page, yes.

Q. And now we go to the page on Donna. It says, "Donna. Single mom in her mid-30s, presents in drab clothing and seems ill at ease. Quote, I feel so anxious and irritable lately, close quotes. Her history is: Reports she has been sleeping more than usual, has trouble concentrating at work and at home. Several appointments earlier she was talkative, elated, and reported little need for sleep."

Next bullet point: "You have treated her with various medications including antidepressants."

Did I read that correctly?

A. You did.

Q. Is there a diagnosis of schizophrenia or bipolar mania on Donna?

A. The Donna profile was approved by our medical folks to represent bipolar mania.

And I think the other important thing to note is along with these we handed out, to our physicians, MDQ, which was a valid screening tool for bipolar disorder.

MR. ALLEN: Objection. Nonresponsive.

QUESTIONS BY MR. ALLEN:

Q. My only question to you is, sir, do you see a diagnosis of schizophrenia or bipolar mania in the Donna profile?

A. Now you're asking a question that -- the words, no, but the symptoms, the cluster of symptoms, actually, might be. I mean, that's part of the reason to have that discussion and have the MDQ so they can screen for bipolar mania.

Q. You said MDQ?

A. MDQ, yes.

Q. Yeah. The MDQ is the mood disorder questionnaire that was only released, I believe, in 2003, and the sales representatives were instructed to only use it with their high prescribers; isn't that right?

A. I don't know if that's the case or not.

Q. And you're not suggesting that in order to prescribe Zyprexa that the physicians needed to get an MDQ filed out, are you?

A. No. But we provided various tools to help them diagnose bipolar mania.

Q. Yes, sir. What do you do when you cash your chips?

A. That's a term that the sales organization used at one point. And it's, actually, not a term I'm that familiar with.

Q. What do you do when --

Didn't you instruct all your sales representatives, weren't they instructed that during the sales call they were to collect chips, collect agreements, and at the close of the call to cash the chips and to create action?

A. I heard verbiage like you just used. Again, that was more of a sales organization, sales process, than kind of a marketing language, so.

Q. Sir, as I told you previously I always admit when I make mistakes. I forgot to ask you a question about the Viva Zyprexa document, and I'd like to you to return to the Viva Zyprexa document, if you don't mind?

MR. GOLD: What exhibit is that, Mr. Allen?

MR. ALLEN: I do not know. I will try to make that determination. I'll find it right here.

MR. GOLD: Oh, good. Thank

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: MDL-1596

ZYPREXA PRODUCTS

LIABILITY LITIGATION

THIS DOCUMENT RELATES TO:

ALL CASES

C O N F I D E N T I A L

- - -

July 10, 2006

- - -

Videotape deposition of

BRUCE KINON, M.D.

- - -

GOLKOW LITIGATION TECHNOLOGIES
1600 John F. Kennedy Boulevard
Suite 1210
Philadelphia, Pennsylvania 19103
(877) DEPS-USA

project was to stop hyperglycemia and diabetes from becoming a top ten attribute as listed right there in the document?

MR. WASSON: Objection to the form. Asked and answered.

THE WITNESS: Could you repeat the question, please?

MR. SUGGS: Can you read it back, please?

Off the record.

(At this time, the parties went off the record, after which the following proceedings were had:)

THE VIDEOGRAPHER: We're back on the record.

MR. WASSON: Just for the record, we heard some people join on the phone recently and, I believe, a Mr. Harris not too long ago.

Could you identify yourselves and state for the record whether, in fact, you have signed CMO3, the protective order, or agree to be

bound by it?

MR. HARRIS: Yes, I agree to be bound by it.

MR. WASSON: Who is that?

MR. ALLEN: Fred Harris.

MR. WASSON: Okay. And someone else just joined a minute ago?

No? Okay, I'm sorry.

QUESTIONS BY MR. SUGGS:

Q. Dr. Kinon, the first page of Exhibit 4517 states that -- a list of project goals, does it not?

A. Yes, it does.

Q. And the number one goal there was to stop hyperglycemia and diabetes from becoming a top ten attribute. Isn't that what's listed there?

MR. WASSON: Objection to the form.

THE WITNESS: Repeat the question, please.

QUESTIONS BY MR. SUGGS:

Q. The very first goal that's

listed for this group was to stop hyperglycemia/diabetes from becoming a top ten attribute; isn't that correct?

A. As far as I understand that was not the goal of this group. I didn't write this document. This document was apparently written by Suni Keeling, whose name is on the bottom of it.

My recollection of the role of this group was to understand from a medical point of view the hyperglycemia and diabetes issues involved with Zyprexa, and try to deliver that information to clinicians in a way that they would have the answers they needed to the questions that they were posing.

MR. ALLEN: Objection, nonresponsive.

QUESTIONS BY MR. SUGGS:

Q. It's your impression that this document was written by Suni Keeling, correct?

A. As I look at the document in front of me, it appears that way. I'm not

sure of that. It certainly wasn't written by me.

Q. Suni Keeling was in the marketing department, correct?

A. That's correct.

Q. And at least, according to this document, the number one goal of this project was to stop hyperglycemia and diabetes from becoming a top ten attribute; isn't that correct?

MR. WASSON: Objection to the form.

A. I'm not able to answer that. I did not write this document.

Q. You can look at the document and that's what's listed there as the first goal, isn't it?

A. If I'm to read the document in front of me the title is hyperglycemia/diabetes project. The second line says: On the forefront of managing the issue. The third line says: Project goals. And the fourth line says: Stop H/D from becoming a top ten attribute.

MR. SUGGS: I was going to get to that.
Q. Including Dr. Kinon; is that correct?
A. I'll have to review the document.
Q. You've reviewed the document, haven't you, sir?
A. Yes, I have.
Q. And this e-mail from Dr. Paula Trzepacz went to both people in the medical department and in the marketing department, correct?
A. That's correct.
Q. And Dr. Trzepacz was who you reported to, correct?
A. That's correct.
Q. And what was her job title again?
A. Medical director.
Q. Medical director. And in this e-mail she's talking about redistributing the medical workload that, in her words, involve important issues that

affect more than one Zyprexa silo. Do you see that language?
A. Yes.
Q. And what's a Zyprexa silo?
A. What she's referring to is, for example, the schizophrenia group would be one silo, the bipolar group would be another silo.
Q. Why were those referred to as silos?
A. Each of those components had a different clinical plan. For instance, there were studies that were being developed for patients suffering from schizophrenia, and there were other studies that were being developed for patients with bipolar disorder. They require two separate teams.
Q. I guess the thing that's confusing me is the only time I've ever heard the term silo, the word silo, has been in conjunction with either the storage of grain or missile silos. Is this some other meaning of the word silo I'm not familiar with?
MR. WASSON: Objection to

form.
Q. Why did you use the word silo?
MR. WASSON: Objection to the form. He didn't use the word silo.
A. I don't know, specifically, what the reference is here.
Q. Did you ever hear the term silo referred to before in the company?
A. I've heard it in the concept of groups of people.
Q. Why that term for groups of people instead of groups of people?
A. I don't know, specifically.
Q. Okay. In any event, in her second paragraph in about the middle of it Dr. Trzepacz says, quote, "The primary person responsible will be held accountable to drive the medical marketing strategy from the medical side." Do you see that?
A. Yes, I do.
Q. Okay. And then her plan was to have you be the number one guy on the issue of weight gain with Dr. Baker and

Dr. Hay being the No. 2s and No. 3s, correct?
A. Yes.
Q. And her plan also entailed you, pardon me, Dr. Baker being the No. 1 guy on glucose issues, with you being the number two man, and Dr. Kennedy being the number three man; is that correct?
A. That's correct.
Q. And was that plan, in fact, carried out?
A. Yes, it was.
Q. So you were the number one guy dealing about the issue of weight gain, correct?
A. I was the number one physician in the U.S. Affiliate Zyprexa team.
Q. And you were the number two guy dealing with issues of glucose, correct?
A. That's correct.
Q. Okay. And how did, when you were dealing with those issues, how did you break out the responsibilities for being the number one guy versus the No. 2 or No. 3 guy?
A. The example that I could

EXHIBIT C
Page 3 of 12

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D

think of is in the analysis of data, developing an analytical plan and a publication strategy. That would be something that I would be involved in as far as the weight gain data was concerned. And Dr. Baker might have a similar type of strategy as far as glucose is concerned.

Q. Okay. Is it fair to say, though, that you were very actively involved in both the weight gain and the glucose issues with respect to Zyprexa?

MR. WASSON: Objection to form. You can answer.

A. My predominant effort was in the weight gain area.

Q. Okay. But were you also involved in the glucose area?

A. To some degree.

Q. Okay. And what did it mean when Dr. Trzepacz said that you were going to be the primary person held accountable to drive the medical marketing strategy from the medical side with respect to weight gain?

A. What I imagine --

THE OPERATOR: Todd Vinson has joined the conference.

MR. WASSON: Could you identify yourself, the person who just joined on the phone, please, and state whether or not you agreed or already signed CMO3?

MR. VINSON: Hi, this is Todd Vinson with Drinker Biddle and Reath and I'm with Janssen Pharmaceutica and we have agreed to the protective order.

MR. WASSON: Thank you.

MR. VINSON: Thank you.

A. Since I didn't write this e-mail I don't know specifically --

THE OPERATOR: Todd Vinson has left the conference.

A. Excuse me. Since I did not write this e-mail I don't know, specifically, what Dr. Trzepacz is referring to.

Q. When you got this e-mail from Dr. Trzepacz, what did you understand her to mean when she told you that you were going to

be held accountable to drive the medical marketing strategy from the medical side with respect to weight gain?

A. I was led to believe, or my understanding of this was, that as part of our evaluation in terms of what are the deliverables, what type of things that we would accomplish in terms of our clinical plan, that we need to clearly define a target, and then try to develop that target. So, for instance, if a particular type of weight gain analysis was our target, we should complete those results and distribute them amongst the team.

Q. Well, and your work product consisted not just of statistical or data analysis, but also write-ups, descriptions of the company's position with respect to weight gain; is that correct?

A. That's correct.

Q. Okay. And all of that was done with an eye towards marketing or selling the drug, correct?

MR. WASSON: Objection to

form.

A. The point of the medical deliverables, writing up that data, was to provide information that clinicians needed in terms of understanding the safety and efficacy of the product.

Q. Well, sir, this was all part of the medical marketing team, correct?

A. In part.

Q. Well, according to Dr. Trzepacz's e-mail again you were going to be the primary person responsible to drive the medical marketing strategy, correct?

A. Drive it from the medical point of view, as she states.

Q. Do you recall that one of your key messages about weight gain was no significant weight gain over the long-term?

THE OPERATOR: Todd Vinson has joined the conference.

A. No, I have no recollection of that message at all.

Q. Do you recall that another of your key messages was "no association between

weight gain with olanzapine and hyperglycemia and diabetes?"

A. I don't, specifically, recall that at all.

MR. SUGGS: Let me show you what's been previously marked as Exhibit 1213.

(Whereupon, MDL Plaintiff's Exhibit(s) 1213, previously marked, was presented to the witness.)

QUESTIONS BY MR. SUGGS:

Q. Sir, I'm going to represent that the database that was produced to us by Lilly in conjunction with the production of documents states that this particular document was produced from your files. Do you have any basis to dispute that?

THE WITNESS: I have to review the document, please.

Q. Do you recall my question?

A. No, I don't.

MR. ALLEN: He just recalls he's instructed to review the

document, kill time, take the air out of the ball, use some air with this document. He's knows what he's doing.

MR. WASSON: Objection. Move to strike.

QUESTIONS BY MR. SUGGS:

Q. Okay. As I mentioned before, the database that was provided to us by Lilly states that this document was produced to us from your files. Do you have any basis to dispute that?

A. I've never seen this document before.

Q. Okay. So are you denying that this document came from your files as represented to us by Eli Lilly?

MR. WASSON: Objection to the form.

A. I have no basis to deny or not. I just have never seen this document before.

Q. Okay. The title of the document is: Olanzapine Issues Surrounding

Weight Gain, Diabetes and Hyperglycemia. Key Messages. Is that correct?

A. That's correct.

Q. And then about midway through the page there's a heading that says: No Significant Weight Gain Over Long-term. Do you see that language?

A. I see that on this document before me.

Q. And that was, in fact, one of the key messages that you wanted doctors to believe about Zyprexa, correct?

MR. WASSON: Objection to form. You can answer.

A. That is certainly incorrect. I have published extensively on the weight gain associated with Zyprexa.

MR. ALLEN: Objection, nonresponsive.

QUESTIONS BY MR. SUGGS:

Q. So you're denying that one of your key messages for physicians was that there was no significant weight gain over the long-term?

MR. WASSON: Objection to the form.

Q. Is that correct?

A. I deny that that was a statement.

Q. Okay. And then the one right below that says, quote, "No association between weight gain with olanzapine and hyperglycemia and diabetes." Do you see that language?

A. I do see that.

Q. And that was another key message that the company wanted doctors to believe; isn't that correct?

A. I have no idea whether these were key messages or not. As far as I could recollect, these were never key messages in terms of our interpretation of the data.

MR. ALLEN: Objection to the portion of the answer that's nonresponsive.

Q. And --

MR. SUGGS: Strike that.

QUESTIONS BY MR. SUGGS:

Q. Directing your attention to the following page. There's a bolded heading about a third of the way down that says: Explain the Data Results and Reemphasize Its Importance. Do you see that?
A. Yes, I do.
Q. And then it says, "In this study, 70 percent of patients treated with olanzapine either lost weight, remained stable, or gained less than or equal to 22 pounds over the long-term." Do you see that language?
A. Yes.
Q. And do you know what study that's referring to?
A. I don't know, specifically. This may be, this may be referring to one of my studies. But I certainly did not write these conclusions.
Q. Did you do a study in which you found that 70 percent of patients treated with olanzapine either lost weight, remained stable, or gained less than or equal to 22 pounds over the long-term?

A. We published on long-term weight gain with Zyprexa. We never presented the data this way at all in the article.
MR. ALLEN: Objection, nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Well, did your study find that 70 percent of the patients treated with Zyprexa either lost weight, remained stable or gained less than or equal to 22 pounds over the long-term?
A. I'm not aware of that calculation. How that was arrived at.
Q. So is that language describing the results from the study false?
A. In my opinion that would be false.
Q. Okay. So if, in fact, that type of language went out to physicians about the results of the study, that would have been false statements being made to physicians?
A. I'm not aware that this statement ever went out to physicians.

MR. ALLEN: Objection, nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Can you answer my question, sir?
THE WITNESS: Could you repeat the question, please?
Q. If, in fact, statements went out to physicians, or the message went out to physicians that an Eli Lilly study found that 70 percent of patients treated with Zyprexa either lost weight, remained stable, or gained less than or equal to 22 pounds over the long-term, would that have been a false statement to physicians?
A. I don't know if that statement ever did go out. If it did go out it would not be representative of the data that we had published upon regarding weight gain.
MR. ALLEN: Objection, nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Did the data that the company

had show that 30 percent of the Zyprexa users gained more than 22 pounds over the long-term?
A. The data would be consistent with that.
Q. Okay. And if, in fact, 70 percent of -- and by the way, there were reports of people gaining like 80, 90 pounds of weight while they were using the drug; is that correct?
A. There were some reports, yes.
Q. Okay. And about 30 percent of them gained more than 22 pounds, correct, over the long-term?
A. It might have been that.
Q. And 22 pounds of weight gain is a lot of weight gain, isn't it?
MR. WASSON: Objection to the form.
A. That would be considered a significant amount of weight.
Q. Clinically significant, correct?
A. Depends upon the amount of

significant weight gain with Zyprexa, correct?
A. That's correct.
Q. Okay. And some people were going to have, because that's your average, some people are going to have a whole lot of weight gain, like 80, 90, maybe even more, right?
A. A small percentage of patients would have that.
Q. And some are maybe even going to lose some weight, right?
A. Approximately, a quarter of the patients lose weight.
Q. But on average, people are going to have 15 pounds or more weight gain, correct?
A. That's correct.
Q. Now if you could direct your attention back to Exhibit 1213, the last bolded item there says Summarize and Disassociate Olanzapine and Weight Gain From Diabetes and Hyperglycemia. Do you see that on there, sir?

A. Yes, I do.
Q. Now, that was a tough goal to accomplish, wasn't it, sir?
MR. WASSON: Objection to the form.
THE WITNESS: Could you repeat that question, please?
MR. SUGGS: Sure.
Q. The goal of disassociating olanzapine and weight gain from diabetes and hyperglycemia was a tough goal to accomplish, wasn't it, sir?
A. I don't know, specifically, what is meant by this statement in this particular document. I did not write it and I'm not aware of it.
Q. Sir, weight gain, trying to say that weight gain is not linked with diabetes is flying in the face of accepted medical principles, is it not, sir?
MR. WASSON: Objection to the form.
A. If one were, tried to remove or distance weight gain from diabetes as a

risk factor, yes, that would be.
Q. Because it's generally accepted that if you gain weight you're more likely to develop diabetes, correct?
MR. WASSON: Objection to form.
A. Weight gain is known to be a risk factor for the development of diabetes.
Q. And, in fact, in 1995, before Zyprexa even went on the market, a group of outside consultants warned Lilly that clinically significant weight gain is a risk factor for developing other medical conditions including type two diabetes. Were you aware of that, sir?
MR. WASSON: Objection to form.
A. I was not aware of that.
MR. SUGGS: Okay. Let me show you what's been previously marked as Exhibit 1586.
(Whereupon, MDL Plaintiff's Exhibit(s) 1586, previously marked, was

presented to the witness.)
MR. SUGGS: For the record this is a document entitled Executive Summary, The Third United States Schizophrenia Advisory Panel Meeting dated December 10, 1995.
Apparently, the meeting was held in San Juan, Puerto Rico.
And at this point, counsel, I'm going to object to your witness taking the time to read through the entirety of this document or we're going to be here all day and we'll need more time for these depositions.
I'm going to be asking him a couple of questions about this document, and I think we can, probably, proceed most efficiently if I just ask him a question, he sees if he can answer it. If he thinks he needs to take the time to read the document after hearing what my question is, then we can discuss

24 pounds at the end of the 24-month" -- pardon me -- "at the end of the 12 months." Did I read that correctly?

A. Yes.

Q. And does that conclusion differ from studies that you did, because earlier you were talking about how the studies you did showed that there was a weight gain of 15 pounds on average, but this is talking about an average of 24 pounds weight gain at the end of 12 months.

MR. WASSON: Objection to the form. You can answer.

A. I have not read this document. I don't know, specifically, how this analysis was done but the difference in the numbers is due to the fact that this analysis was of patients that remained in the study for 12 months.

Q. Okay.

A. The work that I had referenced earlier was patients that had stayed in the study any amount of time. They could have been in for one day, five days,

six months, three years.

Q. Okay. That's very helpful. I appreciate that.

So this study was being reported on here in Exhibit 1586 is saying that if you stayed on Zyprexa for a full year, on average, you were going to gain 24 pounds, correct?

MR. WASSON: Objection to the form.

A. Again, I cannot in any way vouch for the accuracy or reliability of these results unless I read the entire document.

Q. Okay. Were you -- do you recall being informed that the studies that had been done before Zyprexa went on the market found that the average weight gain for people who were on the drug for at least a year was about 24 pounds on average?

A. No. We clearly state in our label, the label we had --

Q. I don't think you understood my question.

MR. WASSON: Counsel, let the witness finish his answer then you can tell him he didn't answer your question.

MR. ALLEN: I'm going to object to it as nonresponsive so I'll let you know right now.

MR. WASSON: You can answer the question.

A. I've never seen this No. 24 pounds the way it's stated here. We have clearly stated the weight gain in patients on Zyprexa in long-term studies as part of our original label and it remains in our label to date.

Q. So is it your testimony as you sit here today that up until now you were not aware of this statement that patients who remained on olanzapine for 12 months gained an average of 24 pounds at the end of 12 months?

A. It's something that I'm not familiar with now, no.

Q. Okay. And you were the guy

who, at least as of 2000, was the number on guy for driving the medical marketing strategy as you were assigned to do by Dr. Trzepacz, correct?

MR. WASSON: Objection. Asked and answered.

A. The sentence following the one you asked me to read clearly indicates that analyses were still being done at the time of this report. I can only come to the conclusion that this is a preliminary draft report.

The final conclusions regarding data were clearly stated in our label and have clearly been published in the articles that I and my colleagues have reported.

MR. ALLEN: Objection, nonresponsive.

Q. Are you familiar with the CATIE study?

A. Yes, I am.

Q. And are you familiar with the fact that the CATIE study found that patients

MR. WASSON: Thank you.
MR. SUGGS: For the record, this is a document dated December 9, 1998, and refers to a Zyprexa Medical Marketing Meeting Agenda for a meeting on December 9, 1998.
QUESTIONS BY MR. SUGGS:
Q. Now you've talked about the medical marketing or we've talked about medical marketing before. I believe you said that you were part of the medical marketing team; is that correct?
A. Yes.
Q. Okay. Were you a member of the medical marketing team as of this date back in 1998?
A. I believe so.
Q. Thank you. But you're not listed as being one of the recipients of this agenda; is that correct?
A. No, I'm clearly not listed as a recipient of this.
Q. But Dr. Charles Beasley was?
A. That's what this memo tells

me.
Q. Did Dr. Beasley and yourself work together on medical marketing issues regarding Zyprexa?
A. No, we did not.
Q. And why is that?
A. Dr. Beasley was on a different team. He was on the global team. He wasn't a member of the U.S. Affiliate which I was a member of.
Q. Okay. So you had medical marketing teams with respect to Zyprexa that were both global and also U.S., correct?
MR. WASSON: Objection to the form.
A. I certainly am aware of the medical marketing team in the U.S. Affiliate. There may have been one on the global side that Dr. Beasley may have been a part of at various times.
Q. Okay. And in about the middle of the page of this particular agenda from December of 1998 it says: Weight gain and link to diabetes question mark. What

does the data say and what is our action plan, question mark.
Do you see that?
A. Yes, I see that.
Q. And was your team, your medical marketing team also engaged in this issue of whether or not there was a link between weight gain and diabetes with Zyprexa?
A. Yes, we were.
Q. Okay. And you see that there are handwritten notes on this document?
A. Yes, I do.
Q. Do you recognize the handwriting?
A. No, I don't.
Q. The very bottom handwritten note says: "Weight gain plus genetic vulnerability lead to hyperglycemia." Do you see that language?
A. Yes, I do.
Q. And that formula, if you will, is a generally-accepted scientific view then; is that correct?

MR. WASSON: Objection to the form.
A. As far as I understand it weight gain is believed to be a risk factor for hyperglycemia in patients with a genetic predisposition.
Q. So you would agree with that statement "weight gain plus genetic vulnerability lead to hyperglycemia," correct?
MR. WASSON: Objection to the form.
A. I would agree to it in terms of general medical knowledge. I have no idea what this person is referring to, specifically.
Q. Would you say, sir, I realize this is calling for an opinion on your part, but based on the discussions you had with people back in Lilly at or around this time back in December of 1998, would it be your belief and understanding that it was well understood by the people that you dealt with in the medical marketing area, that weight

paragraph Dr. Holcombe says, "The point was that Lilly has to be forthcoming with the data to gain and maintain our just credibility. Showing our advisory group a slightly modified analysis with, all, and again the word "all" is in all caps, glucose values would be a vital step forward here." Isn't that what it says?

A. That's what it says. What it means I don't know.

Q. Sir, in fact, you know that the consultants were skeptical of Eli Lilly's presentation of data because of the categorical analyses and they wanted to see all the data and Lilly didn't show it to them; isn't that right?

MR. WASSON: Objection to form.

A. I have no knowledge of that. This is the first time I'm ever hearing that the categorical analysis was considered to be a less than more reliable analysis.

Q. Okay. Now, sir, in the e-mails that we've looked at we've seen that

the outside consultants were concerned about the weight gain with the drug, correct?

THE WITNESS: Specifically, which what e-mail are you speaking of?

Q. For example, in 6998 in the second paragraph of his e-mail Dr. Baker says "that the outside consultants were quite impressed by the magnitude of weight gain on olanzapine and the implications for glucose," correct?

A. That's correct.

Q. And, sir, in fact, Lilly had been minimizing the weight gain problem in its communications with physicians; isn't that correct?

MR. WASSON: Objection to form.

A. Lilly has never minimized the weight gain. We have been very proactive in sharing all of our weight gain data, both prospective as well as retrospective, with all clinicians through scientific presentations, medical letters.

MR. SUGGS: Sir, let me show you what's been previously marked as Exhibit 4532.

(Whereupon, MDL Plaintiff's Exhibit(s) 4532, previously marked, was presented to the witness.)

MR. SUGGS: For the record it's a seven page document, appears to be a PowerPoint presentation with the first page having the title Weight Change Strategy and Tactics.

QUESTIONS BY MR. SUGGS:

Q. Do you recall seeing this document, sir?

A. I'll have to take a look at it and read it, please.

Q. Do you recall seeing this document before, sir?

A. No, I do not.

Q. Let me direct your attention to Page 3. There's a heading on Page 3 Zyprexa Market Research Weight Gain and Other Side Effects June 1999. And below that it

says Key Results with several bulleted items; is that correct?

A. Yes, that's correct.

Q. And the second bulleted item is "Lilly perceived as minimizing weight gain problem," do you see that language?

A. Yes, I do.

Q. And were you informed that the market research showed that physicians believed that Lilly was minimizing the weight gain problem?

A. Yes, I've heard about that.

Q. And from whom did you hear that?

A. We've heard that through market research.

Q. And when did you first learn that physicians believed that Lilly was minimizing weight gain?

A. It wasn't that Lilly was minimizing weight gain, there was the perception that Lilly was minimizing weight gain. From my understanding we were never minimizing weight gain as a side effect.

MR. SUGGS: Move to strike as nonresponsive.

Q. Sir, my question was when did you first learn that Lilly was perceived as minimizing weight gain by physicians?

A. I don't know exactly but certainly around the time of 1999, perhaps, 2000.

Q. And did that perception continue?

A. I don't know.

Q. The third bullet point item on that page three is Need For More Data On Weight Gain?

A. That's correct.

Q. Do you see that?

A. I see that.

Q. And you, as we talked about at the beginning of your deposition, were designated by Dr. Trzepacz as the number one person responsible for driving the medical marketing strategy with respect to weight gain, correct?

A. I was certainly significantly

involved in the weight gain analyses.

Q. And you were certainly significantly involved in reviewing and approving the messages that went out to physicians about that issue, correct?

A. In part.

Q. Okay. Let me direct your attention to the following page. There's a reference to marketing materials. And they make reference to a new visual aid adherence section which accomplished three things, and then they have three bullet point items there, correct?

A. Yes.

Q. And the second one states Added Additional Facts. And the word "facts" is in quotes, to show that it is common with psychotropics, most patients gain little if any weight and few discontinue if they do gain and weight change plateaus over time without intervention." Do you see that language, sir?

A. Yes, I see that language.

Q. Did you review and approve

that material?

A. This --

MR. WASSON: Objection to form.

A. This material, as far as I understand, never left the company. This never went into any promotional pieces that I've had to review. I've never seen this type of language before.

Q. And is that language that "weight change plateaus over time without intervention," is that factually accurate?

A. No, that's not. The published data that we have is that weight plateaus over time.

Q. And the bottom line bullet point there as to, or it says "bottom line weight change is manageable." Did you review and approve that part of the message?

A. No, I did not.

Q. Sir, isn't it a fact that the company repeatedly told physicians that weight gain was manageable?

A. When you say it's a fact, I

don't know what you're referring to.

Q. Didn't the company instruct its sales people that weight gain was manageable?

A. Around this time we were clearly telling clinicians that if weight gain was a problem with their patients they should consider other interventions if not switching the patient off of Zyprexa.

We also provided them with psychoeducational materials to help them with their patients who were gaining weight. This is our Healthy Lifestyle programs, our Solutions For Wellness.

We were doing a lot of things. In addition, we were doing prospective clinical trials to try to show that perhaps there was a treatment that could be added to antipsychotic drugs to reduce the weight gain. That's what we meant by weight gain is manageable.

MR. ALLEN: Objection, nonresponsive.

MR. SUGGS: I have the same

MR. WASSON: Objection to form.
A. It's a relative risk.
Q. But it's a greater risk?
A. In some instances yes, in some instances no.
Q. Well that depends on the individual patient?
A. No, it doesn't. Those patients that complete a successful course of treatment, and I've published on this, if they're treated with risperidone or olanzapine those patients that complete a course of therapy actually gain the same amount of weight.
So it's a very complicated issue. For some patients, actually, on these drugs discontinue treatment very early and that could be one of the reasons why they have a less of a risk of developing weight gain.
MR. ALLEN: Objection, nonresponsive.
QUESTIONS BY MR. ALLEN:

Q. Do you agree or disagree with the fact that Zyprexa causes, on average, a greater degree of clinically significant weight gain than risperidone?
A. The data would indicate that the risk of weight gain, or the weight gain associated with Zyprexa is greater than that, marginally greater than that of risperidone.
Q. And you've known that since 1996?
A. Approximately, 1998 or so when we completed an olanzapine versus risperidone comparative trial.
Q. Do you agree that Zyprexa causes on average a clinically significant weight gain greater than Seroquel?
A. The weight gain associated with Zyprexa appears to be greater than that of Seroquel. Although, in studies that I've completed the weight gain seems to be equivalent on both drugs. So there really is not all that much complete data to make the comparative statement.
Q. What about Geodon? Do you

agree on average that sarazone causes a clinically significant degree of weight gain over and above that of Geodon?
MR. WASSON: Objection to the form. I'm not sure what you said. You said sarazone.
MR. ALLEN: I did say sarazone?
MR. SUGGS: Yeah, not Seroquel.
MR. ALLEN: I'm sorry, I'll come back to that later.
QUESTIONS BY MR. ALLEN:
Q. Did Lilly tell doctors that Zyprexa caused weight gain of clinical significance greater than the other second generation antipsychotics?
A. We try to very clearly indicate the comparative risks associated with weight gain on olanzapine versus the other compounds. And we have clearly presented that at numerous scientific congresses.
MR. ALLEN: Objection.

Nonresponsive.
QUESTIONS BY MR. ALLEN:
Q. Isn't it a fact that you told physicians and as part of the marketing plan that the weight gain was comparable in Zyprexa with the other second generation antipsychotics?
A. No, that's not the case.
Q. It's not. And if I find documents in the marketing file that indicate that the weight message was comparable weights that would be wrong?
MR. WASSON: Objection to form.
A. It may be comparable weights versus risperidone, not the other atypical antipsychotics as I believe that's what you said.
Q. Do you have 4858 and 5565 there in front of your, sir?
THE WITNESS: 4858?
MR. ALLEN: Yes, sir.
MR. WASSON: Give us a little description.

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: ZYPREXA PRODUCTS LIABILITY LITIGATION THIS DOCUMENT RELATES TO ALL CASES	: MDL-1596	
TERRY L. DEPEW V. ELI LILLY et al.	: UNITED STATES DISTRICT COURT : SOUTHERN DISTRICT OF OHIO : NO. 06-CV-00426	
JAMES TSIKAS V. ELI LILLY et al.	: UNITED STATES DISTRICT COURT : SOUTHERN DISTRICT OF OHIO : NO. 1:06-CV-00505	
WILLIAM LEGGETT V. ELI LILLY	: UNITED STATES DISTRICT COURT : CENTRAL DISTRICT OF CALIFORNIA : CV-064323 ABC (CTx)	

- - -

December 15, 2006

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C O N F I D E N T I A L

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Videotape deposition of DENICE M. TORRES, held in the offices of Pepper Hamilton, 301 Carnegie Center, Princeton, New Jersey, commencing at 9:43 a.m., on the above date, before Linda L. Golkow, a Federally-Approved Registered Diplomate Reporter and Certified Shorthand Reporter.

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GOLKOW TECHNOLOGIES, INC.
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Page 242

the year indicated, right?
A. That's correct.
Q. Now, it says "Prelude to Zyprexa Marketing Plan." I'm not going to read the whole thing. I'd like to go to -- "Prelude to Zyprexa Marketing Plan. The atypical market is defined by product usage and not by indications." What does that mean? "The atypical market is defined by product usage and not by indications."
A. In terms of the atypical market, meaning antipsychotics, because there's so much grayness between -- the size of the market, I mean, basically what this is meaning is that the size of the market is the sum total of the sales for all antipsychotics.
Q. Well, it says "Prelude to Zyprexa Marketing Plan. The atypical market is defined by product usage and not by indications." Did I read that correctly?
A. You did read that correctly,

Page 243

yes.
Q. But isn't it true that the marketing of the product is supposed to be defined by the indications?
A. Sir, the word there is "market" and not marketing in the atypical -- with atypicals. Basically what this is saying is that, as we talked about earlier, you could have 30 something percent off-label usage. That still is the atypical, the drug, the basket of uses for the drug. That all equates to a total number of sales. Nowhere does it say that that is -- that this plan is meant to capitalize on the sum total of what is used for the drug. All it is saying is that the market for or, excuse me, atypicals, if you took the basket of them, by and large is defined by the total usage of those drugs.
Q. You're not supposed to try to capitalize on the off-label uses, are you?
A. That's correct.

Page 244

Q. It would be wrong for Eli Lilly to try to capitalize through their marketing on off-label usage. That would be wrong, right?
A. Yes, sir.
Q. It would be a violation of law?
A. Yes.
Q. Violation of regulations?
A. That's correct.
Q. So, if Eli Lilly at any time during marketing of Zyprexa attempted to capitalize on this knowledge, that off-label usage defined the market, if they attempted to capitalize on that, they would be in violation of the regulations as you know them?
MR. WASSON: Object to form.
THE WITNESS: I think, sir, what you're talking about in the first sentence, I think it would be helpful to read the second sentence. "Off-label usage is commonplace with atypicals due to

Page 245

the medical necessity of addressing complicated symptomatology. What is deemed a depression diagnosis for one physician may be viewed as bipolar depression for another," hence, looking at the market in a way of looking at its total usage. And so I think it's -- you know, unfortunately, in these therapeutic areas, sometimes it's very, very difficult to put a diagnosis on a patient of schizophrenia/bipolar. In fact, I've been in situations with world thought leaders where there was a very popular case which a lot of people saw on TV about a woman that drowned her children. And there was great debate on whether or not the woman suffered from bipolar or whether she suffered from schizophrenia. So, basically what this is looking at, if you

Page 246

asked the bipolar experts, they would say her diagnosis was bipolar. If you answer -- asked the schizophrenia experts, they would talk about her diagnosis as schizophrenia. So all this paragraph is talking about is it's very difficult to ascertain with any great preciseness what a usage is for.

MR. FIBICH: Objection, nonresponsive.

MR. ALLEN: Objection, nonresponsive.

BY MR. ALLEN:

Q. Ma'am, my only question to you was, and the record will reflect it and I can almost do it verbatim, it would be wrong in the marketing of Zyprexa, in the marketing plan and activities for Eli Lilly to attempt to capitalize on the off-label usage?

A. That's correct.

Q. And just so -- you talked

Page 247

about --

You wanted to read the sentence, and you talked about diagnoses and medical diagnoses. This is under the heading of "Zyprexa Global Brand Plan." It's a marketing document. And it says, "Prelude to Zyprexa Marketing Plan." Isn't that what the heading is?

A. Yes. That's what the heading is.

Q. I was going to read the next sentence. "Off-label usage is commonplace with atypicals due to the medical necessity of addressing complicated symptomatology." Did I read that correctly?

A. Yes. And "It is important to note what while prescriptions are generated for these off-label uses, we have no intention or planned efforts to influence off-label usage."

Q. Ma'am, my only question was, did I read that question -- read that sentence correctly?

Page 248

A. I believe you did read the sentence correctly.

Q. And I'm going to go down. Does this discussion -- let me ask. Does this discussion of off-label marketing make you nervous?

A. Sir, it doesn't. It's a characterization of the market.

Q. Now, the second paragraph: "Zyprexa, like all medicines used to treat mental illness, is prescribed to address a host of symptoms and disorders. These uses extend beyond schizophrenia and bipolar disorder, into areas such as depression." Did I read that correctly?

A. Yes.

Q. First of all, was Zyprexa -- we've already established was not indicated for depression, right?

A. That's correct.

Q. It could not be marketed for depression?

A. That's correct.

Q. It could not be promoted for

Page 249

depression?

A. That's correct.

Q. It would be wrong for you to do so, you, at Eli Lilly?

A. That's correct.

Q. "Into areas such as depression, borderline personality." Did I read that correctly?

A. That's correct.

Q. Zyprexa was not indicated for borderline personality?

A. Correct.

Q. It could not be promoted for borderline personality?

A. Correct.

Q. It could not be marketed for borderline personality?

A. Correct.

Q. "Dementia," we've already established it's not indicated for dementia, right?

A. That's correct.

Q. It cannot be marketed for dementia?

Page 254

Allen, I don't know.
A. I'm sorry. If you can repeat the question.
Q. Yes. You had other target products that were nonsecond generation antipsychotics that you identified as Zyprexa competitors, didn't you?
MR. WASSON: Object to form.
THE WITNESS: I'm trying to go through the --
BY MR. ALLEN:
Q. We'll move on --
A. Okay.
Q. -- because I want to prove it later.
Let me go on here to what I want to read. "Additionally, we face other marketplace pressures such as new competitive entrants, access challenges, litigation, increasing concerns around the impact of weight, and difficulties in maintaining premier share of voice." Share of voice, it's often seen in the documents as SOV, right?

Page 255

A. That's correct.
Q. Share of voice means are you getting what you consider at Eli Lilly your fair share of talk in the marketplace, right?
MR. WASSON: Object to form.
THE WITNESS: No. Share of voice is basically the amount of presence in a marketplace.
BY MR. ALLEN:
Q. Thank you.
And you at Eli Lilly and Zyprexa had the premier share of the voice, and that's what you wanted to maintain, right?
A. Yes.
Q. Thank you.
"Another factor that may heavily influence the marketplace is the results of the United States NIMH," that's the National Institutes of Mental Health, "CATIE Trial," CATIE is an acronym for Clinical Antipsychotic Trials of Intervention Effectiveness, "a research project to evaluate the clinical effectiveness of atypical antipsychotics in the treatment of schizophrenia. The results represent a significant upside or downside for Zyprexa, depending on the outcome."
Did I read that correctly?
A. Yes, you did.
Q. Now, tell the jury why -- what is the CATIE study?
A. The CATIE study was the -- you know, one of the largest studies that was initiated and I believe sponsored by all the different pharmaceutical companies to look at efficacy rates of new -- the newer antipsychotics and I think versus the older antipsychotics.
Q. And you said, and I'm paraphrasing, it was up on the board a minute ago, we're going to go to another page in a second.
The CATIE study results could affect Zyprexa sales either positively or negatively, right?

Page 256

Page 257

MR. WASSON: Objection to form.
THE WITNESS: That's correct.
BY MR. ALLEN:
Q. What was the result of the CATIE study? Do you know what the results on the CATIE study on effectiveness has been?
A. You know what, I left my position prior to the CATIE results, but my understanding is they were quite positive for Zyprexa.
Q. So, it is your understanding the CATIE results were quite positive?
A. I believe I read that. I couldn't tell you for sure because I was no longer in the job.
Q. All right.
So, you wouldn't consider yourself an expert then?
A. I wouldn't, sir.
Q. Are you familiar, by the way, with the fact that the studies that

hyperglycemia, it would affect your sales? Didn't you know that?

A. Did we know that if there was a warning for diabetes that that could impact sales? Is that the question?

Q. Yes, ma'am.

A. Sure, yes.

Q. Why would a warning about diabetes impact sales?

A. A warning about anything could impact sales because, again, looking at the patients and the characteristics of those patients, everyone comes with their own set of medical considerations that a warning can have implications for certain individuals with those medical conditions.

Q. So, a warning about a medical condition would impact sales because doctors would be less likely to prescribe it, and patients would be less likely to take it with a warning, correct?

MR. WASSON: Object to form.

THE WITNESS: No, sir, I don't think that's a fair characterization. Again, I think I referenced earlier that whether or not a physician prescribes and a patient takes a medication is based on so many factors, what the condition is, whether or not there are alternate treatments, whether they've tried those alternate treatments, what the potential benefit is relative to the risk.

BY MR. ALLEN:

Q. You at Eli Lilly, you said you knew -- you said in one of your answers that Eli Lilly knew a warning about diabetes would affect sales. When did you learn that?

A. When did I learn that a warning about diabetes could impact sales? When did I learn that?

Q. Yes, ma'am.

A. Boy, it's something that I

don't think anyone had to tell me that. One could surmise a warning about anything could impact sales. You wouldn't even have to be an expert in the area to know. If you know anything about pharmaceuticals, a warning, information in the warning could impact sales just like information on efficacy would be a positive -- it could be a positive impact.

Q. So, what you're saying is you wouldn't even have to be in the industry, it was just good old common sense that if there was a warning in the package insert, you knew from your experience and common sense that it would impact sales? Is that what you're telling me?

MR. WASSON: Object to form.

THE WITNESS: I said in general terms that information in a warning could have the potential to impact sales and, again, a number of factors would have to be

taken into consideration.

BY MR. ALLEN:

Q. Can you remember or tell this jury when you knew that a warning about diabetes or hyperglycemia, when you knew that warning would impact sales in regard to Zyprexa. Can you tell us an approximate date or year?

A. I think as I mentioned earlier, I -- no. A date or year? Absolutely not. I could have said that the first day I started work that, you know, again, something in the warning has the potential to impact sales.

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(Whereupon, Deposition Exhibit Torres-11, "Scenario & Contingency Planning Session U.S. Zyprexa Brand Team - June 12, 2003" ZY206555623 - ZY206555626, was marked for identification.)

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BY MR. ALLEN:

Q. Yes, ma'am. Let me hand you

Page 398

My question was, you in global research, global marketing, in your job, while you were on the global marketing team, conducted market research on hyperglycemia, your department, did it not?

A. I would imagine that questions were answered certainly in our brand equity in terms of associations with what was associated with Zyprexa. We could determine things, especially weight, with something that was associated with Zyprexa. So, in terms of overarching research, characteristics of the profile would come up.

Q. Ma'am, just so the record is clear, I didn't prepare this document. People at Eli Lilly did. This isn't talking about weight. It's talking about hyperglycemia and diabetes, isn't it? Hyperglycemia and diabetes, correct?

A. That is what it says.

Q. And it goes on to say after it gives a list, "To maximize Zyprexa's

Page 399

success in the market, it is critical that we actively address the issue." Did I read that correctly?

A. You did read it correctly, yes.

Q. Okay.

Look at the next paragraph. "The overall goals of the team are the following:"

Now, when did you become a member of the team?

A. It was later in the -- I don't know if it was April/May, something like that.

Q. It was right after March, wasn't it?

A. I can't tell you --

MR. WASSON: Object to form.

THE WITNESS: I can't -- it might have been that week, you know. It could have been the same week as this. I mean, it was --

BY MR. ALLEN:

Q. It's been represented to me,

Page 400

ma'am, this came from your files. Do you recognize this document?

A. No.

Q. Okay.

But you would agree that you were on this global marketing team at or near this time of this report of March 30, 2001, right?

MR. WASSON: Object to form.

THE WITNESS: Sure.

BY MR. ALLEN:

Q. Right.

So, the goals, unless they change in a day, the overall goals of the team were as follows:

What's the number one goal of the global marketing team? Let's read it together. "Stop hyperglycemia/diabetes from becoming a Top 10 Attribute influencing prescribing." Did I read that correctly?

A. You did, sir.

Q. Right.

Now, the number one goal was

Page 401

not to warn physicians about the potential of weight gain, hyperglycemia and diabetes, was it?

A. Number one goal?

Q. Yes, ma'am. Was it to warn physicians about diabetes? Yes or no?

A. No.

Q. Was it to warn physicians about weight gain? Yes or no.

A. What goals are you referring to?

Q. The goal listed in this document.

A. The goal is referring to -- I mean, the overall goal is from a global standpoint, and there's actually nothing wrong with this unless you try to twist it around. Goal number 1, "Stop hyperglycemia/diabetes from becoming a Top 10 attribute influencing prescribing." It obviously is a factor, hyperglycemia, to be considered or weight gain to be considered, but, I mean, the goal is to have the prescribers consider

the sum total of the benefits of the product and --

Q. Well, I don't see that listed. You just said the goal was to have the prescribers consider the sum total of the product. Tell me in this document where that is listed as a goal.

A. You asked me to give my opinion about what this means, and I'm telling you. "From becoming a Top 10 attribute influencing prescribing." There are a lot of things that influence prescribing.

Q. And you didn't want --

A. Sometimes they can be very negative things or they can be very positive things. And, again, going back to something I've said, you know, a handful of times now, what a prescriber will do is look at the sum total of an offering. If all they hear about are things like hyperglycemia and diabetes, will that impact prescribing?

Absolutely. If they also hear, though,

about positive things such as efficacy parameters, that is something we wanted to make sure was communicated to the physicians.

MR. ALLEN: Just to protect the record, I'm going to object as nonresponsive. I may withdraw it later.

BY MR. ALLEN:

Q. Ma'am, you said doctors will look at the sum total of information. Is that what you just said?

A. Is that what -- I did say that.

Q. Yes. One thing your goal was in the global marketing team is when doctors look at the sum total of information, you didn't want hyperglycemia or diabetes to be even in the top ten things they'd look at, did you, ma'am?

MR. WASSON: Object to form.

BY MR. ALLEN:

Q. You said "Stop

hyperglycemia" and "diabetes from becoming a top 10 attribute influencing prescribing." Correct?

A. I think the key words are "influencing prescribing," which means influencing the choice.

Q. And you wanted to stop diabetes and hyperglycemia from influencing that choice, correct?

A. From being the overarching things that they considered.

Q. It doesn't say overarching. It's from being even in the top ten things they consider, correct?

A. Sir, I can't tell you what the person meant. But I could tell you, you're asking my opinion, you've given me a document, I have stated my opinion. Why did he choose top 10 and not top 5? How about top 20? I think with the sentiment of the sentences, we need to make Zyprexa seen in the sum total of its attributes. Are some of those attributes negative? Yes. Are there a lot of

attributes positive? Yes. But in the sum total, what are the top attributes physicians associate with Zyprexa, the goal was to ensure that those positive things about Zyprexa were known and communicated.

MR. ALLEN: Ma'am, I object as nonresponsive. We need to take a break to change tapes.

THE WITNESS: Okay.

THE VIDEOTAPE TECHNICIAN: This completes videotape 4. Off the record.

MR. ALLEN: On the transcript record, I'm informing counsel I'm going to request some additional time, probably about 30 to 45 minutes.

I'm also going to inform counsel that the next question I'm going to ask the witness when we return from the break, so you can prepare her for her answer, is the question of whether or not their

Jack Jordan, who is head of the U.S. affiliate marketing, that you made any corrections or criticisms of the e-mail, did you?

A. I wouldn't see that as material. It's just a person with one year marketing using a statement. I wouldn't see that as material. The use of the term "comparable rates" was used in the broader context.

Q. Right.

And so you also, obviously, didn't disagree with what was known in global marking as of the time this e-mail was sent that "Zyprexa does lead to increases in appetite, which can contribute to obesity, a major risk factor in developing diabetes"? Is that correct?

A. Yes.

Q. So, it was known that Zyprexa could lead to weight gain, which was a major risk factor in developing diabetes, correct?

A. Weight gain is a major risk factor in developing diabetes, yes.

Q. Let's read it together again.

"Zyprexa does lead to increase in appetite, which can contribute to obesity, a major risk factor in developing diabetes," correct?

A. That's correct.

Q. Right.

And that was known -- well, let's say at least at by -- we'll go back to some other ones even earlier.

But by September of 2002, in global marketing, Mr. Fiola and to all the affiliates to whom he sent it, and to all the people whom you sent it, including Dr. Breier, it was known that Zyprexa does lead to increase in appetite, it does contribute to obesity, and it is a major risk factor in developing diabetes, correct?

MR. WASSON: Object to form.

THE WITNESS: There was a whole chain there.

BY MR. ALLEN:

Q. Yes, ma'am, there certainly is.

A. Yes. Zyprexa can potentially lead to weight gain, yes. Is weight gain a major risk factor for diabetes? Yes.

Q. One thing leads to another?

A. Not necessarily.

Q. Hip --

A. No. A lot of people are obese, significantly overweight and do not have diabetes. So, that's an incorrect mischaracterization of causal effect with diabetes and weight.

Q. Oh, so you think that if some people are overweight and don't get diabetes, and some people are obese and do get diabetes, that's just, what, tough luck?

MR. WASSON: Object to form.

THE WITNESS: Is getting diabetes tough luck?

BY MR. ALLEN:

Q. Yes, ma'am.

A. Getting diabetes is tough luck. Getting diabetes is not something to be coy about, sir. Diabetes is a serious condition. It impacts the quality of individuals' lives very significantly.

Q. It certainly does.

A. So, it's more than tough luck.

Q. By the way, obesity, which you've clearly stated now, as it says right here, I'm going to use y'all's company's words, I don't want to use my words, Obesity is "a major risk factor in developing diabetes." Is that correct?

A. Yes.

Q. Okay.

Now, if obesity is a major risk factor in developing diabetes and Zyprexa can lead to obesity, we know that, right?

A. Yes.

Page 558

"The presenter of this activity has indicated that there is a relationship which, in the context of this presentation, could be perceived as a real or apparent conflict of interest," for example, "(...honoraria), but does not consider that it will influence the presentation of this continuing education activity." Did I read that correctly?

A. I'm sorry. What page is that?

MR. WASSON: Page 3.

MR. ALLEN: Can you shut that door, please.

THE WITNESS: Yes. You read that paragraph correctly.

BY MR. ALLEN:

Q. Right.

Eli Lilly, if you look on the very last page of this document entitled "Antipsychotic Therapy in Children and Adolescents," was supported by a educational grant from Eli Lilly & Company, right? Very last page?

Page 559

A. "Made possible by an unrestricted educational grant."

Q. Here's what it says. I'll read it slowly. "The continuing educational materials" contained in this activity" were made possible by an unrestricted educational grant from Eli Lilly & Company." Did I read that right?

A. Yes, you did, sir.

Q. Now, why would Eli Lilly provide an educational grant concerning the use of Zyprexa in adolescents and children? Why would they do that, so doctors would prescribe it to adolescents and children?

MR. WASSON: Objection to the form.

THE WITNESS: So, why would Lilly give a grant?

BY MR. ALLEN:

Q. For Zyprexa training or continuing medical education for adolescents and children.

A. That's not what it says, though.

Page 560

MR. WASSON: Objection, form.

THE WITNESS: It says antipsychotic therapy in children and adults. It doesn't say Zyprexa.

BY MR. ALLEN:

Q. Ma'am, we were almost through, but we'll read exactly what it says. First it was supported by an "educational grant from Eli Lilly," right? On page 3, right?

A. Yes.

Q. Under there it says, "By completing this activity, participants will be able to: Discuss the prevalence and epidemiology of childhood onset schizophrenia." Does it say that?

A. Yes.

Q. And then it goes on, "Identify childhood psychiatric disorders that are effectively treated with antipsychotics." Do you see that?

Page 561

A. I do see that.

Q. Now, this Zyprexa was not indicated for any childhood psychiatric disorder, was it?

A. Zyprexa? No.

Q. "Discuss the efficacy and safety of atypical antipsychotics in child and adolescent psychiatry." You weren't even supposed to be detailing child and adolescent psychiatrists, were you, on Zyprexa?

A. Detailing, no.

Q. Why was Eli Lilly providing an educational grant to train physicians on how to use second generation antipsychotics in children and adolescents?

A. One, I don't know about this program, but why would Lilly provide an unrestricted grant? There was a huge market need. Would physicians want to know or psychiatrists want to know about antipsychotic use in children? Of course they would. Why? Huge unmet need. Huge

unmet need. In fact, I think it was Risperdal just recently after all of these years received an indication for the use of Risperdal in children with autism. There's a huge need. Part of a pharmaceutical's responsibility is to support the community. This is nothing more -- I don't know who was behind this, what their intent is, but if you're asking me, give my opinion on this, it's about supporting the community. It's an unrestricted grant. "Unrestricted" meaning you don't control the content.

MR. ALLEN: Objection, nonresponsive.

BY MR. ALLEN:

Q. But, in fact, you did control the content. You gave an honoraria to the person speaking at this seminar, did you not?

MR. WASSON: Objection to form.

THE WITNESS: Sir, I don't know about this program. I don't

know the person. An unrestricted grant means you provide funding for something, and it's hands off. That's what "unrestricted" means.

BY MR. ALLEN:

Q. That's what it's supposed to mean, isn't it?

A. That's what it means.

Q. Well, when you pay the speaker who is going to speak, don't you think that's more than hands off? That's actually hands on?

A. Sir, I don't know about the speaker. I don't know the individual. I don't know who wrote a check to support the program. You handed me something. I gave you my comments. It doesn't say Zyprexa. It says "antipsychotic therapy." It says "Unrestricted grant." That's all I can tell you.

Q. Yes, ma'am. I have one more question for you, and I'm going to pass you to Mr. Fibich.

A. How long is this going to go

on?

Q. Ma'am, I have one more question for you, and I'm passing you to Mr. Fibich.

A. I need to have a time out.

Q. Ma'am --

A. No. I need a break. I'm sorry.

MR. ALLEN: I'm going to let you ask the question. I'm going to pass the witness to Mr. Fibich.

MR. WASSON: Take a break first.

THE VIDEOTAPE TECHNICIAN: Off the record at 6:23 p.m.

- - -

(Whereupon, there was a recess from 6:23 p.m. until 6:26 p.m.)

- - -

THE VIDEOTAPE TECHNICIAN: Back on the record at 6:26 p.m.

- - -

EXAMINATION

- - -

BY MR. FIBICH:

Q. Ms. Torres, we met earlier today, but, again, for the record, my name is Tommy Fibich, and I have some questions for you.

First of all, with respect to your participation here today, you're being represented by a lawyer that is being paid for by Lilly; is that correct?

A. That's correct.

Q. How did that arrangement come to be? Did you ask them to provide you a lawyer?

A. No. No.

Q. How did it come to be that Lilly is providing you a lawyer?

A. Basically I was contacted and instructed that I need to give a deposition. I came to the preparation, I came today, and this is where I'm at.

Q. Did you think you needed a lawyer?

MR. WASSON: Object to form.

THE WITNESS: Seemed like

06-5630 CI

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

DEFENDANT ELI LILLY AND COMPANY'S NOTICE OF FILING MOTION IN LIMINE TO EXCLUDE CERTAIN TESTIMONY OF THE STATE'S EXPERTS UNDER SEAL

COMES NOW Defendant Eli Lilly and Company ("Lilly") and files its Motion in Limine to Exclude Certain Testimony of the State's Experts, under seal, attached to this notice. The exhibits to the Motion have been deemed confidential.

DATED this 4th day of February, 2008.

PEPPER HAMILTON LLP
Nina M. Gussack, admitted *pro hac vice*
Andrew R. Rogoff, admitted *pro hac vice*
Eric J. Rothschild, admitted *pro hac vice*
and
LANE POWELL LLC
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Case # _____ CR/CI
Case Title: _____
Type of Document Enclosed: _____
Date Filed: _____ Judge: _____

SEALED

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Comments: filed 2/5/08

TF-330 (6/99) (TCB Fl. Pink, 4"x5½")

See Judge Rindner's 6/13/08 order
see pages 20 & 21, #15
documents unsealed
Clerk 8/11/08

006413

Pages 6413A-6435

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

[FILED UNDER SEAL]

DEFENDANT ELI LILLY AND COMPANY'S MOTION IN LIMINE TO EXCLUDE CERTAIN TESTIMONY OF THE STATE'S EXPERTS

COMES NOW Defendant Eli Lilly and Company ("Lilly") and hereby requests that the Court bar the State's experts from offering opinions regarding the knowledge or beliefs of the FDA, Lilly or individual physicians. Such opinions are not proper expert testimony.

In his deposition,[1] Dr. John Gueriguian, the State's regulatory expert, testified repeatedly as to what the FDA "knew" or "believed." Because such testimony crosses the boundaries of his expertise, this is not proper expert testimony. Accordingly, defendant Eli Lilly and Company ("Lilly") requests that this Court join several other courts that have barred such testimony by Dr. Gueriguian.

The following excerpts provide examples of Dr. Gueriguian's testimony about what the FDA "knew" or "believed":

> Q. Okay. And your position is that this document suggests that the FDA believes the label should have been written differently than what was ultimately written, I guess, in 2003?

[1] Dr. Gueriguian's deposition, taken in the Zyprexa MDL, became part of the record before this Court when it was incorporated by reference in his expert report, originally produced in the MDL and produced again in this litigation.

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A. (Dr. Gueriguian) The FDA, being a scientific organization, knows and doesn't believe. . . . .

Q. Is it -- based on your reading of this document, is it your impression that the FDA knew that Zyprexa had an increased risk of diabetes and hyperglycemia relative to other atypical antipsychotics?

A. The FDA knew the following. Number one –

Q. Just answer my question. Do me a favor and answer my question.

A. I am answering your question, sir. I am answering your question. Please let me answer.

Q. Go ahead.

A. Otherwise -- the FDA knew the following. I'm answering your question precisely.

Q. Okay.

A. Number one, there wasn't enough studies performed by Lilly or anybody else. And it says published literature is insufficient. Number two, the FDA believes that the preponderance of the evidence appears, and I'm quoting, to offer a strong support for a drug-related event, end of quote.[2] Thirdly, the FDA knew, because of this ping-ponging and coming back and forth and arguing and shuttling, that Eli Lilly didn't share that opinion, ...[3]

---

[2] Dr. Gueriguian's selective quotation, from a 2001 FDA "Review and Evaluation of Clinical Data" (attached as Exhibit A), fails to convey the entire thrust of the language he quotes. The language actually reads, "The published cases of positive dechallenge appear to offer strong support for a drug-related effect, but one must also consider that diabetics can experience "honeymoon" periods where insulin requirements decrease following initial treatment of diabetes. The positive rechallenge cases do provide stronger evidence of a drug-related effect on glucose. Experimental data suggests that antipsychotic exposure may be associated with insulin resistance **but these hypotheses have not yet been fully explored**." Exhibit A, at 10 (emphasis added).

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Similar allusions to what the FDA "knew" or "believed" or "intended" appear later in the transcript of Dr. Gueriguian's deposition. Opinions regarding the intent, motives, or state of mind of corporations, regulatory agencies and others, have no basis in any body of knowledge or expertise and lie outside the bounds of expert testimony.[4] In fact, several other courts have precluded Dr. Gueriguian from expressing such opinions for this reason.[5] Further, "surmising as to what physicians would do with different information is purely speculative and not based on expert knowledge."[6] Accordingly, the State's experts, including but not limited to Dr. Gueriguian, should be precluded from offering opinions as to the knowledge, intent, beliefs, or motives of the FDA, of Lilly, or of physicians. In addition, the State should be precluded from introducing or referring to excerpts of any deposition containing such testimony.

CONCLUSION

For the reasons set forth above, Lilly requests that the Court order any testimony offering opinions as to the knowledge, intent, beliefs, or motives of the FDA, Lilly or

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(. . . continued)

[3] Transcript of the Deposition of John L. Gueriguian, at p. 131, ln.19 – p. 132, ln. 1; p. 132, ln. 22 – p. 134, ln. 5. (A copy of the relevant portion of the transcript of Dr. Gueriguian's deposition is attached as Exhibit B.)

[4] *See In re Baycol Products Litigation*, 495 F. Supp. 2d 977, 1000-01 (D. Minn. 2007). *See also In re Diet Drugs*, 2001 WL 454586 at **2, 24 (E.D. Pa. Feb 1, 2001); *see also In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 546-47 (S.D.N.Y. 2004); *DePaepe v. Gen. Motors Corp.*, 141 F.3d 715, 720 (7th Cir. 1998); *Taylor v. Evans*, No. 94 Civ. 8425 (CSH), 1997 WL 154010, at *2 (S.D.N.Y. Apr. 1, 1997).

[5] *In re Diet Drugs*, 2001 WL 454586 at **2, 24 (precluding Dr. Gueriguian from testifying as to the intent of a drug company and beliefs of FDA officials). *See also, In re Rezulin*, 309 F. Supp. 2d 531, 546-47 (S.D.N.Y. 2004); *DePaepe v. General Motors Corp.*, 141 F.3d 715, 720 (7th Cir. 1998); Taylor, 1997 WL 154010, *2 (S.D.N.Y. 1997).

[6] *In re Rezulin*, 309 F. Supp. 2d at 551 (citation omitted).

physicians, by the State's experts, including but not limited to Dr. Gueriguian, be excluded at trial.

DATED this 4th day of February, 2008.

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Andrew R. Rogoff, admitted *pro hac vice*
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I certify that on February 4, 2008, a copy of The foregoing was served by hand on:

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A B

Review and Evaluation of Clinical Data

NDA: 19-758, 20-592, 20-272, 20-639
Sponsor: Novartis
Drugs: Clozaril (clozapine), Zyprexa (olanzapine), Risperdal (risperidone), Seroquel (quetiapine)
Material Submitted: OPDRA Consult, Division Literature Review
Subject: association with diabetes mellitus
Correspondence Date: 8-26-99, 12-17-99
Date Received: 8-27-99, 1-11-00
Date Review Completed: 5-17-01

1 Background

Dr. E. Koller, a medical officer in the Division of Metabolic and Endocrine Drug Products, along with others presented a poster at the annual meeting of The Endocrine Society in June 1999 describing the association of clozapine therapy with new onset diabetes mellitus (DM) and exacerbation of pre-existing DM. As part of the follow-up of this signal, the Division requested that the Division of Drug Risk Evaluation I (DDRE-1) perform a search of AERS for reports of hyperglycemia, DM, and diabetic ketoacidosis (DKA), and non-ketotic hyperglycemic hyperosmolar syndrome (NKHHS) associated with clozapine and the other "atypical" antipsychotics (olanzapine, risperidone, and quetiapine). The division received this consult on January 11, 2000.

Because the original AERS searches were performed over 18 months prior to the completion of this review, we requested that DDRE-1 perform a follow-up search to identify reports DM, DKA, and NKHHS that have been submitted to AERS in the intervening months. Cindy Kortepeter, Pharm.D., a safety evaluator in DDRE-1, performed this search on 3/9/01. Dr. James Knudsen of this division reviewed these case reports and a summary table of these cases is provided below.

In order to assess the possibility that DM is associated with use of the older antipsychotics as well, we also requested that DDRE-1 perform a search for DM, DKA, and NKHHS associated with the three most commonly used antipsychotic drugs in the 1980's: chlorpromazine, haloperidol, and thioridazine. Dr. Jerry Boehm of this division reviewed these case reports and his findings are included below.

Finally, most of the papers in the medical literature addressing the issue of hyperglycemia, DM, and its complications related to antipsychotic drugs are case reports and case series. Therefore, I will include in this review Dr. Boehm's summary of an exhaustive search of the literature regarding this adverse event.

2 OPDRA Consult

The OPDRA consult includes an overall executive summary and individual reviews of each of the four atypical antipsychotics marketed at the time of the AERS search:

clozapine, risperidone, olanzapine, and quetiapine. AERS was searched on the following days for each of the drugs: end of 7/99-clozapine; end of 6/99- risperidone; 7/28/99-olanzapine; 9/16/99- quetiapine. When the AERS system was searched by terms related to diabetes mellitus, clozapine (#2), olanzapine (#5), and risperidone (#10) were among the ten marketed products with the most reports in the system.

This review will first present the OPDRA reviewers' (Dr. Wysowski and Dr. Bennett) summary table of case numbers and rates, and then it will describe the postmarketing experience with each drug individually.

2.1 Summary Table

Table 1 of the consult addressing the association of atypical antipsychotic drugs and DM summarizes the pertinent points of the case series for each drug. An abbreviated form of the table follows below in Table A[1]. Please note that a prescription length of 30 days was used to calculate the person-years of exposure for risperidone, olanzapine, and quetiapine. A prescription length of 16 days was used for clozapine due to the standard shorter duration of prescription that results from the weekly WBC monitoring requirements.

Table A. Summary of Case Series (adapted from Table 1 of the consult)

		Clozapine	Risperidone	Olanzapine	Quetiapine
Year marketed		1991	1994	1996	1997
Total U.S. outpatient prescriptions		11.4M	14.9M	8.0M	1.1M
Total # AERS reports		17,631	10,607	5,380	484
Reporting period		Drug launch-7/99	Drug launch-6/99	Drug launch-8/99	Drug launch-8/99
	US Background Rate[6]	n [redacted]	n [redacted]	n [redacted]	n [redacted]
New-onset DM, U.S. cases	F- 276 M- 53	90 [redacted]	55 [redacted]	81 [redacted]	1 [redacted]
New-onset DM, with DKA	45	27* [redacted]	10 [redacted]	37 [redacted]	1 [redacted]
New-onset DM, with NKHHS	7	6** [redacted]	4 [redacted]	5 [redacted]	0 [redacted]
# Deaths		3	3	5	1

[6] Data for the new-onset DM cases is from the National Diabetes Data Book, NIDDK, NIH, 1995; the female range is for ages 25-44; the male range is for <=44. Data for the

[1] In the process of checking reporting rate calculations prior to requesting IMS clearance for outside use of the data, the reporting rate calculations for quetiapine were found to be inaccurate. The correct values are entered in the table above.

FDACDER 002155

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EXHIBIT A
PAGE 2 OF 15

B

DKA and NKHHS incidence comes from the National Hospital Discharge Survey, NCHS, 1997.
* per 100,000 person-years; * w/ BS>700 (13 w/ acidosis); ** diagnosed (27 possible)

In her case series for each drug, Drs. Wysowski and Bennett point out the many caveats that must be considered when interpreting the cases of DM reported to be associated with this group of drugs. These include the following:

- Underreporting may be substantial
- Reports generally describe the temporal relationship between the initiation of a drug and the *diagnosis* of diabetes rather than its *onset*, so patients who were reported to be new-onset cases could have been prevalent cases.
- Information on risk factors for DM was not reported uniformly
- Information on drug-related weight gain was not reported uniformly
- Schizophrenia itself may be associated with an elevated risk for diabetes

2.2 *Clozapine*

Because Dr. Koller's presentation reviewed the AERS reports of hyperglycemia-related AEs associated with clozapine use, Dr. Wysowski's review of these same reports focused primarily on how her evaluation differed from Dr. Koller's. Dr. Wysowski's counts of cases of new onset DM and exacerbation of DM were similar to Dr. Koller's; however, their assessments of the hyperglycemia cases differed substantially. Because the hyperglycemia case reports were generally of poor quality (lacking details), Dr. Wysowski did not consider them further.

Dr. Koller identified 92 reports describing newly diagnosed diabetes. The mean age of these patients was 39.2 (range 15-77). About one quarter of patients presented with diabetes in the first month after clozapine initiation and about one half presented within three months (range: two days to five years). Twenty-seven newly diagnosed patients presented with DKA. Of 53 patients who discontinued clozapine, follow-up was reported in 32. Twenty-seven patients reported positive dechallenges. Of six patients who were rechallenged, five reported deterioration of glycemic control after re-exposure to clozapine.

Using the number of dispensed outpatient prescriptions and the average prescription length of 16 days (IMS data) to calculate the person-time exposure, the rates of new-onset DM, alone and associated with DKA or hyperosmolar coma are seen in Table A above. Dr. Wysowski compared these reporting rates to the rates of new-onset DM, alone and associated with DKA or NKHHS as reported by the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) and the National Hospital Discharge Survey. The reporting rates for new-onset DM alone and new onset DM with DKA or NKHHS is of the same magnitude or one level lower than the corresponding background rate. Dr. Wysowski points out that extensive underreporting could account for the reporting rates being lower than the background rates.

Dr. Wysowski concludes that despite numerous spontaneous reports, the causality of DM by clozapine cannot be determined on the basis of these reports alone. She notes that

FDACDER 002156

006419

EXHIBIT A
PAGE 3 OF 15

there is some evidence that schizophrenic patients may have a higher background incidence of DM, and that they may have a higher incidence of risk factors for DM. She suggests that additional study would be needed to establish causality, but in the interim recommends that DM be made more prominent in the clozapine labeling.

2.3 *Risperidone*

The AERS search identified 41 patients with newly diagnosed DM, ten with newly diagnosed DM and mention of ketoacidosis, and four with newly diagnosed DM and mention of NKHHS. Thirty-eight additional patients developed exacerbation of their diabetes after starting risperidone. The median age of the new-onset patients was 31.5 (range 9-96) and the median treatment duration to presentation was 2.5 months (range two days to two years). About half (22/41) the patients had a risk factor for DM (e.g., family history, weight gain, obesity, alcohol abuse) mentioned in their case report. Fifty-nine percent of patients required medical treatment for the DM; three patients had positive dechallenges.

For the ten patients with newly diagnosed DM and ketoacidosis, median treatment duration to presentation was about six weeks (range seven days to 21 months). Seven patients required hospitalization and two died. One patient each was also diagnosed with neuroleptic malignant syndrome (NMS) and rhabdomyolysis. Six patients were taking concomitant valproic acid. Several patients had risk factors for diabetes.

Four patients presented with hyperosmolar states with glucose measurements in the 875-1700 mg/dl range. The treatment duration to presentation for the three patients with this information reported was 12 days, 60 days, and 14 months. At least three of the patients had risk factors for DM. Three patients were treated and recovered; a fourth patient reportedly died of a pulmonary embolism.

Using the number of dispensed outpatient prescriptions and the average prescription length of 30 days (IMS data) to calculate the person-time exposure, the rates of new-onset DM, alone and associated with DKA or hyperosmolar coma are seen in Table A above. Dr. Wysowski compared these reporting rates to the rates of new-onset DM, alone and associated with DKA or hyperosmolar coma as reported by the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) and the National Hospital Discharge Survey. The reporting rates for new-onset diabetes alone, and new onset with DKA or NKHHS are one to two levels of magnitude lower than the corresponding background rate. Dr. Wysowski points out that extensive underreporting could account for the reporting rates being substantially less than the background rates

2.4 *Olanzapine*

The AERS search identified 81 U.S. reports describing patients with newly diagnosed DM; of the 81 reports, 37 also reported ketoacidosis and five also reported hyperosmolar coma. Additionally, twenty-eight patients developed exacerbation of their diabetes after starting olanzapine.

The mean age of the patients with new onset DM and a presenting blood glucose <500 mg/dl (n=22) was 43 (range 13-70), and the median treatment duration to presentation was about 3.5 months (range: one week to 2.25 years). About half (12/22) of the patients had a risk factor for DM (e.g., family history, weight gain, obesity, alcohol abuse) mentioned in their case report. At least eight patients required medical treatment for diabetes. Two patients had a clearly documented positive dechallenge and three had a negative dechallenge.

The mean age of the patients with new onset DM and a presenting blood glucose >500 mg/dl (n=17) was 48.5 (range 16-78) and the median treatment duration to presentation was about three months (range: two weeks to 11 months). Over half of the patients had a risk factor for DM (11/18) mentioned in their case report. At least eight patients required medical treatment for diabetes. One patient had a positive dechallenge and two had a negative dechallenge.

For the 37 patients with newly diagnosed DM and ketoacidosis, mean age was 39 (range 17-72) and median treatment duration to presentation was about three months (range 11 days to 2 years). Just under half of the patients had a risk factor for DM (17/37) mentioned in their case report. Thirty patients required hospitalization and five died; two of the deaths were due to NMS. Five patients had a positive dechallenge and nine had a negative dechallenge.

Five patients presented with hyperosmolar states with glucose measurements in the 1400-1700 mg/dl range. The treatment duration to presentation for the four patients with this information reported was 14 days, 20 days, 6 weeks, and 1 year. The patient who developed NKHHS after one year had had a daily dose increase from 10 mg to 20 mg one week prior to presentation. Three of the patients had a risk factor for DM mentioned in their case report. All patients were hospitalized and none died. Two patients had a positive dechallenge and two had a negative dechallenge.

Of 41 patients who presented with blood glucose >700 mg/dl, 28 (68%) reported at least one risk factor for DM; this compared to 42/81 (52%) patients overall who reported a DM risk factor. Of the 38 with known ages, 32 were 50 years old or younger.

Using the number of dispensed outpatient prescriptions and the average prescription length of 30 days (IMS data) to calculate the person-time exposure, the rates of new-onset DM, alone and associated with DKA or hyperosmolar coma are seen in Table A above. Dr. Bennett compared these reporting rates to the rates of new-onset DM, alone and associated with DKA or hyperosmolar coma as reported by the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) and the National Hospital Discharge Survey. The background rates for new-onset diabetes alone are 1-2 levels of magnitude higher than the reporting rate for olanzapine. However, the background rates for new onset DM with DKA or NKHHS is only one level of magnitude higher than the corresponding reporting rate. Dr. Bennett points out that underreporting and the method by which prescription numbers are converted to exposure make it difficult to compare reporting rates with background rates

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EXHIBIT A
PAGE 5 OF 15

B

2.5 *Quetiapine*

The AERS search identified one U.S. report describing a patient with a possible case of newly diagnosed DM with DKA; there were reports of two additional patients with pre-existing DM who presented with DKA. The patient was a 28 year old man taking quetiapine for an unknown duration who presented to the emergency department with a recent 10-16 pound weight loss, flu-like symptoms, acidosis, and a serum glucose of 2240 mg/dl. The patient developed ventricular fibrillation and disseminated intravascular coagulation and died.

Using the number of dispensed outpatient prescriptions and the average prescription length of 30 days (IMS data) to calculate the person-time exposure, the rates of new-onset DM, alone and associated with DKA or hyperosmolar coma are seen in Table A above. Dr. Bennett compared these reporting rates to the rates of new-onset DM, alone and associated with DKA or hyperosmolar coma as reported by the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) and the National Hospital Discharge Survey. In the summary table, one case each is identified for new-onset alone and new-onset plus DKA. However, in the text of the consult it appears that the new onset case was a literature case. The background rate for new-onset diabetes with DKA is two levels of magnitude higher than the reporting rate for quetiapine. Dr. Bennett points out that underreporting and the method by which prescription numbers are converted to exposure make it difficult to compare reporting rates with background rates.

3 Older Antipsychotics

As part of the safety team's evaluation of the relationship between atypical antipsychotics and diabetes, we asked DDRE-I to provide the spontaneous reports of diabetes and glucose abnormalities for the older antipsychotics. DDRE-I pulled the spontaneous reports for glucose related abnormalities for the three antipsychotics with the greatest use in the 1980s, namely haloperidol, chlorpromazine, and thioridazine. This document summarizes the reports provided by DDRE-I.

DDRE I forwarded to the division 21 glucose abnormality related spontaneous reports for haloperidol, six for chlorpromazine, and six for thioridazine. Dr. Boehm reviewed the reports, specifically looking for cases of diabetic ketoacidosis, non-ketotic hyperglycemic hyperosmolar coma, incident cases of diabetes or cases with reported glucose elevations greater than 500mg/dL.

3.1 *Haloperidol*

One haloperidol spontaneous report noted elevated glucose and ketosis but the patient was also taking diazoxide and had a history of an insulinoma, complicating interpretation of this report. There was a report of an 88-year-old female with diabetic coma (glucose 500mg/dL) but the report noted that this patient was a diabetic with a history of dietary non-compliance. There was a report of elevated blood glucose (>700mg/dL) in a subject enrolled in a trial comparing risperidone to haloperidol and it was not clear which drug this subject was receiving. The remaining reports noted hyperglycemia, often not

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EXHIBIT A
PAGE 6 OF 15

B

quantified and in some cases in the setting of other events like neuroleptic malignant syndrome, overdose, or following resuscitative attempts, thus complicating the interpretation of the reports.

3.2 *Chlorpromazine*

The division received no spontaneous reports of glucose >500mg/dL, diabetic ketoacidosis, or non-ketotic hyperglycemic hyperosmolar coma for chlorpromazine. There was one report of incident diabetes but this followed a 12-year exposure to chlorpromazine.

3.3 *Thioridazine*

We received one thioridazine spontaneous report of diabetic ketoacidosis (glucose 1,323mg/dL) in a patient with neuroleptic malignant syndrome. There was also a report of a patient who developed diabetes three months after starting thioridazine (no glucose reported) and the patient was reported to be "recovering after withdrawal".

3.4 *Discussion*

A review of the available spontaneous reports for the older antipsychotics did not strongly suggest glucose abnormality associations. Despite the spontaneous report findings with the newer antipsychotic agents, we did not identify non-confounded reports of new onset DKA or hyperglycemic non-ketotic hyperosmolar coma for the older agents. Whether the absence of such reports is due to differences in risk for these events between the newer and older agents, or differences in reporting is not known.

4 March 2001 Update

Since approximately 18 months passed since the original search of the AERS database, the division requested a follow-up search for cases of DM and its complications associated with the atypical antipsychotic agents. James Knudsen, MD, Ph.D. reviewed these cases using the same criteria as the safety evaluators who prepared the original consult.

Table B. Unduplicated U.S. Cases of Altered Glucose Metabolism Associated with Antipsychotic Drug Exposure from the AERS Database: 7/99-3/01 and Reporting Rates

Reporting period: 7/99-3/01	Clozapine		Risperidone		Olanzapine		Quetiapine	
Total US outpatient prescriptions*	2.5 million		10.4 million		9.0 million		3.3 million	
	n	[redacted]	n	[redacted]	n	[redacted]	n	[redacted]
New-onset DM	52	[redacted]	14	[redacted]	95	[redacted]	12	[redacted]
N-O DM, with DKA	8	[redacted]	1	[redacted]	36	[redacted]	3	[redacted]
N-O DM, with NKHHS	5	[redacted]	1	[redacted]	7	[redacted]	1	[redacted]
Deaths	10		2		7		2	

*Source: IMS HEALTH National Prescription Audit Plus™
#Rate in cases per 100,000 person-years

FDACDER 002160

006423

EXHIBIT A
PAGE 7 OF 15

Predictably, the reporting rates have gone down since the original consult. Over time, use of new drugs increases and reporting of adverse events decreases as they are recognized as being drug-related. Two observations can be made, though: 1) cases have been reported for all four of the atypical antipsychotic drugs; 2) reporting rates continue to be substantially higher for clozapine and olanzapine as compared with risperidone and quetiapine.

5 Summary of Literature Review

As part of the safety team's evaluation of the antipsychotic/diabetes mellitus relationship, we reviewed the medical literature on this topic. Lilly submitted many of the reviewed publications as part of their response to the division's request for information about olanzapine and diabetes. We identified additional relevant articles from a search of Pub-Med.

5.1 *Schizophrenia and diabetes*

We did not identify any publications that provided incidence or prevalence data indicating that untreated schizophrenic patients were at increased risk for glucose abnormalities, yet it is clear that investigators were examining this question via experiments. Published articles from the 1920s-1950s documented experiments testing glucose tolerance and response to insulin in schizophrenics. Although investigators reported findings suggestive of resistance to insulin and abnormal glucose tolerance[1-4], these findings were not uniform and there are difficulties in comparing results across studies due to differences in psychiatric diagnostic terms describing the populations studied, and variations in study designs.

5.2 *Diabetes and Antipsychotics*

5.2.1 Typical Antipsychotics

5.2.1.1 Humans

In the years after chlorpromazine became available and was being used to treat schizophrenics, investigators reported that chlorpromazine might be associated with increased risks of hyperglycemia and diabetes. One article reported that the prevalence of diabetes on a psychiatric service increased in the years after chlorpromazine and other phenothiazines became available, and that a higher percentage of those treated with a phenothiazine had diabetes compared to those not treated with a phenothiazine[5]. Experiments were conducted wherein normal volunteers and schizophrenics, some with diabetes and others without, were exposed to a chlorpromazine for varying lengths of time. They then underwent glucose tolerance testing, had response to iv administered insulin measured, or both. Results offer conflicting evidence of chlorpromazine effect on glucose metabolism with decreased responses to insulin or decreased glucose tolerance in some studies[6,7] and little or no effect on response to insulin or glucose challenge in another study[8].

As more antipsychotic agents became available for the treatment of schizophrenia, studies were conducted to look at their effects on glucose and to compare the effects of new drugs with previously available drugs. In separate short-term experiments, neither haloperidol[9] nor sulpiride[10] appeared to affect glucose. Investigators reported what appeared to be unexpectedly high prevalences of glucose abnormalities among patients chronically treated with perazine[11], fluphenazine[12] and pimozide[12], although the lack of non-treated control groups makes interpretation of the results difficult.

In addition to experimental data, investigators reported cases of patients who developed glucose abnormalities following treatment with chlorpromazine or other antipsychotics[13-15]. We did not identify reports of typical antipsychotic treatment associated diabetic ketoacidosis or non-ketotic hyperosmolar coma from our PubMed search.

5.2.1.2 Animal Studies

Animal studies were conducted to examine the effect of chlorpromazine and other phenothiazines on glucose, and the effect following adrenalectomy or administration of drugs that act on the sympathetic nervous system. In several species, phenothiazines appeared to have an effect on glucose and or insulin release[16-20], although the validity of the animal models is unclear and there are concerns that the techniques used (e.g., intraperitoneal administration) in some of the experiments could have contributed to the reported findings[21].

5.2.2 Atypical Antipsychotics

5.2.2.1 Clozapine

In 1994 a case report was published describing the development of diabetic ketoacidosis temporally related to the initiation of treatment with clozapine[22]. Since then there have been additional case reports and case series describing glucose abnormalities ranging from worsening glycemic control to diabetic ketoacidosis or non-ketotic hyperosmolar hyperglycemia in patients treated with clozapine[23-33]. There are reports describing improvement or normalization of blood glucose, allowing cessation of hyperglycemic therapy following withdrawal of clozapine[23,24,30,32], and reports of positive rechallenges characterized by increases in blood glucose after clozapine therapy was reintroduced[22,26,28].

Several groups of investigators have attempted to further examine the risk of hyperglycemia associated with clozapine. In one study, investigators found that the prevalence of diabetes and glucose intolerance was higher among 60 schizophrenics treated with clozapine (12% and 10% respectively) compared to 63 schizophrenics treated with conventional neuroleptics (6% and 3% respectively)[34]. In another study, investigators found that on-clozapine mean serum glucose at 60 minutes following a glucose load was higher for six schizophrenics compared to their pre-treatment values[35]. Another group of investigators found a correlation between insulin levels and clozapine levels but no correlation between insulin levels and classical antipsychotic levels, which they interpreted as evidence supporting clozapine-induced insulin resistance[36]. Another group of investigators reported on a cohort of 82 schizophrenics with no history of

FDACDER 002162

EXHIBIT A
PAGE 9 OF 15

diabetes and normal baseline glucose results who were started on clozapine treatment[37]. Over the five year observation period, 36% were diagnosed with diabetes mellitus. Further analysis found that sex, weight, change in weight, BMI, change in BMI, clozapine dose, and valproate use were not significant risk factors for the development of diabetes, but that age was a significant risk factor. The investigators noted the lack of comparator data and acknowledged the need for more information about the background risk of diabetes among schizophrenics.

5.2.2.2 Olanzapine, Quetiapine, Risperidone

As with clozapine, there have been reports of glucose abnormalities among patients treated with the other recently approved atypical antipsychotics. There have been published case reports[38-42] and a case series[43] describing glucose abnormalities ranging from poor glucose control to diabetic ketoacidosis in patients treated with olanzapine. Like clozapine, there are reports of improvement in glucose control following olanzapine withdrawal[39,40,41,43] and reports of worsening of glucose following reintroduction of olanzapine[38,43]. There have been two case reports of glucose abnormalities among quetiapine users[44,45] and one case report of diabetic ketoacidosis in a risperidone user[46]. In addition to the reports for single drugs described above, there have been three case series published where investigators described a range of glucose abnormalities in patients treated with a variety of atypical antipsychotics including clozapine, olanzapine, quetiapine[47-49].

5.3 *Discussion*

The published medical literature related to glucose abnormalities among schizophrenics and associated with the use of antipsychotic medications is extensive. The medical literature that pre-dated the introduction of antipsychotic medications includes studies designed to determine if schizophrenics were at higher risk of glucose abnormalities. Following the introduction of chlorpromazine, concern developed about increased risk of glucose abnormalities and diabetes mellitus in patients treated with this and similar medications. Presently, phenothiazines are commonly identified among the group of drugs that can cause hyperglycemia. Experiments have been conducted to clarify the nature of the effect of phenothiazines on blood glucose but no definitive mechanism has been identified. Despite case reports of hyperglycemia in chlorpromazine-treated patients, we did not find published reports of diabetic ketoacidosis associated with chlorpromazine or the use of other typical antipsychotics.

Following the introduction of clozapine, case reports and case series of glucose abnormalities in clozapine users were published in the medical literature. Although development of diabetic ketoacidosis in adults treated with clozapine seems unexpected, there have been no published comparisons of the incidence of diabetic ketoacidosis in this group to untreated schizophrenics. The published cases of positive dechallenge appear to offer strong support for a drug-related effect, but one must also consider that diabetics can experience "honeymoon" periods where insulin requirements decrease following initial treatment of diabetes. The positive rechallenge cases do provide stronger evidence of a drug-related effect on glucose. Experimental data suggests that

FDACDER 002163

006426

EXHIBIT A
PAGE 10 OF 15

antipsychotic exposure may be associated with insulin resistance but these hypotheses have not yet been fully explored.

5.4 Conclusions

The published literature generally supports the hypothesis that schizophrenics treated with antipsychotics are at increased risk of glucose abnormalities. However, the magnitude of the effect is difficult to discern especially considering that schizophrenia may be associated with increased risk for developing glucose abnormalities. The amount of information available about glucose abnormality risk differs among the antipsychotic agents. The published medical literature lacks sufficient information for valid comparisons of glucose abnormality risks across the class of antipsychotic agents.

6 Reviewer Comments

The DDRE-1 review of reports of DM and its complications in users of the four marketed atypical antipsychotic drugs[2] and Dr. Boehm's review of the pertinent medical literature suggests that users of these drugs are at risk for DM and its complications. The strongest evidence for the elevated risk is the presence of positive rechallenges. Positive rechallenges were observed in association with clozapine, olanzapine, and risperidone. Positive dechallenges also occurred in many patients, but others reported negative dechallenges.

Typically, when weighing the strength of a safety signal, we expect the reporting rates to be similar to or higher than the expected background rates for the adverse event. In this case, however, the reporting rates did not approximate the background rates, and in some cases, were 2-3 levels of magnitude lower. One explanation for this observation, as pointed out by Drs. Wysowski and Bennett would be substantial underreporting. Furthermore, even the reports that were submitted are "underreported" in a sense, because we often did not receive the full information on the patient regarding risk factors for DM, response to hypoglycemic therapy, and ultimate outcome following discontinuation and possibly reinitiation of the drug.

There is some suggestion from the data that DM and its complications might be more frequently associated with clozapine and olanzapine than with risperidone and quetiapine. The higher reporting rates for those two drugs observed in the original AERS search persisted into the second search period, despite the overall decrease of all the rates. Clozapine and olanzapine also accounted for the majority of literature cases, although this is not a particularly sensitive measure of the strength of a safety signal.

Spontaneous reports and published case series stimulate many questions, but provide few answers. Further study will be needed to elucidate the potential causality of DM by the atypical antipsychotic drugs. Prospective studies may provide some insight by eliminating from the cohort patients with pre-existing, but undiagnosed diabetes, and

[2] In the time since the consult was submitted, the Division approved an additional atypical antipsychotic drug, Geodon (ziprasidone).

FDACDER 002164

006427

EXHIBIT A
PAGE 11 OF 15

B

stratifying patients by risk factors such as obesity and family history. Even this type of study has limited utility, though, because physicians choose treatments for their patients based on a variety of factors that would likely differ from treatment group to treatment group. Randomization to the various therapies is likely to be the only way to sort out the differential effects of these drugs on glucose tolerance.

Judith A. Racoosin, MD, MPH

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FDACDER 002165

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EXHIBIT A
PAGE 12 OF 15

B

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FDACDER 002166

EXHIBIT A
PAGE 13 OF 15

B

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FDACDER 002167

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EXHIBIT A
PAGE 14 OF 15

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C O N F I D E N T I A L

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Videotape deposition of JOHN L. GUERIGUIAN, M.D., held in the offices of Pepper Hamilton, 3000 Two Logan Square, 30th Floor, Philadelphia, Pennsylvania 19103, commencing at 9:43 a.m., on the above date, before Linda Rossi Rios, RPR, CSR and Notary Public.

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EXHIBIT B
PAGE 1 OF 4

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- - -

- - -

INDEX

WITNESS PAGE NO.
JOHN L. GUERIGUIAN, M.D.
By Mr. Fahey 7

- - -

EXHIBITS

NO. DESCRIPTION PAGE NO.
Gueriguian-1 Report of Plaintiff's Expert John L. Gueriguian, M.D. 7
Gueriguian-2 Document list 33
Gueriguian-3 Zyprexa Thematic: Diabetes summary 86
Gueriguian-4 Zyprexa Thematic: Regulatory summary 97
Gueriguian-5 Zyprexa Thematic: Weight Gain summary 146
Gueriguian-6 Zyprexa Thematic: Residual Issues summary 146
Gueriguian-7 Quotations from depositions from a number of Eli Lilly sales representatives 146
Gueriguian-8 10/9/00 Communication 191
Gueriguian-9 Letter, ZY 4091 10 - 12 242

EXHIBITS (cont'd.)

NO. DESCRIPTION PAGE NO.
Gueriguian-10 Review and Evaluation of Clinical Data, FDACDER 00247, 325, 327, 328, 357 264
Gueriguian-11 The New England Journal of Medicine articles 309
Gueriguian-12 Antipsychotics & Metabolic Effects: 2002-2003 Update, ZY 200581125 - 581128 415

- - -

DEPOSITION SUPPORT INDEX

Direction to Witness Not To Answer
Page Line Page Line
None

Request For Production of Documents
Page Line Page Line
None

Stipulations
Page Line Page Line
None

Questions Marked
Page Line Page Line
None

- - -

EXHIBIT 8
PAGE 2 OF 4

clozapine. Correct?
A. Sir, I am not the one -- I'm the one asked the same question over and over again, and I cannot be any more clearer than I was, so it's not my problem.
Q. That's why I'm trying to stop you. And when I --
A. You don't have to try to stop me.
MR. SUGGS: Time out. Let me -- let me interrupt here for a second. Why don't we just have the ground rule, ask a question, you answer the question. If you feel like you need to inquire further about the question, fine, but let him finish his answer, because I mean, otherwise, he's just going to get distracted.
MR. FAHEY: I'm not trying to distract him. I'm trying to understand what his testimony is. And he's suggesting that there's a

basis for why this relates to olanzapine. I'm just trying to understand that.
MR. SUGGS: What's your -- put a question to him and we'll see if we can go.
BY MR. FAHEY:
Q. Okay. Let's -- let's start this clean.
Do you believe, based on this document, that the FDA disagreed with Lilly's position with respect to the comparable rates message that Lilly was --
A. I don't believe, I know that the opposite is true, that Lilly resisted the opinion of the FDA as to how the label should be written.
Q. Okay. And your position is that this document suggests that the FDA believes the label should have been written differently than what was ultimately written, I guess, in 2003?
A. The FDA, being a scientific

organization, knows and doesn't believe. I have to insist, because this is at the core of scientific pursuit.
Now, there are -- to answer your question, it's the Eli Lilly that never agreed with the FDA's opinion as to what the label should read. And I have answered that question in that form for several times now, and I'm not going to change, because that's how I see it.
Q. Okay. Do you believe the FDA knew based on this document that olanzapine carried a greater risk of the development of hyperglycemia and diabetes than other anti -- atypical antipsychotics?
A. I don't know what a do you believe question addressed to a scientist means. I don't know.
Q. Do you --
A. It's not a matter of fate.
Q. Is it -- based on your reading of this document, is it your impression that the FDA knew that Zyprexa

had an increased risk of diabetes and hyperglycemia relative to other atypical antipsychotics?
A. The FDA knew the following. Number one --
Q. Just answer my question. Do me a favor and answer my question.
A. I am answering your question, sir. I am answering your question. Please let me answer.
Q. Go ahead.
A. Otherwise -- the FDA knew the following. I'm answering your question precisely.
Q. Okay.
A. Number one, there wasn't enough studies performed by Lilly or anybody else. And it says published literature is insufficient.
Number two, the FDA believe that the preponderance of the evidence appear, and I'm quoting, to offer a strong support for a drug-related event, end of quote.

EXHIBIT B
PAGE 3 OF 4

Thirdly, the FDA knew, because of this ping-ponging and coming back and forth and arguing and shuttling, that the Eli Lilly didn't share that opinion, didn't want to change the label as the FDA wanted it, and adhered and adheres to this day to the theory of the so-called class effect.

Q. Okay. You would agree that this document does not ask Lilly to change its label. Correct?

A. I don't know what this document says or doesn't say. All I know is that the FDA and Lilly went on endlessly and Lilly didn't relent, it was -- to this day its label is not right from the point of view of the FDA and my own point of view.

Q. Okay.

A. Always adhering to this day to the class effect.

Q. But there's nothing in this document that you can point me to that says that we believe Zyprexa's label

should be changed. Correct?

MR. SUGGS: I would note for the record that the witness does not have a copy of the document in front of him.

MR. FAHEY: Yes, he does.

MR. SUGGS: No, he doesn't. He doesn't have a copy of the exact document.

MR. FAHEY: I gave it to him.

MR. SUGGS: Well, he handed it back to you. That's what you're looking at right now.

MR. FAHEY: Okay.

BY MR. FAHEY:

Q. There's nothing in this document, sir, is there, that asks or suggests or even hints that Lilly should change its label. Correct?

A. I'll answer the question when I've had a chance to see.

In page 11 or 2164 of the document, the exhibit, under the heading

5.4 conclusions, it states, and I'm quoting, the published literature generally supports the hypothesis that schizophrenics treated with antipsychotics are at increased risk of glucose abnormalities. However, the magnitude of the effect is difficult to discern, end of quote. This clearly means to an experienced company such as Lilly, an important company such as Lilly, that the FDA is saying we don't have enough studies because you didn't perform the studies. So that's number one.

Q. Okay.

A. I haven't finished. The amount of information available about -- and I'm quoting again. The amount of information available about glucose abnormality risk differs among the antipsychotic agents. This in clear means, without ambiguity, you are wrong in persisting that this is a class effect only.

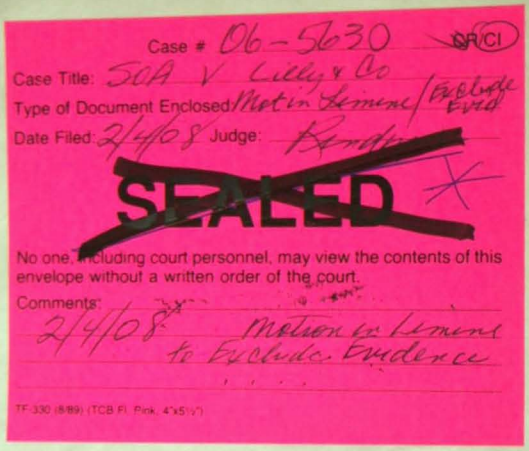
Q. Okay.

A. The published medical literature, and I continue the quotes, lacks sufficient information for valid comparisons of glucose abnormality risk across the class of antipsychotic agents, and that includes olanzapine, end of quote. That includes olanzapine. And this is a reiteration of the opinion of the FDA. Since you haven't done the study, since the available study, literature and evidence points that hypothesis that individuals treated with antipsychotics are at increased risk of glucose abnormalities, you either do the study or you change this statement that this is only a class effect. It couldn't be clearer. That's how scientists talk to each other.

Q. Okay.

A. They're not lawyers, they don't say I'm giving you now the legal opinion that you have to do this and that. This is very clear.

EXHIBIT B
PAGE 4 OF 4



Case # 06-5630 DR/CI

Case Title: SOA v Lilly & Co

Type of Document Enclosed: Motion to Remove/Exclude Evid

Date Filed: 2/4/08 Judge: Rindner

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* See Judge Rindner's 6/13/08 order page 21, #16

documents unsealed lwade 8/11/08

Pages 6436A-6460

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

DEFENDANT ELI LILLY AND COMPANY'S NOTICE OF FILING MOTION IN LIMINE TO EXCLUDE EVIDENCE RELATING TO NEW YORK TIMES ARTICLES UNDER SEAL

COMES NOW Defendant Eli Lilly and Company ("Lilly") and files its Motion in Limine to Exclude Evidence Relating to New York Times Articles, under seal, attached to this notice. The Motion and exhibits thereto may be the subject of prior confidentiality rulings.

DATED this 4th day of February, 2008.

See Judge Rindner's 6/13/08 order, page 21, #16

Documents unsealed per Judge 8/11/08

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Andrew R. Rogoff, admitted *pro hac vice*
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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

ORDER

THIS COURT, having considered defendant's Eli Lilly and Company's Motion in Limine to Exclude Evidence Relating to New York Times Articles, all responses thereto, as well as applicable law:

IT IS HEREBY ORDERED that Lilly's motion is GRANTED. The State of Alaska is prohibited from introducing at trial any evidence referring or relating to The New York Times articles regarding Zyprexa and Eli Lilly and Company.

ORDERED this _____ day of February, 2008.

The Honorable Mark Rindner
Judge of the Superior Court

I certify that on February 4, 2008, a copy of the foregoing was served by hand on:

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006436A

A

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

[FILED UNDER SEAL]

DEFENDANT ELI LILLY AND COMPANY'S MOTION IN LIMINE TO EXCLUDE EVIDENCE RELATING TO NEW YORK TIMES ARTICLES

Defendant Eli Lilly and Company ("Lilly") requests that this Court bar the State of Alaska from introducing at trial any evidence relating to a series of articles published in *The New York Times* in December 2006, regarding Zyprexa®, as well as the surrounding controversy which led to the February 13, 2007 injunction precluding further disclosure of confidential Lilly documents entered in the Zyprexa multidistrict litigation "MDL."

I. INTRODUCTION

The State intends to introduce into evidence a series of articles containing allegations about Zyprexa published in *The New York Times* in December 2006. The State will also introduce at least two documents referring to those articles through the designated deposition testimony of Lilly employee Robin Pitts Wojcieszek. The State intends to use this evidence in support of its claim that Zyprexa's product labeling was inadequate. This evidence should be excluded as irrelevant, unfairly prejudicial, misleading, and inadmissible hearsay.

Judge Jack B. Weinstein found that the publication of the Zyprexa articles in *The New York Times* resulted from a conspiracy – entered into by a *Times* reporter, an expert for plaintiffs in the Zyprexa MDL, and an Alaska lawyer unconnected to the MDL or this case – to violate a protective order issued by Judge Weinstein in the MDL. *See In Re Zyprexa*

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Injunction, 474 F.Supp.2d 385, 392 (E.D.N.Y. 2007). That protective order restricted distribution of Lilly's internal confidential documents. In violation of the order, the conspirators released several documents, resulting in the barrage of articles published in the newspaper (containing excerpts from, and summaries of, the protected documents), extensive public disclosure, and public controversy.[1]

In February 2007, the MDL court ordered the disclosed documents returned to the court-appointed Special Master for Discovery, and entered an injunction preventing the conspirators and other named individuals from further harming Lilly through disclosure of the confidential documents. *Id.* at 429-30.

II. ARGUMENT

A. The New York Times Articles Are Inadmissible Hearsay.

The State cannot offer *The New York Times* articles into evidence because they are inadmissible hearsay not redeemed by any exception to the hearsay rule. The allegations in the articles substantially track several of the State's primary claims regarding the Zyprexa label. They draw conclusions unfavorable to Lilly that the State will attempt to use to support its arguments. Out of court statements "offered in evidence to prove the truth of the matter asserted" are inadmissible as hearsay. Alaska R. Evid. 801 and 802. Accordingly, this evidence must be excluded. This same conclusion was reached just last week, when a federal court in Texas refused to consider these articles on hearsay grounds:

> Plaintiff's evidence of Defendant's [wrongdoing] consists of three articles that Plaintiff submits are from The New York Times . . . . However, these articles riddled with hearsay, whether from

[1] *See e.g.*, Alex Berenson, *Eli Lilly Said to Play Down Risk of Top Pill,* N.Y. Times, Dec. 17, 2006 at A1; Alex Berenson, *Drug Files Show Maker Promoted Unapproved Disparity Emerges in Lilly Data on Schizophrenia Drug,* N.Y. Times, Dec. 21, 2006, at A1; Editorial, *Playing Down the Risks of a Drug*, N.Y. Times, Dec. 19, 2006; Alex Berenson, *Disparity Emerges in Lilly Data on Schizophrenia Drug*, N.Y. Times, Dec. 21, 2006, at A1.

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The New York Times or not, are inadmissible evidence that will not be considered. Fed. R. Civ. P. 56(e); Fed. R. Evid. 802.

Exhibit A. *Ebel v. Eli Lilly and Company*, Civil Action No. B-04-194, Opinion and Order (January 29, 2008). *See also W.E. Green v. Baca*, 226 F.R.D. 624, 638 (C.D. Cal., 2005) (granting motion in limine to exclude *Los Angeles Times* articles offered for the truth of the matter asserted); *Kim v. Bridgestone/Firestone, Inc.*, 2007 WL 2439715 (C.D. Cal., 2007) (court granting motion in limine in products liability case to exclude evidence referencing news reports regarding product testing and safety, and also to redact such references from expert report).

B. The New York Times Articles Are Irrelevant and Inadmissible in This Case.

The content, existence, and media discussion of the articles are irrelevant to this Alaska case. "Relevant evidence means evidence having any tendency to make the existence of any fact that is of consequence to the determination of the action more or less probable than it would be without the evidence." Alaska R. Evid. 402. That three conspirators' violation of a court order resulted in headlines does not tend to make any fact pertinent to this litigation more or less probable. That the State's claims track allegations in newspaper articles slanted against Lilly likewise does not lend relevance to them.

The New York Times articles are also prejudicial. Indeed, one of the participants in the conspiracy later admitted in a Declaration filed with the MDL court that the documents released "did not represent the entire set of information concerning Lilly's action and knowledge," did not "publicize Lilly's perspective on the side effects of Zyprexa," and did not "get Lilly's perspective on the side effects publicized to doctors and patients." The Declaration admits that "there was another side to the Zyprexa story." *See* Declaration of D. Egilman, M.D., M.P.H, filed September 7, 2007. However, the resulting publications appear authoritative and thus could mislead the jury. Even if relevant, "evidence may be excluded if its probative value is outweighed by the danger of unfair prejudice, confusion of the issues,

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or misleading the jury." Alaska R. Evid. 403. The bias of these articles outweighs any potentially probative value.

C. References to the New York Times Articles in Other Documents are Equally Inadmissible.

1. FDA Response

Soon after *The Times* published the articles, the FDA sent Lilly a letter inquiring into the allegations in them. On February 20, 2007, Lilly submitted a three-part response to the FDA. The State intends to introduce this document into evidence through the designated deposition testimony of Lilly employee Robin Pitts Wojcieszek. The first part of this response is inherently based upon, and structured around, *The Times* articles. It restates the newspaper's allegations, offers Lilly's interpretation of those allegations, and provides point-by-point replies. This part of the response is so intertwined with the articles and allegations that it cannot be disentangled. Accordingly, this document should be excluded from evidence. The second part of this response contains requested literature, and the third part contains requested data.

Additionally, use of this submission to the FDA as a source of evidence would be an unfair and prejudicial approach. Lilly's submission to the FDA simply was generated to respond to an array of statements put forth by a *Times* reporter, a layperson without any subject matter expertise in the area of drug safety or regulatory action. The State's arguments regarding the Zyprexa label would be more adequately and more fairly addressed with other appropriate evidence.

2. March 28, 2007 Letter from the FDA

Also through the designated deposition testimony of Robin Pitts Wojcieszek, the State will introduce a letter sent to Lilly by the FDA on March 28, 2007, following Lilly's September 2006 Supplemental New Drug Application seeking FDA approval for use of

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Symbyax[2] for treatment resistant depression.[3] The FDA letter asks for more information from Lilly regarding data submitted in support of the application, noting Lilly's response previously provided to the FDA in relation to *The New York Times* articles. Such ongoing dialogue is commonplace in the FDA's regulation of prescription drugs, whether for Symbyax, Zyprexa, or any other medication. However, Lilly anticipates that the State will attempt to introduce this evidence in support of its allegation that Zyprexa's warnings were inadequate at the time of the prescriptions in question. For the reasons stated above, this document, linked to *The Times* articles, should be excluded from consideration by the jury.

III. CONCLUSION

Lilly requests this Court enter an order excluding from evidence *The New York Times* articles, and any reference to same.

DATED this 4th day of February, 2008.

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Andrew R. Rogoff, admitted *pro hac vice*
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I certify that on February 4, 2008, a copy of The foregoing was served by hand on:

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[2]Symbyax is a Lilly product not involved in this lawsuit. It combines olanzapine (the active ingredient in Zyprexa) and fluoxetine, and previously was approved only for treatment of bipolar depression.

[3] By separate motion, Lilly requests upon additional grounds that this Court bar the State of Alaska from introducing this letter at trial.

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United States District Court
Southern District of Texas
ENTERED

JAN 29 2008

Michael N. Milby, Clerk of Court
By Deputy Clerk

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF TEXAS
BROWNSVILLE DIVISION

BEATRIZ E. EBEL, §
§
Plaintiff, §
§
V. § CIVIL ACTION NO. B-04-194
§
ELI LILLY AND COMPANY, §
§
Defendant. §

OPINION & ORDER

BE IT REMEMBERED that on January 29, 2008, the Court **GRANTED** Defendant Eli Lilly and Company's Motion for Summary Judgment. Dkt. No. 47. Defendant's other motions, Dkt. Nos. 46, 48, 67, are thereby rendered **MOOT**. This Court **VACATED** its opinion and order dated November 14, 2007. The Court considered Defendant Eli Lilly and Company's Motion for Summary Judgment, Dkt. No. 47, Plaintiff's Response and Memorandum in Opposition to Lilly's Motion for Summary Judgment, Dkt. No. 55, Defendant Eli Lilly and Company's Reply Brief in Support of Its Motion for Summary Judgment, Dkt. No. 59, Defendant Eli Lilly and Company's Objections to Plaintiffs' Summary Judgment Evidence, Dkt. Nos. 60, 63, and Plaintiff's Response to Defendant's Objections to Plaintiff's Summary Judgment Evidence, Dkt. No. 66. The Court **GRANTED** Plaintiff's Unopposed Motion to Withdraw Document No. 54, Dkt. No. 57.

I. Background

Plaintiff Beatriz E. Ebel filed suit against Defendant Eli Lilly and Company on November 9, 2004 alleging that Defendant was liable for the death of decedent, Philip Wayne Ebel. Dkt. No. 1. Defendant is a pharmaceutical company which developed and markets olanzapine, a drug sold as Zyprexa®. *Id.* at 2. Plaintiff alleges that decedent took Zyprexa®, Defendant failed to adequately warn that Zyprexa® could cause suicide or akathisia, and decedent committed suicide because he took Zyprexa®. *Id.* at 5, 7.

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EXHIBIT A
PAGE 1 OF 19

Decedent began taking Zyprexa® in July 2002 after Dr. Robert B. Nett prescribed it to him. *Id.* at 7. Defendant does not dispute that decedent took Zyprexa®. On November 9, 2002, a different doctor prescribed decedent Paxil® in addition to Zyprexa®. *Id.* On November 11, 2002, decedent committed suicide. *Id.* Similarly, Defendant does not dispute that decedent was taking Zyprexa® on or around the date he committed suicide.

Plaintiff asserts that Defendant should be liable for decedent's death because Defendant "(a) den[ied] the association between Zyprexa and suicide, (b) refus[ed] to warn about this risk, [and] (c) blam[ed] the deaths on the 'disease' and publicity on trial lawyers, the media, and others." Dkt. No. 1, at 5-6. Plaintiff states that Defendant further failed to adequately warn of the dangerous "drug-drug interaction between Zyprexa and Paxil." *Id.* at 7-8. Plaintiff sued Defendant based on three causes of action strict liability, negligence, and breach of warranty. *Id.* at 9. Defendant denies that Zyprexa® caused the decedent's death and that Defendant failed to adequately warn of the risks associated with the medication. Dkt. No. 4, at 2-4.

II. Standard of Review

Summary judgment is appropriate when the movant has established that the pleadings, affidavits, and other evidence available to the Court demonstrate that no genuine issue of material fact exists, and the movant is thus entitled to judgment as a matter of law. FED. R. CIV. P. 56(c); Piazza's Seafood World, LLC v. Odom, 448 F.3d 744, 752 (5th Cir. 2006); Lockett v. Wal-Mart Stores, Inc., 337 F. Supp. 2d 887, 891 (E.D. Tex. 2004). The Court must view all evidence in a light most favorable to the non-moving party. *Piazza's Seafood World, LLC*, 448 F.3d at 752; *Lockett*, 337 F. Supp. 2d at 891. However, factual disputes are resolved in favor of the nonmovant "only when an actual controversy exists, that is, when both parties have submitted evidence of contradictory facts." Olabisiomotosho v. City of Houston, 185 F.3d 521, 525 (5th Cir. 1999).

If the movant satisfies its burden, the non-moving party must then come forward with specific evidence to show that there is a genuine issue of fact. *Lockett*, 337 F. Supp. 2d at 891. The nonmovant may not merely rely on conclusory allegations or the pleadings.

Id.; Isquith for and on Behalf of Isquith v. Middle South Utilities, Inc., 847 F.2d 186, 199 (5th Cir. 1988). Rather, the nonmovant must demonstrate specific facts identifying a genuine issue to be tried in order to avoid summary judgment. FED. R. CIV. P. 56(e); *Piazza's Seafood World, LLC*, 448 F.3d at 752; *Lockett*, 337 F. Supp. 2d at 891. Summary judgment should be granted "when the nonmoving party fails to meet its burden to come forward with facts and law demonstrating a basis for recovery that would support a jury verdict." *Little*, 37 F.3d at 1071.

III. Learned Intermediary Doctrine

The Texas learned intermediary doctrine applies to all of Plaintiff's claims because they are state law claims based on a manufacturer's failure to warn of potential risks. While the Texas Supreme Court has not applied the learned intermediary doctrine in a products liability case involving prescription medication, it has acknowledged use of the doctrine by Texas appellate courts. *See* Humble Sand & Gravel, Inc. v. Gomez, 146 S.W.3d 170, 185 (Tex. 2004) ("[W]e noted that other courts had held that a pharmaceutical manufacturer is not required to warn patients of the dangers of a prescription drug as long as physicians who prescribe the drug - "learned intermediaries" - have been adequately warned."); Alm v. Aluminum Co. of America, 717 S.W.2d 588, 591 (Tex. 1986) (acknowledging the learned intermediary doctrine in a prescription drug context). *See also* Wyeth-Ayerst Laboratories Co. v. Medrano, 28 S.W.3d 87, 91 (Tex. App. 2000) (listing other appellate cases applying the learned intermediary doctrine to prescription drug cases and indicating that "the most common use of this doctrine is in prescription drug cases"). Moreover, the Fifth Circuit has applied the learned intermediary doctrine when applying Texas law to prescription drug cases. *In re* Norplant Contraceptive Prods. Liab. Lit., 165 F.3d 374, 379 (5th Cir. 1999). Therefore, this Court will similarly apply the learned intermediary doctrine to this case.

The learned intermediary doctrine is a products liability defense that explains "[p]harmaceutical companies . . . [that] sell[] prescription drugs are required to warn only the prescribing physician, who acts as a 'learned intermediary' between the manufacturer and consumer." Reyes v. Wyeth Laboratories, 498 F.2d 1264, 1276 (5th Cir. 1974). In the

case of prescription drugs, a patient does not have access to the medication absent a prescription from a physician, therefore a manufacturer need only warn the physician. *In re Norplant Contraceptive Prods. Liab. Lit.*, 165 F.3d at 91. However, where the warning provided to the physician is inadequate or misleading, the manufacturer does not escape liability. *Humble Sand & Gravel, Inc.*, 146 S.W.3d at 198-99. A manufacturer may nonetheless escape liability for an inadequate or misleading warning where the doctor is otherwise informed of the risks of the prescription medication, in spite of an inadequate warning. *Id.* at 199; Porterfield v. Ethicon, Inc., 183 F.3d 464, 468 (5th Cir. 1999); Koenig v. Purdue Pharma Co., 435 F. Supp. 2d 551, 555-56 (N.D. Tex. 2006).

Essentially, in the context of the defense of the learned intermediary doctrine, Defendant has the initial burden of proving that decedent received the medication through a physician with whom the decedent had a physician-patient relationship and that the warning Defendant provided to the prescribing physician was adequate. In the alternative, Defendant may escape liability with evidence that the prescribing physician was aware of all of the drug's risks that would have been mentioned in an adequate warning. Once Defendant meets its initial burden, Plaintiff must provide some evidence that Defendant's warning was inadequate or misleading, and that the prescribing physician was not otherwise aware of the risks of Zyprexa® when he prescribed it to decedent. Where Defendant meets its burden and Plaintiff fails to rebut with a genuine issue of fact, summary judgment in favor of Defendant may be granted.

A. Scope of the Doctrine

The learned intermediary doctrine applies to all of Plaintiff's claims against Defendant. Where the crux of the suit is based on a failure to adequately warn, the learned intermediary doctrine may apply to strict liability, negligence, misrepresentation, and breach of warranty claims. *In re* Norplant Contraceptive Products Liab. Lit., 955 F. Supp. 700, 709 (E.D. Tex. 1997), *aff'd* 165 F.3d 374 (5th Cir. 1999). "If the doctrine could be avoided by casting what is essentially a failure to warn claim under a different cause of action . . . then the doctrine would be rendered meaningless." *Id.* All of Plaintiff's claims require proof that Defendant's warning was inadequate. *In re Norplant Contraceptive Prod.*

Liab. Lit., 955 F. Supp. at 709; Gerber v. Hoffmann-La Roche Inc., 392 F. Supp. 2d 907, 914 (S.D. Tex. 2005) (citing Lucas v. Tex. Indus., Inc., 149 S.W.2d 372, 377 (Tex. 1984)); Morgan v. Wal-Mart Stores, Inc., 30 S.W.3d 455, 461 (Tex. App. 2000). Therefore, the learned intermediary doctrine applies to all of Plaintiff's claims. *In re Norplant Contraceptive Prod. Liab. Lit.*, 955 F. Supp. at 709.

It is undisputed that decedent and Dr. Nett[1] had a physician-patient relationship at the time Dr. Nett prescribed decedent Zyprexa®. Dkt. No. 1, at 7; Dkt. No. 47, at 5; Dkt. No. 55, at 3. Defendant argues that summary judgment is appropriate because the 2002 warning label for Zyprexa® is presumptively adequate and Dr. Nett testified that he was aware of all of the risks Plaintiff complains of even if Defendant did not adequately warn of risks. Dkt. No. 47, at 7, 10. Moreover, Defendant asserts that Plaintiff has failed to raise a genuine issue of material fact as to its defense. Dkt. No. 64, at 1-5.

B. Adequate Warning for Zyprexa®

The learned intermediary doctrine disposes of Plaintiff's claims as they relate to the failure to warn of any suicidal risk of Zyprexa®. The doctrine does not require that manufacturers adequately warn patients taking the manufactured medication as long as the manufacturer adequately warned the prescribing physician of the medication's potential risks. *Porterfield*, 183 F.3d at 467-68.

1. Presumption of Adequacy from FDA approval

Defendant asserts that the warning provided for Zyprexa® was adequate. Dkt. No. 46, at 6. In support, Defendant provided evidence that the United States Food and Drug

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[1] Plaintiff impliedly challenges the application of the learned intermediary doctrine to Defendant because Dr. Nett, decedent's prescribing physician, collaborated with decedent's previous physician when Dr. Nett decided to prescribe decedent Zyprexa®. Dkt. No. 55, at 1, 10. However, Dr. Nett was the prescribing physician and the physician who Defendant was required to inform of the risks of Zyprexa®. *See In re* Norplant Contraceptive Prod. Liab. Lit., 955 F. Supp. 700, 706 (E.D. Tex. 1997), *aff'd* 165 F.3d 374 (5th Cir. 1999) (indicating that if a physician becomes a mere conduit of information and fails to make an independent decision complete with an individualized risk and benefit analysis the manufacturer is not liable for the physician's poor judgment).

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EXHIBIT A
PAGE 5 OF 19

Administration, ("FDA"), approved Defendant's warning labels for Zyprexa® in 2002. Dkt. No. 46, Ex. A. Plaintiff concedes that Defendant's 2002 label was approved by the FDA. Dkt. No. 55, at 13. Under Texas law, that FDA approval creates a rebuttable presumption that the approved warning is adequate. TEX. CIV. PRAC. & REM. CODE ANN. § 82.007(a). *See* Holland v. Hoffman-La Roche, Inc., slip op., 2007 WL 4042757, at *2 (N.D. Tex. 2007). Section 82.007(a) provides,

> In a products liability action alleging that an injury was caused by a failure to provide ***adequate warnings or information*** with regard to a pharmaceutical product, there is a rebuttable presumption that the defendant . . . manufacturer . . . [is] not liable . . . if (1) ***the warnings or information*** that accompanied the product in its distribution were those approved by the United States Food and Drug Administration . . . .

TEX. CIV. PRAC. & REM. CODE ANN. § 82.007(a) (emphasis added).

Nonetheless, Plaintiff argues that this presumption is not applicable here because "the 2002 label did not include *any warning whatsoever* about a risk of akathisia[2] or suicidality." *Id.* (citing Dkt. No. 55, Ex. 4) (emphasis added). *See also* Dkt. No. 55, at 2 (citing Dkt. No. 55, Ex. 4); *id.* at 21 (indicating that this is a case where the drug label provided no warning or information cautioning the risk of suicide and distinguishing this case from a case of inadequate warnings where the label does not adequately communicate the extent of the risk). Plaintiff asserts that because Defendant did not attempt to demonstrate that it provided an adequate warning, the presumption should not apply. *Id.* at 14 (relying upon a case from the district of Wyoming which did not involve a statutory presumption of adequacy from FDA approval).

However, the 2002 label for Zyprexa® did contain information about akathisia and suicide. Dkt. No. 55, Ex. 4 at 2-3. The 2002 label mentions akathisia multiple times. *Id.* at 3. Five separate charts delineate results from various clinical trials of olanzapine, marketed as Zyprexa®. *Id.* In four of the charts, akathisia is mentioned and reported has having a higher rate of occurrence among participants taking olanzapine than among

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[2] Akathisia is a condition sometimes referred to as restlessness. Dkt. No. 55, at 12 n. 22; Dkt. No. 55, Ex. 5 at 81:20, 82:16. Moreover, akathisia can be a precursor to suicide. *See* Dkt. No. 47, Ex. B at 129:13; Dkt. No. 55, at 11-12.

participants taking the placebo. *Id.* The 2002 label also mentions an association with suicide. On the second page of the FDA approved label, in the first column and under the bold heading, "**PRECAUTIONS,**" the label states, "Suicide – The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy." *Id.* (emphasis in original). On the third page, under the subheading, "*Other Adverse Events Observed During the Clinical Trial Evaluation of Olanzapine*," the 2002 label indicates frequent events which affected the body as a whole include, "dental pain, flu syndrome, intentional injury, and *suicide attempt*." *Id.* at 3 (emphasis added). Therefore, this is not a "no warning" case because the risks Plaintiff complains of are mentioned in the label. *See* McNeil v. Wyeth, 462 F.3d 364, 368 (5th Cir. 2006) ("[W]hen 'a warning specifically *mentions* the circumstances complained of, the warning is adequate as a matter of law.'") (quoting Rolen v. Burroughs Wellcome Co., 856 S.W.2d 607, 609 (Tex. App. 1993)) (emphasis added).

Plaintiff cites *McNeil* in support of her challenge to the application of the presumption. Dkt. No. 55, at 16. However, the plaintiff in *McNeil* alleged a different problem with the label; the plaintiff alleged that the label was inadequate because it was "misleading as to the risk level for developing the condition." *McNeil*, 462 F.3d at 386. The label mentioned the risk, but the plaintiff alleged that it downgraded the risk such that a reasonable physician might have been induced to undertake the risk. *Id.*

Plaintiff did not raise such a challenge to the 2002 label for Zyprexa®. Rather she repeatedly asserts that this is a "no warning" case. *See* Dkt. No. 55, at 13, 17, 19-20, 21. The Court finds that the 2002 label for Zyprexa® does mention akathisia and suicide, the risks of which Plaintiff complains. Therefore, the § 82.007(a) presumption applies.

Plaintiff further argues that because Defendant failed to assert that it did warn about the risks of Zyprexa®-induced suicidality this Court should not apply the presumption. Dkt. No. 55, at 7 n.17 ("Lilly does not even argue that it has warned *doctors* about the risks of Zyprexa-induced suicidality. . . . [T]hat failure is also fatal to its motion.") (emphasis in original). However, Plaintiff does not distinguish this argument from her "no warning" argument against the application of the presumption in this case. Defendant asserted that the label was adequate through its argument that the § 82.007(a) presumption applied.

Dkt. No. 47, at 8. And, "[w]hen a presumption arises, it shifts the burden of producing evidence to the party against whom the presumption operates." Ackermann v. Wyeth Pharmaceuticals, 471 F. Supp. 2d 739, 749 (E.D. Tex. 2006) (citing Gen. Motors Corp. v. Saenz, 873 S.W.2d 353, 359 (Tex. 1993)). As Plaintiff has not met her burden of rebutting the presumption, Defendant need not provide further evidence that the label is adequate. *See Rolen*, 856 S.W.2d at 609.

2. Exception[3] to the § 82.007(a) Presumption

Plaintiff alleges that if the TEX. CIV. PRAC. & REM. CODE ANN. § 82.007(a) applies, so do its exceptions. Plaintiff asserts that the exception of overpromotion, TEX. CIV. PRAC. & REM. CODE ANN. § 82.007(b)(3), defeats the presumption. Dkt. No. 55, at 18-19.

Overpromotion can include promotion of illegal off-label use,[4] or promoting a use of a drug not approved by the FDA. Salbu, *Off-Label Use*, 51 FLA. L. REV. at 188 ("Off-label use of a prescription drug occurs whenever the consumer of the drug uses it in a manner that varies in some way from the instructions in the drug's labeling, which are limited to FDA-approved uses."). Plaintiff asserts that her exhibit 8 at ZY1 00041186 demonstrates that Defendant had a "marketing plan to 'exploit' the off label use of Zyprexa to treat migraines in the Primary Care market," Dkt. No. 55, at 8 n.18, and that the exhibit is ample evidence to cause the § 82.007(a) presumption to disappear. *See id.* at 10, 21. However, this Court disagrees. While *Ackermann* establishes that the presumption is

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[3] Both Defendant and Plaintiff debate the legal status of exception (b)(2) concerning fraud on or withholding information from the FDA. Dkt. No. 47, at 10-14; Dkt. No. 55, at 19, 21-24; Dkt. No. 64, at 12-13. However, Plaintiff has provided no evidence of fraud on the FDA or that Defendant withheld information from the FDA. *See* Dkt. No. 55, at 19, 23-24. Therefore, the only exception to § 82.007(a) that this Court may consider is overpromotion, TEX. CIV. PRAC. & REM. CODE ANN. § 82.007(b)(3).

[4] It is illegal for a manufacturer to promote off-label use of a drug; however, it is not illegal for a physician to prescribe the drug for an off-label use. Buckman Co. v. Plaintiffs' Legal Committee, 531 U.S. 341, 351 n. 5 (2001); Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 190 (April 1999) [hereinafter "Salbu, *Off-Label Use*"].

rebutted after Plaintiff presents "some evidence" contradicting the presumption, 471 F. Supp. 2d at 749-50, Plaintiff's evidence does not satisfy that burden.

Plaintiff's argument of overpromotion is based on poorly drawn inferences. She reasons that although Zyprexa® is indicated for only two disorders, Defendant makes billions of dollars in annual sales from the drug. Dkt. No. 55, at 8. Therefore, Plaintiff reasons that Defendant must have overpromoted Zyprexa®. *Id.* Plaintiff offers no data or even a citation to support these conclusions. *Id.* Plaintiff's evidence of Defendant's overpromotion consists of three articles that Plaintiff submits are from The New York Times. *Id.* (citing to internet print outs without web addresses or headings which would indicate from what source the article was retrieved). However, these articles riddled with hearsay, whether from The New York Times or not, are inadmissible evidence that will not be considered. FED. R. CIV. P. 56(e); FED. R. EVID. 802.

Plaintiff indicates that the key evidence of overpromotion is her exhibit 8 at ZY1 00041186. Dkt. No. 55, at 8, 10, 21. Plaintiff maintains that "although there are a number of documents, and other evidence, which attest to [the overpromotion], one page from one document is sufficient evidence to defeat summary judgment under these pretenses." *Id.* at 9-10 (citing Dkt. No. 55, Ex. 8 at ZY100041186). *See id.* at 8 n.18 ("[B]ecause Lilly has not alleged that there is no evidence of overpromotion, and, thus, has not met its 'initial burden' under *Celotex* [*Corp. v. Catrell*, 477 U.S.317 (1986)] to put that allegation into issue, we will not burden the Court at this juncture with too much evidence. Exhibit 8 at ZY1 00041186 is direct evidence of Lilly's marketing plan to 'exploit' the off label use of Zyprexa to treat migraines in the Primary Care market.").

First, there is a concern with the admissibility of this document, which Plaintiff admits was obtained from a website, www.joysoup.net. *See* FED. R. EVID. 901 (requiring authentication prior to an admissibility analysis). It appears that this document was not provided by Defendant during discovery. There was no motion to compel production of this document or any other motion indicating Defendant possessed this document and withheld it from Plaintiff during the discovery process. Plaintiff fails to provide any information which would establish that this exhibit is in fact an internal document created by Defendant. The document does have labeling down the side indicating that it may have been included

among evidence submitted as part of the Zyprexa® Multi-District Litigation suit. Dkt. No. 55, Ex. 8 at ZY1 00041186. Such a marking does not authenticate the document. However, while Defendant challenged the admission of this document, the challenge was general and lacked any legal authority. Dkt. No. 63, at 1 ("Exhibit No. 8 – Eli Lilly and Company objects to this document as it contains hearsay within hearsay, is incomplete and irrelevant, and plaintiffs have not laid a proper foundation for admissibility."). Absent a more specific objection, this Court will not grant Defendant's motion to strike this exhibit.

Second, even if this Court were to consider exhibit 8 at ZY1 00041186, it is still not the smoking gun that Plaintiff declares it to be. At the top right of the document is the label "EXAMPLE," set apart from the rest of the document with lines above and below it. Dkt. No. 55, Ex. 8 at ZY1 00041186. Moreover, the heading in bold states that the document contains, "***POTENTIAL* ACTIONS TO EXPLOIT [PRIMARY CARE PHYSICIANS'] POTENTIAL FOR ZYPREXA." *Id.* (emphasis added). The document organizes information in three columns and five rows. *Id.* Plaintiff argues that the text in the third column, under the heading "Additional ideas," and in the row labeled "Clinical profile," indicates that Defendant had a marketing plan to persuade physicians to prescribe Zyprexa® off-label. Dkt. No. 55, at 8 n. 18. The text is as follows, "[w]hat could be other more primary care focused indications or uses of Zyprexa (e.g., behavioral disorders in the elderly, migraines)?" Dkt. No. 55, Ex. 8 at ZY1 00041186. The words "example," "potential," and "ideas" as well as the *question* inquiring as to the viability of the drug for other indications, *id.*, fail to support Plaintiff's claim that Defendant adopted and implemented a marketing plan which attempted to persuade physicians to use Zyprexa® off-label.

Plaintiff reasons that assertions by Defendant's officials support her allegation of overpromotion. Plaintiff points to the deposition of the previous Executive Director of Global Marketing for Zyprexa® in which he confirms that promoting Zyprexa® for treatment of headaches would be illegal. Dkt. No. 55, at 9. Plaintiff also provides an excerpt of the deposition of the Brand Leader for Zyprexa® which includes a statement acknowledging that it would be inappropriate to train sales representatives to promote Zyprexa® off-label. *Id.* Plaintiff argues that these statements further substantiate her allegation that Defendant

006451

EXHIBIT A
PAGE 10 OF 19

overpromoted Zyprexa®. *Id.* Neither statement provides this Court with evidence of an alleged marketing plan to overpromote Zyprexa®.

Furthermore, to establish the exception of overpromotion, Plaintiff must not only provide some evidence of a marketing plan to promote the off-label use of Zyprexa®, she must also provide proof that the marketing plan actually reached the prescribing physician, Dr. Nett. *In re* Norplant Contraceptive Prod. Liab. Lit., 1997 WL 81092, at *1 (E.D. Tex. 1997) (holding that evidence of a marketing plan to overpromote a drug is irrelevant where there is no accompanying evidence the marketing plan reached and effected the prescribing physician); Sita v. Denek Medical, Inc., 43 F. Supp. 2d 245, 263 (E.D.N.Y. 1999) ("To prevail, plaintiff must establish that [the prescribing physician] was influenced by the illegal marketing efforts.").

Plaintiff has not offered any evidence to establish that Dr. Nett was influenced by the alleged overpromotion marketing scheme. Plaintiff only points to the estimation of Defendant's employee in her deposition that "maybe 30 to 40 percent" of the uses of Zyprexa® are off-label as evidence of the implementation of an illegal marketing scheme. Dkt. No. 55, at 10 (citing Dkt. No. 55, Ex. 7 at 136:6-15). Plaintiff has not met her burden. Therefore, Defendant's 2002 label for Zyprexa® is presumed adequate.

3. Read and Heed Presumption

Plaintiff also attempts to rebut the § 82.007(a) presumption with the heeding presumption.[5] Dkt. No. 55, at 16-18. Plaintiff cites three Texas cases which applied the read and heed presumption in support of her claim, *Technical Chem. Co.*, 480 S.W.2d at 606, *Magro v. Ragsdale Bros.*, 721 S.W.2d 832, 834 (Tex. 1986), and *Dresser Indus. v. Lee*, 880 S.W.2d 750, 753 (Tex. 1993). However, none of those cases involved prescription drugs prescribed to a patient by a physician. *Technical Chem. Co.*, 480

[5] The Texas Supreme Court in *Technical Chem. Co. v. Jacobs*, held that when a manufacturer of a product fails to provide an adequate warning, there is a rebuttable presumption that the consumer of that product would have read and heeded the adequate warning or instruction. 480 S.W.2d 602, 606 (Tex. 1972). The presumption is rebutted by evidence that the consumer was blind, illiterate, intoxicated while using the product, lax in judgment, or affected in someway as to demonstrate that improper use would have occurred despite an adequate warning. *Id.*

006452

EXHIBIT A
PAGE 11 OF 19

S.W.2d at 605; *Magro*, 721 S.W.2d at 833; *Dresser Indus.*, 880 S.W.2d at 752. In fact, a federal district court has already reasoned that the Texas Supreme Court would not apply the read and heed presumption in the prescription drug context. *Koenig*, 435 F. Supp. 2d at 556-57. *Compare* Anderson v. Sandoz Oharmaceuticals Corp., 77 F. Supp. 2d 804, 809 (S.D. Tex. 1999) (applying the read and heed presumption in a prescription drug case as an alternative in one sentence and without reasoning to bolster a finding that the physician was not adequately apprized of the risks of the drug).

The court in *Koenig* reasoned that the Texas Supreme Court would not apply the read and heed presumption in a prescription drug case because such an application would be inconsistent with the Texas Supreme Court's rationale behind the presumption. 435 F. Supp. 2d at 556. The court explained that neither Texas courts nor the Fifth Circuit have applied the read and heed presumption to prescription drug cases; "[i]n th[ose] cases, the plaintiff, not the defendant, bore the burden of production as to causation." *Id.* Moreover, the Texas Supreme Court explained that the purpose of the read and heed presumption was, "(1) to excuse plaintiffs from having to make self-serving assertions that they would have followed adequate instructions, and (2) to assist plaintiffs in cases where the person to whom the warnings are directed has died, and evidence . . . is unavailable." General Motors Corp. v. Saenz, 873 S.W.2d 353, 359 (Tex. 1993). The court in *Koenig* reasoned that, "[n]either of these factors are relevant in a case involving a learned intermediary because it is the physician, not the plaintiff, who testifies about his decision to prescribe the product." 435 F. Supp. 2d at 557. This Court is persuaded by the reasoning of *Koenig* and shall not apply the read and heed presumption in this case.

C. Physician Informed of Risks, Irrespective of Source

In order to survive summary judgment based on the learned intermediary doctrine, Plaintiff must respond to Defendant's motion with evidence that (1) Defendant's warning label for Zyprexa® was inadequate, ***and*** (2) with an adequate warning Dr. Nett would not have prescribed Zyprexa®. *Koenig*, 435 F. Supp. 2d at 555. Even if Defendant's label were not presumed adequate, Plaintiff still succumbs to summary judgment as Dr. Nett's

deposition indicates that he knew of the very risks associated with Zyprexa® of which Plaintiff complains.

As an alternative argument, Defendant asserts that even if Defendant's warning was inadequate, it was not the proximate cause of decedent's injury because the prescribing physician, Dr. Nett, was aware of the risks. Plaintiff asserts that had Dr. Nett received an adequate warning he would have dealt with Zyprexa® differently, and may not have prescribed it at all. Dkt. No. 55, at 14. Plaintiff further states that Defendant has not met its burden of proof that Dr. Nett, at the time of the prescription, knew of all the risks an adequate warning would have provided. *Id.* Plaintiff argues,

> Dr. Nett does say that he was aware of a low risk of 'akathisia,' but there is nothing to indicate that he recognizes that to be a precursor of suicidality. . . . Moreover, Dr. Nett subsequently testified that, to know the side effect profile, 'I would have to get a PDR.'

Id. at 3 (citing Dkt. No. 47, Ex. B at 81-83, 120). *Compare* Dkt. No. 47, Ex. B at 120, *infra* (completing Dr. Nett's sentence after he was interrupted by the attorney conducting the deposition). This Court finds this depiction of Dr. Nett's deposition testimony to be grossly misleading. Provided below are brief excerpts of Dr. Nett's deposition.

> Q . . . [D]o you remember this class of antipsychotic medications can cause some restlessness, or what's sometimes called akathisia?
> A Yes.
> Q And at the time you prescribed that for him, you were aware of that?
> A Yes. Akathisia is fairly rare as far as, you know, fullblown. But it's the irritability . . . . I described it as you might get irritable as though you had two extra cups of coffee and you're kind of jumpy a little bit. And I wanted him to report that.

Dkt. No. 47, Ex. B at 81-82.

> Q . . . [Y]ou know, Zyprexa is known as an atypical psychotic?
> A Yes.
> . . .
> Q What about restlessness, or akathisia, do the atypicals have that same possibility of a rare side effect?
> A It – it does.

Id. at 82.

006454

EXHIBIT A
PAGE 13 OF 19

Q In July of 2002 when you prescribed [Zyprexa], what did you know about the side effect profile of Zyprexa? And if you'd give me some specifics, you know, what it caused –

A It can cause –

Q – frequency of cause – of what it caused.

A I mean, I would have to get a PDR to be exact –

Q Sure.

A – to the amount of sedation. But sedation, lightheadedness, dizziness, moodiness, irritability, agitation, can be easily observed with this product. . . . And [decedent] was to report any rage, violent anger, intrusive thoughts.

Id. at 120.

Q . . . Had anyone from Eli Lilly ever discussed with you the potential for Zyprexa induced suicides, or suicidality?

A I believe that's been brought up. . . .

Q . . . [W]e really need to focus on 2002. . . .

A Yeah, I mean, I am reasonably sure that such dialogue had occurred.

. . .

A I'm aware of akathisia enhanced suicides if I'm going to prescribe a product. . . . Because of enhanced concerns for side effects, including suicide, risk benefit in [decedent] at that time was valuable to try [sic].

. . .

A He would have been told, as illustrated in chart notes, concerns for irritability and agitation that go beyond that. He was asked specifically for depression, suicidal thoughts, intrusive thoughts –

Id. at 128-29.

Dr. Nett's testimony establishes that he was aware that patients who take Zyprexa® could develop akathisia, akathisia may be a precursor to suicide, and suicidal thoughts may be a risk for patients taking Zyprexa®. These are the very risks of which Plaintiff argues that Defendant failed to adequately warn. See Dkt. No. 55, at 13.

Similarly, in *Koenig*, a district court was persuaded that the prescribing physician was adequately aware of the risks associated with the medication because in his deposition the physician testified that he was aware of the risks the plaintiff complained of. 435 F. Supp. 2d at 555. However, the court was also persuaded that an alleged inadequate warning did not cause plaintiff's injury because the physician testified that none of the additional information provided to him after he prescribed the medication would have changed his mind. *Id.*

The district court in *Norplant* likewise held that where the physicians were unequivocal that new information about the risks would not have changed their decision to prescribe the medication, an inadequate warning was not the proximate cause of plaintiff's injury. 955 F. Supp. at 710-11. The court went further to explain that where a physician testifies that he was aware of the risks of which plaintiff complains, it is then the plaintiff's burden to prove that a different warning would have changed the physician's decision to prescribe the medication. *Id.* at 711.

To contrast, in *Anderson*, a district court found that a drug label that did not adequately warn the prescribing physician of the medication's risks was the proximate cause of the plaintiff's injury. 77 F. Supp. 2d at 808. While the prescribing physician testified that he did believe that he had ample knowledge about the risks associated with the drug, he also conceded that he had no knowledge of a variety of studies which linked the drug and the injury plaintiff suffered. *Id.* at 808-09. The court then reasoned that the physician was not "in a position to fully appreciate [the drug's] risks." *Id.* at 809.

While Dr. Nett did not explicitly state that even with recent evidence about the risks of Zyprexa® he would have nonetheless prescribed it to decedent, he did state that he knew of all of the risks at the time he wrote the prescription. Moreover, unlike in *Anderson*, there is no evidence that Dr. Nett was unaware of studies out at the time he prescribed Zyprexa® which linked the drug to akathisia or suicide attempts. Rather Dr. Nett indicated that he was aware that Zyprexa® could cause akathisia in some patients and that akathisia could cause suicidal thoughts. Dkt. No. 47, Ex. B at 82, 128-29. In fact, Dr. Nett further pointed to evidence that he knew of this risks when he prescribed Zyprexa® for decedent when he indicated that decedent was asked to report "depression, suicidal thoughts, intrusive thoughts." *Id.* at 128-29. Plaintiff has not provided this Court with evidence that Dr. Nett would have not prescribed Zyprexa® had Defendant provided him with an alternate warning label. Therefore, even if the Zyprexa® warning label was inadequate, it was not the proximate cause of decedent's death as Dr. Nett was informed about the risks of Zyprexa®.

006456

EXHIBIT A
PAGE 15 OF 19

D. Adequate Warning for Mixing Zyprexa® with other drugs

To the extent that Plaintiff's complaint may be construed to contain another cause of action for failure to warn of risks associated with "polypharmacy," the claim similarly succumbs to summary judgment. There is no summary judgment evidence that Dr. Nett knew of any potential risk if a patient were prescribed Zyprexa® and Paxil®. Summary judgment is appropriate because there exists no genuine issue of material fact as to whether the warning provided was adequate.

As explained above, the FDA approved the warning labels Defendant provided for Zyprexa®. Dkt. No. 46, Ex. A. Therefore, this Court may presume that the warning was adequate. TEX. CIV. PRAC. & REM. CODE ANN. § 82.007(a). It was Plaintiff's burden to demonstrate a genuine issue of material fact and provide evidence which would rebut the presumption. *Id.*; *Ackermann*, 471 F. Supp. 2d at 749. Plaintiff did not. Plaintiff asserted that Defendant failed to warn against mixing Zyprexa® with Paxil®; again, arguing that this is a "no warning" case as opposed to an inadequate warning case. Dkt. No. 55, at 15, 16.

However, exhibit 4, provided to this Court by Plaintiff and identified as the label for Zyprexa® in 2002, does warn against prescribing olanzapine with other drugs. Dkt. No. 55, Ex. 4 at 2. It warns physicians that they should discuss with their patients, "*Drug Interactions* – . . . Given the primary [Central Nervous System] effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs . . . ." Moreover, this Court takes judicial notice that Paxil® is a centrally acting drug. *See Paxil®, Prescribing Info., available at* http://www.fda.gov/Medwatch/SAFETY/2006/Paxil_PI.pdf, at 3:84.

Defendant merely asserts that its label is adequate and argues that FDA approval warrants a presumption that the label is adequate. The report of Plaintiff's expert witness, Dr. Healy, provides no evidence that the warning label is inadequate. It states only,

> As early as 1991, in an article by Montgomery et al these authors noted that the addition of Prozac to an antipsychotic could exacerbate extrapyramidal problems and cautioned that the possibility of such hazards need to be borne in mind when these groups of drugs were combined. [citation omitted] It has remained *clinical wisdom* ever since that the risk of extrapyramidal problems including akathisia is increased by combinations of an SSRI and an antipsychotic.

Dkt. No. 35, Ex. 1 at 23 (emphasis added). This statement about "clinical wisdom" alone does not defeat the statutory presumption that the Zyprexa® warning label is adequate.

IV. Exceptions to the Learned Intermediary Doctrine

Plaintiff argues that if this Court postulates that the Texas Supreme Court would adopt the learned intermediary doctrine, it follows that the Texas Supreme Court would similarly adopt exceptions to the doctrine recognized by other jurisdictions. Dkt. No. 55, at 7. Plaintiff correctly indicates that Defendant has the burden of carrying the affirmative defense of the learned intermediary doctrine; however, should this Court also apply the exceptions to this case, the burden shifts to Plaintiff.

A. Overpromotion of Zyprexa

Plaintiff argues that Texas law will incorporate the exception for overpromotion to the learned intermediary doctrine. Dkt. No. 55, at 6. However, as discussed above, this Court finds that Plaintiff has not provided evidence to establish overpromotion. Therefore, this Court will not opine whether Texas courts would adopt the exception of overpromotion to the learned intermediary doctrine.

B. Use of Mass Media to Promote Zyprexa

Plaintiff asserts that the mass media exception bars application of the learned intermediary doctrine to this case. Dkt. No. 55, at 11. First, Plaintiff provided no evidence of Defendant's mass media distribution of information in 2002. Second, this Court does not predict that the Texas Supreme Court would adopt that exception to the learned intermediary doctrine.

Plaintiff alleges that Defendant used the mass media, i.e., a website, to promote Zyprexa® in 2002. Dkt. No. 55, at 11. However, Plaintiff provided this Court with the 2007 website. *Id.*, Ex. 10. Plaintiff merely states, "[t]his website was up and running at the time [decedent] received his Zyprexa prescription." Dkt. No. 55, at 11. Plaintiff offered no evidence from depositions, interrogatories, or documents received from Defendant during discovery which would substantiate this allegation.

Moreover, Plaintiff asserts that "there was, and is, no warning whatsoever on . . . the website . . . about any link with suicidality or its precursor conditions like akathisia. *Id.* at 11-12. However, this Court examined exhibit 10 and on the portion of the website marked, "Important Safety Information for Olanzapine," Defendant states that in a six week clinical trial of olanzapine, five percent of participants taking the drug reported experiencing akathisia as compared with only one percent of the participants who took the placebo. *Id.* at 7. Furthermore, on the portion of the website marked, "Important Safety Information about Zyprexa® (olanzapine)," Defendant warned, "[t]he symptoms of bipolar disorder or schizophrenia may include **thoughts of suicide** or of hurting yourself or others. If you have these thoughts, tell your doctor or go to an emergency center immediately." *Id.* at 10 (emphasis in original).

The Fifth Circuit has already predicted that the Texas Supreme Court would not adopt mass marketing as an exception to the learned intermediary doctrine. *In re Norplant Contraceptive Prod. Liab. Lit.*, 165 F.3d at 379. The Court, looking to Texas appellate court cases, declared, "as long as a physician-patient relationship exists, the learned intermediary doctrine applies." *Id.* Furthermore, Plaintiff failed to cite any legal authority to persuade this Court that the Texas Supreme Court would adopt the exception. *See* Dkt. No. 55, at 11-13.

In *Norplant*, the plaintiffs accused the defendant of engaging in "'aggressive' marketing." 165 F.3d at 379. The Circuit Court found the facts unpersuasive. *Id.* The Court reasoned that the use of mass media could not subject a manufacturer to liability where the plaintiffs failed to provide evidence that they "actually saw, let alone relied, on any marketing materials [distributed to the patients]." *Id.*

Similarly, in this case, Plaintiff admits that there is no evidence that the decedent saw Defendant's website. Dkt. No. 55, at 12. Therefore, even if this Court were to predict that the Texas Supreme Court would adopt the exception to the learned intermediary doctrine for the use of mass media, which it does not, Plaintiff has nonetheless failed to present evidence to warrant application of the exception.

V. Conclusion

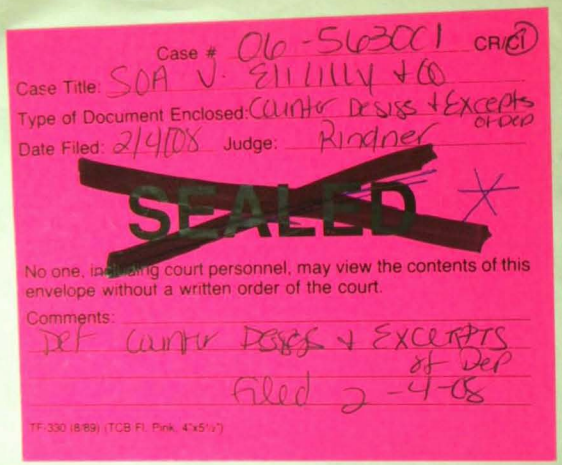
Summary judgment is appropriate as the learned intermediary doctrine properly applies to this case and shields Defendant from liability. Plaintiff failed to raise a genuine issue of material fact as to the doctrine or any exception to the doctrine. The Court therefore **GRANTS** Defendant Eli Lilly and Company's Motion for Summary Judgment. Dkt. No. 47. This Court **VACATES** its opinion and order dated November 14, 2007. Defendant's other motions, Dkt. Nos. 46, 48, 67, are rendered **MOOT**. The Court **DISMISSES WITH PREJUDICE** all of Plaintiff's claims against Defendant. The Court futher instructs the District Clerk to close this case.

DONE at Brownsville, Texas, on January 29, 2008.

Hilda G. Tagle
United States District Judge

006460

EXHIBIT A
PAGE 19 OF 19


Case # 06-563001 CR/C1

Case Title: SOA v. Eli Lilly + CO

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Date Filed: 2/4/08 Judge: Rindner

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* See Judge Rindners 6/13/08 order pages 19; 20, # 14

documents unsealed Linda 8/11/08

Pages 6461 - 6603

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, v. ELI LILLY AND COMPANY, Defendant.	Case No. 3AN-06-05630 CI **DEFENDANT ELI LILLY AND COMPANY'S DEPOSITION COUNTER-DESIGNATIONS FOR TRIAL**

Defendant Eli Lilly and Company ("Lilly") counter-designates for trial the following deposition transcript excerpts in response to Plaintiff State of Alaska's Trial Deposition Designations:

A. Deposition of Charles Beasley, Jr. M.D. – Volume 1, designated pages Exhibit A.

Start (Page:Line)	End (Page:Line)
58:22	59:1
81:16	81:18
81:20	81:24
82:1	82:10
83:2	83:8
106:1	106:1
109:15	109:16
114:8	114:24
142:24	143:7
143:21	143:23
144:1	144:12
148:5	148:18
149:20	149:24
184:23	185:15
186:24	187:4
187:6	187:10
202:17	203:9

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208:20	209:10
210:2	210:11
210:16	211:13
218:9	218:11
234:5	234:8
234:10	234:17
235:8	235:12
236:2	236:2
236:19	236:22
243:24	243:24
248:5	248:10
253:11	253:13
253:15	253:16
258:24	258:24
272:18	272:22
272:24	273:8
391:3	391:7
391:10	391:18

B. Deposition of Charles Beasley, Jr. M.D. – Volume 2, designated pages Exhibit B.

Start (Page:Line)	End (Page:Line)
446:10	446:18
514:18	515:11
516:8	516:23
516:24	518:10
518:11	519:6
519:7	520:6
522:6	523:15
523:19	525:12

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C. Deposition of Alan Breier, M.D. – Volume 1, designated pages Exhibit C

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27: 14	28: 12
95: 6	95: 23
96: 5	96: 8
96: 11	97: 11
97: 14	98: 12
98: 15	98: 16
98: 19	100: 20
101: 9	101: 19
105: 21	105:24
112: 3	112: 10
122: 1	122: 17
123: 12	123: 14
140: 12	140: 14
140: 17	140: 24
141: 3	141: 18
163: 22	164: 3
164: 6	164: 10
164: 16	165: 13
185: 24	186: 19
189: 23	190: 8
201: 10	202: 2
222: 1	223: 1
273: 22	274: 5
291: 9	291: 24
303: 24	303: 24
304: 1	304: 7
352: 20	352: 22
353: 6	353: 12
358: 7	358: 10
358:13	358:24

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D. Deposition of Alan Breier, M.D. – Volume 2, designated pages Exhibit D.

Start (Page:Line)	End (Page:Line)
406: 13	406: 13
428: 17	429: 8
433: 10	433: 21
451: 15	451: 16
451: 19	452: 17
457: 12	458: 10
480: 4	480: 6
526: 6	526: 9
526: 12	526: 22
406: 13	406: 13
428: 17	429: 8

E. Deposition of John C. Lechleiter, Ph.D, designated pages Exhibit E.

Start (Page:Line)	End (Page:Line)
40:13	40:24
71:3	71:10
92:17	92:19
111:23	112:9
120:14	121:7
122:6	122:18
124:21	125:2
125:15	125:19
149:3	149:12
267:16	268:11
275:23	276:14
277:12	277:17
280:11	280:18
286:22	287:2
293:7	293:10
300:13	300:21
310:14	310:20

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F. Deposition of David Noesges, designated pages Exhibit F.

Start (Page:Line)	End (Page:Line)
114:20	115:8
118:20	119:17
165:10	165:11
173:2	173:4
173:19	173:21
195:24	196:6
200:17	201:16
209: 14	209: 21
212:8	213:11

G. Deposition of Sidney Taurel, designated pages Exhibit G.

Start (Page:Line)	End (Page:Line)
60:10	60:17
74:1	74:3
74:5	75:7
77:17	77:23
78:1	78:14
78:16	78:20
78:22	79:8
80:22	81:1
81:3	81:14
85:2	85:14
85:16	86:5
86:7	86:19
94:11	94:18
94:20	95:4
95:8	95:12
95:21	96:6
103:17	103:18
103:20	104:3
104:5	104:7
104:9	104:24
120:6	121:7
122:10	122:22
123:2	123:3

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Start (Page:Line)	End (Page:Line)
123:6	123:21
168:23	169:6
187:18	188:3
202:1	202:3
202:5	202:22
213:3	213:19
218:18	218:24
220:19	221:4
237:8	237:15
245:14	245:19
245:21	246:10
246:19	247:4
247:22	247:24
248:15	249:8
249:14	249:15
249:17	249:19
250:3	250:7
256:9	257:2
259:19	260:2
266:14	267:4
267:10	267:15
267:21	268:8
293:10	293:14
293:17	294:5
294:19	295:3
306:11	306:18
307:4	307:9
307:11	307:21
308:9	308:14
309:15	310:8
330:8	330:8
336:10	336:18
336:22	337:3
337:7	337:11
337:13	337:16
350:18	351:7
354:21	355:9

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Start (Page:Line)	End (Page:Line)
366:2	366:4
366:6	366:16
367:11	367:24
368:13	368:22
391:9	391:13
396:6	396:17
409:3	409:8

H. Deposition of Gary Tollefson, M.D. , designated pages Exhibit H.

Start (Page:Line)	End (Page:Line)
82:6	82:15
86:12	89:8
96:23	97:13
97:16	97:23
98:2	98:13
126:10	127:11
142:15	143:9
152:6	153:5
153:22	155:23
156:6	156:10
157:3	157:6
157:9	157:19
203:13	204:3
208:10	208:23
225:1	225:8
225:11	225:19
225:22	225:23
226:2	226:4
226:16	227:5
250:4	250:7
270:15	271:4
276:21	277:5
301:6	301:9
301:12	301:16

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I. Deposition of Robin Pitts Wojcieszek, designated pages Exhibit I.

Start (Page:Line)	End (Page:Line)
28:1	28:12
90:12	90:22
124:17	124:17

Lilly's counter-designations are subject to this Court's rulings on Motions in Limine. Lilly reserves the right to introduce any of the deposition testimony set forth in plaintiff's deposition designations. Lilly further reserves the right to counter- designate any deposition testimony not yet taken in this or any other matter. Lilly further reserves the right to introduce additional deposition testimony not included above, if deemed necessary for the rebuttal of testimony from witnesses called by plaintiff or exhibits introduced by plaintiff at the trial of this action.

DATED this 4th day of February, 2008.

PEPPER HAMILTON LLP
Nina M. Gussack, admitted *pro hac vice*
Andrew R. Rogoff, admitted *pro hac vice*
Eric J. Rothschild, admitted *pro hac vice*
and
LANE POWELL LLC
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I certify that on February 4, 2008, a copy of The foregoing was served by hand on:

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IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: MDL-1596

ZYPREXA PRODUCTS

LIABILITY LITIGATION

THIS DOCUMENT RELATES TO:

ALL CASES

CONFIDENTIAL

- - -

July 26, 2006

- - -

Videotape deposition of

CHARLES BEASLEY, JR., M.D.

- - -

GOLKOW LITIGATION TECHNOLOGIES
1600 John F. Kennedy Boulevard
Suite 1210
Philadelphia, Pennsylvania 19103
(877) DEPS-USA

A. Yes, sir. In this case, the approximate size of that new drug application was a million and-a-half pages and 18 CD-ROMs.

Q. Okay. And, did you say a million and-a-half pages?

A. A million and-a-half pages.

Q. Okay. That would be -- I'll do the calculation later, but there's, approximately, 2500 pages of paper in a box of documents. Do you know how many boxes that was?

A. I don't recall the specific number of boxes. Of course, these were in notebooks. I remember seeing the total set.

Q. Yeah. If my math is right, I think that works out to about 500 boxes?

A. It could be.

Q. Okay. And you also said there were 18 CD-ROMS?

A. That's correct.

Q. Okay. And the FDA then reviews those reports that were prepared and written up by Lilly in this case, correct?

A. That would be correct.

Q. And often, the FDA has an outside advisory committee composed of independent doctors and scientists who are expert in the field that the drug is going to be used in, to review the safety and efficacy data and advise the agency whether it would be appropriate for the drug to be marketed; isn't that correct?

A. That occurs on occasion, yes.

Q. In fact, that's generally the case, is it not?

A. At the current time, I don't know whether that is a majority or a minority of drugs. I'm just not aware of --

Q. Okay. Was there an FDA advisory committee that reviewed the Zyprexa NDA?

A. No, there was not.

Q. Okay. Do you know how it was that the FDA took the step of not having an FDA advisory committee review the drug?

A. No, I do not.

Q. Okay. Did Lilly lobby FDA not to have an FDA advisory committee?

A. No, we did not.

Q. Okay. I got the impression from reading some of your documents that you really very much enjoyed working on the development of Zyprexa but that you became unhappy about how the drug was marketed at some later point after 2000. Was that a correct impression on my part?

A. I really had very little experience with the marketing after that, actually, after the initial marketing development in preparation of the drug. I wouldn't characterize myself as necessarily unhappy or dissatisfied with how the drug was marketed.

Q. You said you wouldn't necessarily call yourself unhappy. What would you say?

A. That I had very little input into marketing at that point in time, after the initial -- after the initial marketing in 1996, 1997. I am -- sitting here today, I don't know whether I would have rather had

more or less.

I was not consulted on marketing issues as we had taken the company and made very clean breaks, generally, between the team, the global team, and all of the affiliates that became responsible for marketing.

Q. At the time, did you feel that you should have been consulted more with respect to safety issues?

A. Certainly, the team consulted -- the team consulted me. And my feeling was that I was providing good input to the product team and medical, in general, and that these individuals were then advising the marketing folks in their individual affiliates.

Q. Okay. And when you saw how those -- how that advice got transmitted to the marketing folks, were you happy with what they did?

A. You know, I haven't really thought about whether I was happy or unhappy. I was certainly very convinced that the --

is used potentially clinically significant.
Q. Okay. And that paragraph goes on to note that, "Patients who remained on olanzapine for 12 months gained an average of 24 pounds at the end of 12 months," correct?
A. That's correct.
Q. Okay. By the way, if 40 percent of the people who took the drug for any period of time had more than -- had equal to or more than 7 percent body weight that means that 40 percent of the people who took the drug for any length of time had potentially clinically significant weight gain, correct?
A. That's correct.
Q. Okay. And then there's a paragraph below that that's in italics which states quote, "Several advisors commented on the association of olanzapine with weight gain and encouraged Lilly to subject the data to a full analysis. Clinically significant weight gain is a risk factor for other conditions such as increased blood pressure,

increased cholesterol and type II diabetes. The advisors also noted that Lilly has an opportunity to develop strategies to help manage the weight gain." Do you see that language?
A. Yes, I do.
Q. If we got 40 percent of the people who take the drug for any length of time having potentially significant weight gain, that means that those people are going to be at risk for those conditions that are referred to there, increased blood pressure, increased cholesterol and type II diabetes, correct?
MR. SEE: Object to the form.
A. That means that what they have is one risk factor for potentially developing these conditions.
Q. Um-hum. And you would expect in a population of people that if you enhance the risk by taking the drug that some people are, indeed, going to develop increased blood pressure, increased cholesterol, and type II diabetes as a result of using the drug,

correct?
MR. SEE: Object to the form.
A. Individuals might or might not experience these phenomena either as a result of any number of things. And these would be appropriate for analysis.
Q. Well, you may not be able to predict which individual is going to actually contract any of those illnesses as a result of taking the drug. But if, in fact, the drug increases the risk of those adverse reactions as a population of people taking the drug, you would expect that some people would, indeed, develop those adverse reactions as a result of using the drug, correct?
MR. SEE: Object to the form.
A. Individuals might or might not. And that's why it would be important to analyze the incidence of those things amongst patients taking the drug.
Q. But if you step away from the individuals and look at the population, it's a virtually certainty that if you increase

the risk of an adverse reaction that some people within that group will, in fact, contract the adverse reaction as a result of using the drug, correct?
MR. SEE: Object to the form.
A. That is certainly the theory that would be intuitive and logical. What I am pointing out is that one would then need as, I think these advisors were doing, suggesting, scrutinizing our data and looking for whether or not those phenomena were observed.
Q. And, in fact, those phenomena were observed, weren't they?
MR. SEE: Object to the form.
Q. Didn't your clinical trials show that there was increased cholesterol and also type II diabetes?
MR. SEE: Object to the form.
A. I do not recall the specifics of the results of all the analyses of cholesterol. My recollection is that taking all of the data in total, we did not see an association between the drug and cholesterol.

Page 82

And with respect to diabetes, the same.
Clearly cases were observed in what we would call temporal association, individuals in the clinical trials did develop diabetes, a small number, and we did not, in looking at all the data, see the compound as -- given the data that we had, as there being an increased or excessive development within our clinical trial database.
Q. With respect to the weight issue, your labeling did not inform physicians that for all patients treated with olanzapine for any amount of time 40 percent gained more than or equal to 7 percent of the body weight; is that correct?
MR. SEE: Object to the form.
A. Well --
Q. You got to answer that question "yes" or "no" or "I don't know?"
A. Well, it, specifically, did not. What our label did --
Q. Thank you.
MR. SEE: You can finish your answer.
A. Did inform physicians about, from my perspective, was a rather excellent characterization of the weight gain. And we indicated that 56 percent of individuals treated long-term in our clinical studies overall, gained 7 percent or more body weight.
MR. ALLEN: Object to everything after "it did not" as nonresponsive.
MR. SUGGS: I join in the objection.
QUESTIONS BY MR. SUGGS:
Q. Your labeling also did not, specifically, inform physicians that patients who remained on olanzapine for 12 months gained an average of 24 pounds at the end of those 12 months, correct?
A. No, it did not.
Q. Okay. And on Page 8 at the bottom there's a -- in the last paragraph, there's a heading that says Laboratory Analytes?

Page 84

A. Yes.
Q. And what does that phrase mean?
A. This would refer to all of those things that are measured in blood or urine, specific measurements such as sodium, glucose, or white blood cells, that are measured in a laboratory.
Q. And, in fact, the laboratory testing that was done on HGAJ subjects showed that there was a statistically significant increased incidence of high glucose and also high cholesterol; isn't that correct?
MR. SEE: Object to the form.
A. Again, without benefit of looking at the -- at the entirety of the data, my only recollection is with regard to a analysis of the, what we call the categorical incidence of elevated glucoses relative to haloperidol, based on what we call anytime data. I recall this number as being statistically significant. That is one number that needs to be appropriately put in the context of, actually, about nine analyses.
Q. You say "based on what we call anytime data I recall this number as being statistically significant." What was "this number" that you're referring to?
A. I believe it was the percentage of individuals who showed a shift from a normal glucose to what would be considered a high glucose.
Q. Okay. And you were aware of that at what point in time?
A. I don't know the specific. It would have been when the data were analyzed.
Q. It would be sometime between when the data was cutoff in February of 1995 and when it was submitted to FDA in September of 1995, correct?
A. That would have been correct.
MR. SUGGS: Okay. Let me show you a computer printout from that time. I'm handing you what's been previously marked as Plaintiff's Exhibit 1605.

Page 106

you point out to the group that "not everybody gained weight, but there are some patients who gained a substantial amount. In fact, that's the most consistent nontherapeutic physical finding you're talking about." Do you see that?
A. Yes, I do.
Q. Then there's a question from a Dr. Casey -- was that Dr. Daniel Casey?
A. Yes, it was.
Q. And he was one of your outside experts, correct?
A. Yes.
Q. And is he a psychiatrist or endocrinologist?
A. He's a psychiatrist.
Q. But he has a special interest in this issue of whether diabetes is related to antipsychotic drugs, correct?
A. I think he has -- I believe that he has published or at least presented data on this issue.
Q. Okay. And had he as of that time or did this become a matter of interest

Page 107

to him after 1995, if you know?
A. I don't believe it was an interest of his. And I say that because I know that his interest at that time was particularly in the area of tardive dyskinesia.
Q. Okay. But in any event, at this meeting in December of 1995, Dr. Casey asked you after you told him about the weight gain, he says quote, "Did any develop diabetes?" And I'm just going to read the interchange that goes on there. You responded by saying, "Very few people have developed type II diabetes during the time of this trial. We have over 400,000 patient days of olanzapine exposure, and the rate for diabetes, a couple of these cases I know are type I who got out of control. Treatment-emergent diabetes, does," and then you're interrupted by Dr. Potkin who asked, "Does that happen more often on olanzapine?" And then there's a response by Todd Sanger, who said, "I don't believe it did." Who is Mr. Sanger?

Page 108

A. Dr. Sanger was the chief statistician for the project.
Q. Okay. And then you went on to say quote, "We don't have comparative data long term for haloperidol analyzed at this point. We need six-week data."
Then Todd Sanger jumped in and said, "We had 16 cases of treatment-emergent diabetes, which is .6 percent, of all 2500 patients. This is adverse event."
Then you jumped in and said, "Spontaneous adverse event."
And then Dr. Potkin -- by the way, he was another one of the outside consultants?
A. That's correct.
Q. Okay. And where was he from?
A. I believe he was from a university in southern California, although I'm not sure which institution.
Q. Do you know if he's still there?
A. I'm not sure.

Page 109

Q. Was he a psychiatrist or an endocrinologist?
A. He's a psychiatrist.
Q. Okay. Anyway, Dr. Potkin asked quote, "You were measuring glucose all along?" You see that question?
A. Yes.
Q. And then your response to him was, "And we don't see anything," correct?
A. That's correct.
Q. You made no mention of the results of that computer printout that we discussed some minutes before, correct?
A. No, I did not. This was a statement made that was based on interpreting the totality of our data.
MR. SUGGS: Move to strike that portion of your answer which is nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. You would agree with me, wouldn't you, sir, that the advisory committee of your outside consultants -- by the way, these folks were all hired and

to have; isn't that correct?
A. It is intended to be a summary of the data that would allow the effective and safe use of the medication. That is correct.
Q. And it's absolutely necessary that the information in there is complete and accurate, correct?
A. Again, it's important that it allow for the safe and effective use of the medication. From a concept of complete, again, all 1.5 million pages can't be contained.
So the intent is that it is a summary of the most pertinent information that will allow the drug to be prescribed appropriately.
Q. And the doctor uses that information contained in the package insert to weigh both the risks and the benefits of using a drug and make an evaluation as to whether it is appropriate for him to prescribe that drug to his patient, correct?
A. That's correct.

Q. Okay. And in the labeling there is a hierarchy of significance of information about adverse reactions or potential safety issues, is there not?
MR. SEE: Object to the form.
A. There are a series of different sections in the U.S. label.
Q. For example, there's, there can be a warning section in the drug label, correct?
A. Generally, there is a warning section.
Q. And there's also what's referred to as a precaution section, correct?
A. That's correct.
Q. And there's also what's referred to as an adverse reaction section, correct?
A. That is correct.
Q. And that is a decreasing hierarchy of significant, if the you will, is it not?
MR. SEE: Objection to the form.

A. I'm not exactly sure what you mean by significance. If I may?
Q. Sure.
A. Significance could be the extent of which there is understood to be an association, so degree of association. That can be one thing that you might mean by significance.
The other thing that you could mean by significance would be the clinically significance of an -- of an individual term or observed event.
If you mean the latter, then those three sections don't have decreasing significance.
Q. Okay. Well, if, for example, your -- if, for example, you've got an adverse reaction or that can occur with a drug, let's call it syndrome X, okay? If you've got syndrome X that's -- and it's listed in the --
MR. SUGGS: I want to wait for the fire engine to go by.
MR. ALLEN: That won't be the

last one of those either.
MR. SUGGS: There was one this morning at 5:30.
MR. ALLEN: We have at least three a day.
MR. SUGGS: I heard the one this morning at 5:30. Okay. I think we're safe now. Let me go back to my question.
QUESTIONS BY MR. SUGGS:
Q. Let's assume that a particular drug has something bad that can happen with it that's called syndrome X. Okay? If it's just listed in the adverse reaction section, then that means that it has been seen, syndrome X has been seen in people who have used the drug, correct, and it really means not much more than that, isn't that true?
MR. SEE: Object to the form.
A. It means that it has been seen. I believe that the standard language that the Food and Drug Administration would include in a preamble to that is that that

Page 142

from literature, for example, as well as other sources.

Q. Okay. And are you aware, sir, that it's generally estimated that only 1 percent, maybe 10 percent of the number of adverse events that, actually, occur in the use of a drug ever get reported?

MR. SEE: Object to the form.

A. The literature that I am familiar with estimated between 1 in 5 and 1 in 30 cases would be reported. This was in this time frame when I was more involved with doctors Funk and Hornbuckle. I believe that more recent literature has suggested it may be as low as one in a hundred.

Q. Okay. So if, for example, you got ten adverse event reports of -- I'll use syndrome X that we were talking about before, based on the current literature that would indicate that probably out in the real world there's maybe a hundred times that amount, which would be what, a thousand?

MR. SEE: Object to the form.

Q. I take it back. You said one

Page 143

in a hundred.

A. I said you would multiply, and the best understanding that I have of the literature is that there is not a good estimator for what this is, but you could multiply by between 5 and 100, that would be the range.

Q. Okay, between 5 and 100.

A. So if you had 10 it might be 50.

Q. Or it might be --

A. Or it might be a hundred -- thousand.

Q. Okay.

A. A pretty wide range.

Q. Okay. In any event, the main thing is though, that if you get one adverse event report you've got to assume that there's a bunch more out there.

MR. SEE: Object to the form.

Q. How big that bunch is we're not sure about but there's, probably, a bunch more out there, right?

MR. SEE: Object to the form.

Page 144

A. There may be. One thing that we take into consideration when we consider that, and it's supported by some of the literature, is to what extent the drug -- a drug is having an event reported is new, how serious the event is, and to what extent the event has been described in either the medical literature or the -- or the public nontechnical literature.

So there are a number of things that we take into consideration when we do an estimate of this range.

Q. Okay. If I could direct your attention, sir, to page, I believe it's 14. And as it turns outs there is --

A. May I --

Q. -- there's two sets of numbers on these pages.

A. May I, just since I opened this document up.

Q. Sure.

A. It has refreshed my memory with respect to the reporting structure for Doctors Hornbuckle and Fung. There is a

Page 145

reference to Edmundo, so I believe that they would have reported to Dr. Muniz.

Q. How do you spell that?

A. I must confess I have difficulty with spelling Beasley on occasion, so, I believe it would be M-U-N-I-Z.

Q. Okay.

MR. ALLEN: Or something thereabout.

A. It's a -- he's originally from the Dominican Republic. It's a Latin name. It's hard for me to spell.

Q. If I could direct your attention to Page 14, and I'm referring to the bottom most number of Page 14.

A. Okay.

Q. I believe you're on the same.

A. Is it --

Q. It has two numbers, one -- it's my 14 as opposed to the 13 that was on the original document. You're there. This is the section on showing blood sugar elevation, correct?

A. Clintrace Database. This

Page 146

would be spontaneous adverse events, yes.
Q. Showing blood sugar elevation, correct?
A. Actually, not necessarily. For example, you see the term "ketosis."
Q. Right.
A. That might not refer to an actual case of blood sugar increase. These were terms that were thought to be possibly related, not definitely related. Some of them are clearly definitely related.
Q. In any event, whoever prepared this report, well, Doctors Hornbuckle and Fung, have a bold heading there entitled Blood Sugar Elevation, correct?
A. That's correct.
Q. And then below that they have six different subcategories, including hyperglycemia, diabetes mellitus, diabetic acidosis, diabetic coma, ketosis, and glucose tolerance decreased, correct?
A. That's correct.
Q. And then below that they have

Page 147

another bold heading that says Unduplicated Reports, correct?
A. That's correct.
Q. And that totals the numbers of each of those categories, correct?
A. Again, not technically. For example, if we take the first column it's 27, 28, 29, 30, 32, but yet the number is 28.
Q. Let me restate, it totals the unduplicated reports?
A. Yes.
Q. Okay. And it shows that if you looked at all four quarters of -- or I guess eight quarters from '96 to '98 there were a total 194 unduplicated reports of what they had grouped together as blood sugar elevation, correct?
A. That's correct.
Q. Okay. And again, using the numbers we've talked about before, if we multiplied by -- well, the numbers we talked before in terms of what the range might be with respect to what's happening out in the real world. If we multiply the 194 by 5

Page 148

that's almost a thousand and if we multiply by a hundred it would be almost 20,000 cases of blood sugar elevation, correct?
A. That is correct. As I said, there are -- there are things that influence how we use these numbers in our multipliers.
We would have thought about the midrange to potentially the upper range for, let's say, hyperglycemia or glucose tolerance decreased for the terms of diabetic acidosis and diabetic coma, we would have thought that these would be much toward the lower end of the range, again, because these are more serious.
So we would have, in general, if we were trying to do our best estimate, apply different correction factors or different ranges of correction factors.
MR. ALLEN: Object to everything after "that is correct" as nonresponsive.
Q. If you look, though, at group, the same grouping that Doctors Fung and Hornbuckle created for this report, we

Page 149

would have a range of between, roughly, a thousand and 20,000 unduplicated reports of events in that grouping, correct?
MR. SEE: Object to the form.
A. If we used the -- and I think you have correctly used the five to a hundred rounding off to 200.
Q. Okay. Very good. Do you recall that by December of 1998, which was just a couple months after this -- well, let me back up for a second.
With respect to Exhibit 988. The one you have there. It's marked confidential on every page. Was it standard drill at Eli Lilly to mark reports of adverse event reports as confidential?
MR. SEE: Object to the form.
A. Actually, I don't know whether all such reports would be so marked. Clearly these are information that are, the reports themselves and analysis similar to this are not confidential because they are shared with Food and Drug Administration and other regulatory bodies.

Page 182

I do have concerns regarding making any connections between olanzapine induced weight gain and hyperglycemia. Therefore, in my opinion, I would not include your following statement, quote, Patients who gain weight may develop insulin resistance which may lead to hyperglycemia and diabetes, end quote. Do you see that language, sir?

A. Yes, I did.

Q. Were you made aware that Dr. Kinon had made that recommendation that the marketing department not state that patients who gain weight may develop insulin resistance which may lead to hyperglycemia and diabetes?

MR. SEE: Object to the form.

THE WITNESS: If I can -- I think I got the question right. Was I made aware that Dr. Kinon had sent this e-mail?

MR. SUGGS: Yes.

A. I don't recall that.

Q. Okay. Did you work with Dr. Kinon?

Page 183

A. Minimally. Dr. Kinon was in the U.S. Affiliate, one of the physicians in the U.S. Affiliate that worked with olanzapine. Some of my -- so I did have some interaction with him, as I was a consultant to the team, but not on a daily basis.

MR. SUGGS: Okay. Well, let's talk a little bit about the teams who were working on Zyprexa. I'm going to hand you what's been previously marked as MDL Plaintiff's Exhibit 8042.

(Whereupon, Deposition Exhibit(s) 8042 previously marked, was presented to the witness.)

MR. SUGGS: Which for the record is a November 29, 1999, e-mail from Michele Sharp to Gail Uminger, which then copies several other e-mails.

QUESTIONS BY MR. SUGGS:

Q. The first of which is an e-mail on November 28, 1999, from Edmundo Muniz to Michael Clayman, Timothy Franson with copies to Gregor Brophy, Kenneth Hornbuckle, Kenneth Kwong, correct?

Page 184

THE WITNESS: I was trying to look at the -- at the e-mail. Could you, again, direct me to, I guess --

MR. SUGGS: I'm directing you to the e-mail that was sent by Edmundo Muniz on November 28, 1999, to Michael Clayman, Timothy Franson with copies to Gregory Brophy, Kenneth Hornbuckle, Kenneth Kwong.

THE WITNESS: Yes.

QUESTIONS BY MR. SUGGS:

Q. Okay. And I believe you said earlier that Mr. Muniz -- am I pronouncing his name, right?

A. Muniz, Dr. Muniz, but yes.

Q. He was head of the pharmacovigilance department; is that correct?

A. That's correct.

Q. And who was Michael Clayman, one of the recipients of this?

Page 185

A. He was -- I believe at the time, he would have been the International Director for regulatory.

Q. Okay. And who is Timothy Franson?

A. And Timothy Franson, at the time, I believe, was the head of regulatory for the United States.

Q. Okay. And who is Gregory Brophy?

A. And Gregory Brophy would have been one of the regulatory people for the United States that interacted, specifically, with the Neuropharmacology division of the FDA.

Q. Okay. And then the other recipients of that e-mail were Kenneth Hornbuckle and Kenneth Kwong, both of whom we've discussed before, correct?

A. That's correct.

Q. And in his e-mail Dr. Muniz says, "Mike and Tim, below you will find the summary of issues discussed this week regarding hyperglycemia and Zyprexa. There

Page 186

are two types of initiatives," and then he lists what those two different types are, correct?
A. There are two types of initiatives, yes.
Q. And the first is a, what he refers to, as a cross-functional team -- pardon me -- cross-functional action team led by Alan Breier. Do you see that?
A. Yes, I do.
Q. And it states that the goal of this team is to bring to the same table all the groups and functions working to address the hyperglycemia issue, correct?
A. Yes.
Q. And the hyperglycemia issue was the fact that by November of 1999 there were published medical articles linking hyperglycemia with Zyprexa and you also had a number of adverse event reports linking hyperglycemia and Zyprexa, correct?
MR. SEE: Object to the form.
A. Yes, that would be correct.
Q. And, in fact, as we saw

Page 187

earlier, your clinical trials back in 1995 showed a statistically significant increased incidence of hyperglycemia with use of Zyprexa?
MR. SEE: Object to the form.
Q. Correct?
A. And I disagree with that. As we discussed, there was one finding in one clinical trial of many analysis showing that finding.
Q. Okay. He goes on to state in his memo, "This Action Team has a Steering Committee formed by N. Ascroft, A. Breier, J. Caro, R. DiMarchi, C. Fibiger, S. Paul, G. Probst and G Tollefson," correct?
A. Correct.
Q. And could you identify who N. Ascroft was?
A. She was, I believe, in medical plans so she was serving as a coordinator for the group.
Q. And Dr. Alan Breier, we've talked about him before. But I don't believe we've discussed his medical specialty. Do

Page 188

you know what it is?
A. He is a psychiatrist.
Q. Who is J. Caro?
A. J. Caro was, I believe, the head of the preclinical diabetes area and diabetes metabolism area.
Q. Who is R. Demarchi?
A. I do not recall what his, he's a Ph.D. I don't recall if he was a chemist or a pharmacokinetics.
Q. And who is C. Fibiger?
A. That would be Chris Fibeger, he was the head of preclinical psychopharmacology at the time.
Q. And who is S. Paul?
A. That, I believe, would have been Steve Paul, who was -- I don't know if as of yet he was the head of Lilly Research Laboratories or not.
Q. And who is G. Probst?
A. G. Probst was the head of toxicology.
Q. And Dr. Tollefson, we've talked about before. Do you know what his

Page 189

title was at that point?
A. I, again, think he was president of the -- of the Neuroscience Unit.
Q. And do you know what his medical specialty was?
A. Psychiatry.
Q. Okay. In that cross-functional action team, which was to bring to the same table all the groups and functions working to address the hyperglycemia issue, there wasn't, in what you've described to me, a single endocrinologist there?
A. That would have been Dr. Caro, a very eminent diabetologist.
Q. Okay. And the second type of initiative was the regulatory slash PHV and the Zyprexa team as described by Dr. Muniz, correct?
A. That's correct.
Q. Now, when it says regulatory slash PHV, is that regulatory pharmacovigilance?
A. That's correct.

Page 202

post-marketing safety surveillance of hyperglycemia, exploring the possibility of using GPRD to conduct database analysis, what's GPRD?

A. That is a database that, I believe, is available in the UK. So this was an intended epidemiologic study.

Q. Okay. And then Item D -- pardon me -- Item C rather, was "discuss Zyprexa label at a GPLC session and evaluate potential proactive regulatory strategies." Did I read that correctly?

A. Yes.

Q. Am I correct that GPLC stands for Global Product Labeling Committee?

A. That's correct.

Q. And what was the Global Product Labeling Committee?

A. This is a committee made up of a number of individuals holding fairly senior positions within the company. At the time it was chaired by, I believe, Dr. Clayman, so --

Q. I'm sorry?

Page 203

A. Dr. Clayman.

Q. Okay.

A. So it was a regulatory -- it was, essentially, a regulatory committee. But members from various components of medical, toxicology, adme, manufacturing and other individuals that would ultimately make decisions, approve or disapprove labeling changes.

MR. ALLEN: Objection to portions of the answer as completely nonresponsive and unnecessary.

Q. Is marketing a member of the GPLC?

A. No.

Q. Is legal?

A. There is legal representation, yes.

Q. Okay. Are there regular minutes kept of GPL meetings?

A. I believe there are, yes.

Q. Okay. Do you have any explanation for why such minutes have not been produced in this litigation?

Page 204

MR. SEE: Object to the form.

A. I wouldn't know that, no.

Q. If you wanted to get the minutes of Global Product Labeling Committee meetings that related to Zyprexa, how would you go about getting those?

A. I would, probably, contact the chairman of the committee who, I'm sure, would contact the secretary, who -- I don't know if there's an archivist --

Q. Okay.

A. -- available.

Q. And it's your understanding that Dr. Clayman is the head of the Global Product Labeling Committee?

A. Not at this time, no.

Q. Okay. Was he, though, back in, say, 2000?

A. I do not recall the specific time at which he transitioned off that position.

Q. Do you know who succeeded him?

A. It is currently co-chaired by

Page 205

Dr. Franson and Dr. Breier.

Q. Okay. And do you know how long Dr. Breier has been a co-chair of that labeling committee?

A. I'm not sure of the specific length.

Q. Do you have an approximation?

A. It's been a short number of years --

Q. Okay.

A. -- since the time that he became chief medical officer, I believe.

Q. Okay. And do you recall when it was he became chief medical officer?

A. And again, because I can't recall when he -- and again, I think it's approximately, several years.

Q. Okay.

A. Two would be an approximate number.

Q. And was the Zyprexa label the subject of a GPLC session in the weeks or months following this e-mail?

A. I don't recall.

Page 206

Q. Did you ever give a presentation to the Global Product Labeling Committee on Zyprexa labeling?
A. I think I was, probably, present for discussions about the molecule at GPLC, I cannot recall the specifics of those conversations.
Q. Okay.
A. I may have been simply in attendance as opposed to doing a presentation.
MR. SUGGS: Let me hand you what's been previously marked as Plaintiff's Exhibit 990.
(Whereupon, Deposition Exhibit(s) 990 previously marked, was presented to the witness.)
MR. SUGGS: For the record this is a seven-page document, the first page of which is labeled Confidential, Do Not Forward, To be distributed only by Global Operations Labeling Department,

Page 207

Indianapolis, Attachment E.
QUESTIONS BY MR. SUGGS:
Q. And, Dr. Beasley, if I could refer you to the second physical page of the document.
A. Um-hum.
Q. There is a heading towards the top of the page below the confidential label that says, "Olanzapine Labeling Change on Hyperglycemia For February 21, 2000, GPLC Meeting." Do you see that?
A. Yes, I do.
Q. And have you seen this document before?
A. Yes, I have.
Q. When was the last time you saw it?
A. Sometime during the last week.
Q. And if you could direct your attention to the last physical page, there is a box there referring to consultation process?
A. Yes.

Page 208

Q. And it says "reviewed by," and it has, "Global Product Physician Charles Beasley," with the date of February 15, 2000?
A. Yes.
Q. And does that refresh your recollection that you would have seen this document or reviewed it back in February of 2000?
A. Oh, I'm very certain that I was very much involved in putting this document together. A technical correction, I was not the Global Product Physician, as I have explained. I was a consultant, not part of the team.
Q. Okay.
A. But I consulted to the team.
Q. Okay. And apparently this was also reviewed by Kenneth Kwong?
A. Yes.
Q. Okay. And did you and Dr. Kwong prepare this document?
A. Physically we didn't, but we certainly had input into this proposal.
Q. Who would have?

Page 209

A. This --
Q. I'm sorry. Go ahead.
A. This would have arisen from the work that we'd undertaken that I discussed previously.
Q. Okay. By that you mean your review of the spontaneous data, the published literature, the clinical trials and so forth?
A. And this component, specifically, the clinical trial data.
Q. Okay. And who -- you said you weren't sure that you, actually, put this physically together. Did you -- did you and Dr. Kwong write the text of what's contained in here?
A. I don't recall who, specifically, wrote this text. It -- it well may not have been us, I think, that probably wrote what's contained up in the -- or parts of what is contained in the top box here.
Q. And regardless of whether you personally drafted the text that's in here, would it be fair to say you not only reviewed but approved this language?

Page 210

A. Yes.
Q. Okay. And by approving it you believed that what was stated in there was accurate and truthful, correct?
A. At the time --
Q. Sure. That's all you can do.
A. -- yes, recognizing that the basis for the specific numbers that had been included in here were from the very first preliminary analysis of our clinical trial data.
MR. ALLEN: Object to everything after "yes" as nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. I'm not sure what you meant when you said that the basis for the specific numbers that had been included in here were from the very first preliminary analysis of our clinical trial data. Can you explain that?
A. Yes. Thank you. The numbers contained in here were brought forward for review by GPLC and we clearly suggested and

Page 211

thought that a labeling change was appropriate. The basis for this, as I said, is someplace between 50 and a hundred studies.
I brought forward to, I believe, Dr. Breier and Dr. Tollefson and other individuals the results of the very first successful run of that data. And so that was the basis for what went in here.
Q. Okay.
A. It's very much like the first time that you run a long column of numbers on an adding machine and get a result.
Q. Okay. Below the title there's a box that says, "Proposal of the Product Team and PhV."
A. Yes.
Q. Okay. Now, you said earlier that you were not really a member of the product team but were a consultant or was -- you were a consultant for --
A. I was a consultant to --
Q. -- the product team. Did this proposal have to get signed off on by

Page 212

somebody in the product team before it was put forward as a proposal?
A. I think that was the case, but I'm not familiar with whether there was an explicit sign-off or who would have been the sign-off individuals.
Q. And who was in charge -- who was the lead person on the product team, was that Dr. Breier?
A. That would have been Dr. Breier.
Q. Okay. In that section of the proposal it states that the, "Spontaneous reporting rate for hyperglycemia, less than .01 percent, is currently in the Core Data Sheet as a Core Adverse Event in the Adverse Drug Reaction Table." What was the Core Data Sheet?
THE WITNESS: The core -- and I'm sorry, but I was listening to you and I just was not following where you were -- where you were reading.
MR. SUGGS: At the very top

Page 213

of that box that's of the proposal.
THE WITNESS: Okay.
QUESTIONS BY MR. SUGGS:
Q. And my question was what is the Core Data Sheet?
A. The Core Data Sheet is a -- is an internal document that is used as the basis for labeling internationally. To some extent from a efficacy perspective but, primarily, from a safety perspective.
It lists those things that are the absolute minimum for inclusion in all actual product labeling throughout the world.
Q. Okay.
A. Product labels, unless a regulator says, "No, you can't put that in."
Q. Okay. And you state here that, The proposal was to add the following information regarding hyperglycemia to the Core Data Sheet in a particular section, correct?
A. That's correct.
Q. And then below that follows the new statement, correct?

Page 218

A. That's correct.
Q. Okay. So your analysis, as reflected in this document, for the clinical trial data yielded results that showed that the frequency of hyperglycemia was common or frequent, correct?
A. Yes, by this nomenclature, absolutely.
Q. Okay.
A. And again, our preliminary set of analyses.
Q. Okay. And then there's a box below that that says, "How Has this Proposal Arisen?"
A. Yes.
Q. And then the language of that says, "Recent review of random glucose levels of patients in olanzapine clinical trials revealed that the incidence of treatment-emergent hyperglycemia in olanzapine group, 3.6 percent, was higher than the placebo group, 1.05 percent. For common events, instances from clinical trials provide more meaningful information." Did I

Page 219

read that correctly?
A. That's correct.
Q. Okay. Now, this recent review that's being referred to there was the review that you and Dr. Kwong had done on your own initiative because you felt it was important to do; is that correct?
A. That's correct.
Q. Okay. And you talk about that that review revealed that the incidence of treatment-emergent hyperglycemia in the olanzapine group was 3.6 percent, correct?
A. That's correct.
Q. And when you use the term treatment-emergent hyperglycemia, that means that that's hyperglycemia occurring in people who did not have hyperglycemia before they had the treatment, correct?
A. By the -- by the definition that we established. If you had to be less than 140, I don't know really, precisely, whether those patients did or did not have it. And who then went to, as I said we used -- we used two cutoffs in our complete

Page 220

analysis. And in fact, we had different patterns that we analyzed. Some patients would go up and clearly stayed up and they would come back down.
So this is a representation of the total number -- or I should say the total percentage or instances that were presented to us on the first successful run of the analysis.
Q. Okay. And you also looked at the incidence of treatment-emergent hyperglycemia in the placebo group, correct?
A. That's correct.
Q. Now, those are the people who didn't get the drug, correct?
A. That's correct.
Q. Okay.
A. In those patients who were directly compared, in other words, this is not just all the olanzapine patients in total and all of the placebo patients in total. It was only those olanzapine patients who actually participated directly in studies that compared the two treatments.

Page 221

Q. Okay. And why did you restrict your analysis to those people?
A. Because that constitutes what we would consider to be from a statistical or analytical purpose, the most appropriate comparison.
Q. Okay. Using that most appropriate comparison that you yourself chose, you found that the incidence of treatment-emergent hyperglycemia in the olanzapine group was 3.6 percent and the placebo group was only 1.05 percent, correct?
MR. SEE: Object to the form.
A. And again, I was provided with these two incidence -- incidences, percentages, in the first set of analyses that were successfully run on these data.
MR. ALLEN: Objection, nonresponsive.
MR. SUGGS: I don't think you responded to my question, sir. Let me rephrase it. Because you really didn't answer it directly.
THE WITNESS: Okay.

Page 234

Dr. Casey about that?
A. I do not recall any conversations about that specific study with Dr. Casey.
Q. Was it a matter of concern to you that he had found that 18 percent of the people with normal blood sugar developed diabetic levels of glucose?
MR. SEE: Object to the form.
A. There are certainly a lot of things I could say about this, I would characterize as a report by Dr. Casey. But it was obviously one of the pieces of information that increased our interest and our view of the importance of continuing to analyze -- well, controlled data in this area.
Q. Okay. Well, you never warned doctors in your Zyprexa labeling of Dr. Casey's finding that 18 percent of people who had used Zyprexa for at least four months had fasting glucose levels that met the ADA criteria for diabetes, correct?
A. Well, this is -- this, again,

Page 235

is a retrospective chart. The answer to your question is no.
Q. Thank you.
THE WITNESS: But if I may.
MR. SUGGS: You can say whatever you want, I'm just going to move to strike it.
THE WITNESS: Okay. This was not considered to be, by any stretch, a study. It was something that warranted systematic investigation.
MR. SUGGS: Move to strike as nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. And, sir, your company never warned in your labeling that in your analysis in February of 2000 you had found that the incidence of treatment-emergent hyperglycemia in patients treated with Zyprexa was 3.6 percent as compared to the placebo group where the incidence was 1.05 percent, correct?
MR. SEE: Object to the form.

Page 236

A. No, but we did place the finalized numbers in the package insert.
MR. SUGGS: Move to strike that portion of your answer which is nonresponsive.
Q. In fact, the label change that ultimately came about within months after your proposal here in February, asserted that there was, essentially, no change in glucose levels between patients who used Zyprexa and those who were on placebo, correct?
MR. SEE: Object to the form.
A. My recollection is that we did report something close to 3.6 percent for olanzapine.
MR. ALLEN: Objection, nonresponsive.
A. And that the number for placebo was slightly less but not substantially less than olanzapine. And I don't recall the specific numbers.
MR. SUGGS: Again, move to strike as nonresponsive.

Page 237

Sir, maybe you don't remember what your labeling, actually, said, so let me show that to you. I'm going to hand you what's been previously marked as Plaintiff's Exhibit 4858.
(Whereupon, Deposition Exhibit(s) 4858 previously marked, was presented to the witness.)
MR. SUGGS: For the record this is a May 9, 2000, letter to FDA from Gregory T. Brophy with several attachments.
THE WITNESS: I've looked at the document.
QUESTIONS BY MR. SUGGS:
Q. And have you seen it before, sir?
A. Yes, I have.
Q. How recently?
A. I believe in the last week to two weeks.
Q. And had you seen the document

on the record. This is the beginning of tape four of the deposition of Dr. Charles Beasley.

QUESTIONS BY MR. SUGGS:

Q. Dr. Beasley, the second -- could I get you to direct your attention to the first page of this Exhibit 4858?

A. Yes.

Q. The second numbered item in this letter refers to the change that was, actually, made regarding hyperglycemia, am I correct?

A. It's with reference to the laboratory findings of hyperglycemia.

Q. Okay. And that's the same type of laboratory findings that you were referring to in your proposed label, correct, was to discuss what the incidences were and with respect to laboratory findings?

A. Actually, I believe, in the original proposal there was no suggestion that we included any specific incidences or numbers.

Q. Okay.

A. I should --

Q. But the basis -- I'm sorry.

A. I should add other than to indicate that the frequency for olanzapine was between one and 10 percent.

Q. Okay. And that was in the common or frequent category, correct?

A. That's correct.

Q. Okay. There is nothing in the labeling language that was, actually, implemented in May which refers to hyperglycemia as being common or frequent, correct?

A. From my perspective that is not --

Q. Sir, I need to have you answer my question. And my question is, just with respect to the language that was used in the label change, did you tell doctors that the incidence of hyperglycemia was common or frequent? Did you use those words?

A. We did not use those words.

Q. Very good.

A. We provided the numbers.

Q. In fact, sir, you said in one of your earlier answers, if I can find it here. I have a rough transcript of the -- of your testimony here on my computer and you said quote, "My recollection is that we did report something close to 3.6 for olanzapine," referring to 3.6 percent of hyperglycemia.

A. That's correct.

Q. Can you point to me any language in the text that was, actually, used that uses the figure 3.6 percent?

A. No. You add the numbers together for the two --

Q. Okay.

A. -- treatments.

Q. Can you -- would you read for the jury the language that is used?

A. Yes. "In the olanzapine clinical trial database, as of September 30, 1999, 4,577 olanzapine-treated patients begin paren, representing, approximately, 2,255 patient-years exposure," end paren, "and 445 placebo-treated patients who had no history

of diabetes mellitus and whose baseline random plasma glucose levels were 140 milligrams per deciliter or lower were identified. Persistent random glucose levels greater than or equal to 200 milligrams per deciliter," paren, "suggestive of possible diabetes," end paren, "were observed in 0.8 percent of olanzapine treated patients," paren, "placebo 0.7 percent," end paren". Transient," paren, "i.e., resolved while the patients remained on treatment," end paren, "random glucose levels greater than or equal to 200 milligrams per deciliter were found in 0.3 percent of olanzapine treated patients," again, paren, "placebo, 0.2 percent, end paren. Persistent random glucose levels greater than 160"-- excuse me -- "greater than or equal to 160 milligrams per deciliter observed in 1.0 percent of olanzapine treated patients," begin paren", placebo, 1.1 percent," end paren. "Transient random glucose levels greater than or equal to 160 milligrams per deciliter but less than 200 milligram per deciliter were found in

Page 246

1.0 percent of olanzapine treated patients," paren, "placebo, 0.4 percent," end paren.

Q. And that's the final language that went into the labeling, correct?

A. That's correct.

Q. And this is the language that came out of the end process that began with you and Kenneth Kwong suggesting a label change because your review of random glucose level of patients revealed an incidence of treatment-emergent hyperglycemia in the Zyprexa group of 3.6 percent as compared to 1.05 percent in the placebo group, correct?

A. And again, I believe what I have testified to is that the numbers that you have just quoted were, in fact, the result of the initial preliminary data analysis.

Q. And after you tortured the data for some period of time you came up with this language which, essentially, shows no difference between Zyprexa users and placebo users in terms of hyperglycemia, correct?

MR. SEE: Object to the form.

Page 247

A. And again, I would disagree with your characterization of tortured. I would again refer to checking and double checking. There is a numerical deference with more on olanzapine but the numbers are certainly closer together.

Q. Is it your testimony that the change here that we see, from what was in the rationale for original proposal versus what came out of the end of the process, is because you checked your arithmetic and you found the numbers were wrong?

A. Well, it would not be appropriate to characterize it as arithmetic. It's the process of checking the computer programs that result in finding the results that you have.

Q. Well -- sir, in fact --

MR. SEE: I'm sorry. You can finish your answer, Dr. Beasley, if you weren't finished.

A. There are --

MR. ALLEN: Under that criteria we'll be here all day because he never finishes.

MR. SEE: As I said, Dr. Beasley, you can finish your answer if you haven't.

A. These were complex studies that had to be combined in appropriate fashion, and my understanding is that the final numbers represented here were after multiple rechecking of the computer programs that obtain the numbers.

Q. Who was it that finally crunched the numbers, was it you or someone else?

A. It was not me. I am not a statistician a -- or versed in either the systems or the statistical programs that provide these numbers.

Q. My question was who was it that crunched the numbers, do you know?

A. I think, probably, Mr. Paul Berg would have been involved. Whether he was the only statistician or systems person I would not know.

Q. Earlier when we were talking about your original proposal which found a rate of hyperglycemia --

MR. SUGGS: Strike that.

QUESTIONS BY MR. SUGGS:

Q. Earlier when we were talking about your analysis, that you and Dr. Kwong had done, which found a rate of hyperglycemia in Zyprexa users about three and-a-half times higher than placebo users, I think, you referred to that as the first successful run of the analysis, am I correct?

A. That's correct.

Q. Who ran the numbers when you did that?

A. Okay. I believe that, again, Mr. Burg was the statistician who would have overseen or, actually, performed all of the -- all the analysis.

Q. So is it your testimony that this was just some computer error that takes the difference between Zyprexa and placebo users from three and-a-half times to virtually nothing?

MR. SEE: Object to the form.

Page 248

Page 249

A. And, again, I've characterized there continuing to be a slight numerical difference between drug and placebo with more on drug. And that is my understanding. The process of running these programs, as I understand it, is quite complex.

Q. Well, sir, do you recall that you did later analyses in which you concluded that, "our continuous analyses showed that olanzapine does result in statistically significant mean increases in random glucose relative to placebo and haloperidol?"

A. I don't recall that specific set of analyses.

Q. Okay, well, we'll talk about that in just a minute. Let's finish up with this label change that you guys did in May of 2000. What happened, five months later, was that FDA came back and made you take it out -- made you take that language out of the label; is that correct?

A. That's correct.

MR. SUGGS: Okay. Let me show you what's been previously marked as Plaintiff's Exhibit 195.

(Whereupon, Deposition Exhibit(s) 195 previously marked, was presented to the witness.)

MR. SUGGS: Which for the record is an October 11, 2000, letter from Russell Katz, the director of the Division of Neuropharmacological Drug Products at FDA to Gregory Brophy.

QUESTIONS BY MR. SUGGS:

Q. Have you seen this document before?

A. I believe I have.

Q. And have you -- how recently have you seen it?

A. I believe during the last few weeks.

Q. And did you see it before then?

A. I don't recall whether I would have seen this specific letter. I was certainly made aware of its contents.

Q. And who made you aware of the contents?

A. I don't know the specific person. It would have likely been one of the regulatory people for the compound.

Q. And if we just cut to the chase here, what happened was FDA five months after you made that label change on your own without prior FDA approval, FDA came back on October 11, 2000, and said you have to take that language out, correct?

A. That's correct.

Q. And the reason why they made you take it out is because the FDA said, this is on the second page of the document, "The descriptive data that is provided expresses a certain level of implied safety with respect to treatment emergent hyperglycemia." Do you see that language, sir?

A. Yes, I do.

Q. And in fact, that that was the case. The data that you reported in there, the statements that you had in the labeling showed that there was, essentially, no difference between hyperglycemia in Zyprexa users versus placebo patients. And the FDA concluded that that expresses a certain level of implied safety; is that correct?

MR. SEE: Object to the form.

A. I think you've asked me two questions. With respect to the FDA's impression, that is correct. I view these data, quite frankly, as not reassuring, although not ominous, not reassuring because of the difference.

Q. Let me ask you this --

A. I clearly felt it was important to report these incidences.

Q. When you did the analysis for your proposed label change in February of 2000, and we've talked about it several times before, the 3.6 percent for the Zyprexa users versus the 1.05 percent for placebo users, did you do any tests of statistically significant to determine whether that finding was statistically significant?

Page 258

know who the statisticians were that were working with her.
Q. Okay. I want to make sure I understand the time frame here. In February of 2000, a year before this e-mail, you and Kenneth Kwong do an analysis which finds an incidence of treatment-emergent hyperglycemia three and-a-half times higher in Zyprexa users versus placebo users, correct?
MR. SEE: Object to the form.
A. And again you've characterized that, I believe, as a final finding.
Q. I'm not characterizing as final, partial, whatever. You did an analysis that you thought was important enough and you felt confident enough in to submit to the Global Product Labeling Committee which said that the incidence of treatment-emergent hyperglycemia was three and-a-half times higher in Zyprexa users as compared to placebo users, correct?
A. That is correct and I'm trying to provide the context.

Page 259

MR. SUGGS: Move to strike the nonresponsive portions.
Q. Three months later, you and others jen-up language that goes into the labeling under the special supplement changes being effected, which shows, essentially, no difference between the incidence of hyperglycemia in Zyprexa users versus placebo users. And five months after that, FDA makes you take out that language because they say it's -- it gives an implied sense of safety, correct?
MR. SEE: Object to the form.
A. And I would agree with you --
Q. You need to answer the question, first, sir.
MR. SEE: I think he's answering your question.
A. I agree with you with respect to the action of the FDA. In your question you characterized our actions in a certain fashion that I would disagree with.
Q. And then five months after the FDA makes you take out that language,

Page 260

which they said was expressing a certain level of implied safety with respect to treatment-emergent hyperglycemia, you do another analysis which finds a statistically significant mean increase in random glucose for Zyprexa relative to placebo and haloperidol, correct?
A. That was my understanding at the time having not been involved in those analyses.
Q. And, sir, if I could direct your attention to the remaining language in that paragraph, you go on to state, "These increases are occurring as early as week one," correct?
A. Yes.
Q. That would be week one after beginning use of the drug?
A. That's correct.
Q. And you say "These changes are accounted for, in part but not entirely, by weight increase," correct?
A. I think you have excluded a parenthetical in the -- in this but -- that

Page 261

states, "may not represent a true deterioration in glycemic metabolism but simply an increase in food intake since these are random and not fasting glucoses."
Q. And then you go on to say, "These changes are accounted for, in part but not entirely, by weight increase," correct?
A. That's correct.
Q. And then you say: Categorical analyses to values above a set of thresholds, 126, 140, 160, 200 milligrams per deciliter, do not reveal significant findings, but trends are there, except for the comparison of clozapine to olanzapine to the lower two thresholds, clozapine more, correct?
A. That's correct.
Q. And so, when you do categorical analyses like that, you are splitting the data up into different chunks, correct?
A. That's correct. We have been talking -- most of what we've been talking about so far has been categorical analysis.

Page 270

Q. Okay. And we know that on October 11, the FDA comes out and says you've got to take that label language out, right?
A. Correct.
Q. Okay. So within days after you meet with the outside experts, FDA tells you to take the label out, right?
A. Yes.
Q. Dr. Baker in Exhibit 6998, goes on in his e-mail to say, "They kindly allotted two hours for discussion of olanzapine's potential hyperglycemia risks and Charles Beasley, Chris Bomba, Patrizia Cavazzoni, Suni Keeling and I attended. Unfortunately, this consultation reinforced my impression that hyperglycemia remains quite a threat for olanzapine and may merit increasing even further medical attention and marketing focus on the topic." Did I see that?
A. Yes, that's correct.
Q. Okay. In the second paragraph he goes on to state, "They were, however, concerned by our spontaneous AE

Page 271

reports." That's referring to adverse event reports, correct?
A. That's correct.
Q. "And quite impressed by the magnitude of weight gain on olanzapine and implications for glucose. Much of their input for helpful steps came back to addressing weight gain."
Did I read that correctly?
A. That's correct.
Q. And you had been warned about the weight gain problem by another panel of outside experts as we said -- as we talked about right at the beginning of your deposition back in December of 1995, correct?
A. That's correct. And this was something that we described and from my perspective, given Dr. Breier's efforts, we were attending to.
Q. And continuing on in his e-mail Dr. Baker said, "Citing methodological questions, at least the vocal members were not reassured adequately by our analyses, such that the finding that relative risk was

Page 272

not higher than comparative drugs. Disconcertingly, one member compared our approach to Warner-Lambert's reported argument that Rezulin did not cause more hepatic problems than other drugs in its class." Do you see that language, sir?
A. Yes, I do.
Q. Were you familiar with what Warner-Lambert was doing with respect to Rezulin?
A. No. I was familiar with the drug and I was familiar with the fact that it was, ultimately, withdrawn from the market.
Q. Because of safety problems, correct?
A. Because of the perception that it had a risk of hepatic dysfunction.
Q. And these outside experts were making comparisons between what you guys were doing, with respect to Zyprexa, and what Warner-Lambert was arguing in connection with their drug Rezulin, correct?
MR. SEE: Object to the form.
A. That is not consistent with,

Page 273

at least, my recollection of the meeting. My recollection is that they were advising us not to take the approach, whatever that was, that Warner-Lambert took. They wanted to see that we maintained an image of being a company of high integrity, which they presumably felt, or at least the individual who expressed this, Warner-Lambert had lost.
Q. And you must have had a different impression than Dr. Baker then, because in the last sentence in that paragraph he said quote, "Disconcertingly, one member compared our approach to Warner-Lambert's argument that Rezulin did not cause more hepatic problems than other drugs in its class," correct?
A. And again, my recollection is that the emphasis that was being placed was on not evolving to a point where we produced a negative image for ourselves.
Q. Okay. As I said, it appears your recollection is different than Dr. Baker's, correct? It least according to this e-mail?

exhibit. October 10, 2000, this is your words. "These guys were really concerned about the weight gain. Not only because of diabetes risk but all the other potential health risks." Those would be some of the risks we discussed in All About Diabetes, right?

A. That's correct.

Q. So the doctors in Atlanta, who talked about why they were concerned about weight gain were concerned because weight gain can lead to hyperglycemia, which is prediabetes, and diabetes can occur and all those risks such as peripheral neuropathy, amputations, and blindness are concerns, right?

MR. SEE: Object to the form of the question.

A. Those would be consequences or adverse outcomes of diabetes.

Q. Right. And these -- and that's exactly what these doctors were concerned about?

A. I think my reference here is

to the other potential health risks such as cardiac disease and those things.

Q. Very good. And I'm glad you corrected me. I very much apologize. They were also concerned that the weight gain could lead to cardiovascular disease and high triglycerides and things of that nature?

MR. SEE: Object to the form of the question.

A. Again, I think, triglycerides being a marker, that wouldn't be necessarily something they would have expressed concern about. And again, I don't recall them directly expressing concern about "X" or "Y" or "Z". Clearly, the sentiment was that their focus was on weight gain. That, because this had been best established with the molecule.

Q. Thank you, sir. Let's go on. They initially thought it might simply be a response to improvement in schizophrenia with a few outliers. And you put this parenthetically, parens, "a rather naive view but they ain't shrinks."

A. See, I'm just a good old boy.

Q. Yes, you are. You know what, I'll tell you something, I read your e-mails, you've got a good sense of humor. At some point in one of these e-mails you talk about it being, this weight gain issue, being a weighty problem. Do you recall that?

A. I think I saw that in --

Q. Right.

A. -- the message today.

Q. Right. So you were just using normal sense of humor as a pun, weren't you?

MR. SEE: Object to the form of the question.

A. It was certainly a matter that was important to us and another way of characterizing that was that it was weighty.

Q. Right, sir. I'm just asking. You're speaking like a regular person right now, right?

A. Correct.

MR. SEE: Object to the form of the question.

Q. Let's go back and continue to look at what you said on that day internally at your company. You said, "They were naive to think" -- by the way when you said it was a rather naive view you were saying the reason weight gain was occurring wasn't because people were getting better on schizophrenia, that's what you're saying here, right?

MR. SEE: Object to the form of the question.

A. Well, it was the issue with their belief -- and I'm not sure how they got this impression -- that it was a few outliers, that would influence the mean change.

Q. And you thought that was a rather naive view, correct?

A. That's correct.

Q. When they understood this is seen in nonpsychotic normals, which you told Mr. Suggs, we see weight gain in individuals who are not schizophrenic and psychotic, correct?

B C D F G H I

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK
IN RE: MDL-1596
ZYPREXA PRODUCTS
LIABILITY LITIGATION
THIS DOCUMENT RELATES TO:
ALL CASES

C O N F I D E N T I A L

- - -

July 27, 2006

- - -

Videotape deposition of

CHARLES BEASLEY, JR., M.D.

VOLUME 2

- - -

GOLKOW LITIGATION TECHNOLOGIES
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EXHIBIT B
Page 1 of 6

Page 445

right?
A. And my understanding at the time is that in some of the analysis there had been found to be a correlation.
Q. Well, your answer is a little more clear than that. It says weight accounts for some but not all increase in glucose?
A. That's correct. In statistical models we discuss whether a number of variables can account for an observation.
Q. And by the way, you said the weight accounts for some. What accounted for the rest of the increase?
A. I don't recall at this time anything other than baseline glucose in those analysis that were done.
Q. Okay, sir. And that is in February of 2001, when you say weight accounts for some, right?
A. That's correct.
Q. And it was February of 2001 when you had sent the e-mail saying "our

Page 446

continuous analysis shows there's a statistically significant difference in blood glucose levels comparing Zyprexa to placebo and Haldol?"
A. That's correct.
Q. And then shortly after that you're sent to Cialis, aren't you?
A. I was transitioned to Cialis in 2001, in the middle of 2001.
Q. In the middle of 2001. You're transitioned to Cialis after you've been working on Zyprexa since 1991.
A. And I think for, for some very good reasons for Cialis.
MR. ALLEN: Objection. Nonresponsive.
A. I moved to that team as medical director, yes, sir.
Q. I haven't even asked a question. But you're anticipating my question.
Now I'm going to put this back to where we were because I'm lost. In 2001, after you wrote the memos we've just

Page 447

gone over concerning weight gain and hyperglycemia and continuous analysis you're sent to Cialis; is that correct?
A. I was sent to Cialis.
Q. Is that in the Central Nervous System department?
A. No, it is not.
Q. And you had spent your entire career since you started at Eli Lilly in the CNS department?
A. That's correct.
Q. And you are the man that's being asked the questions about the continuous analysis, you give your answers, and the next thing you know what department do you ship to?
A. As I've stated, my responsibilities were changed to Cialis.
Q. Who changed your responsibilities?
A. I believe it would have been Mike McDonald, who was the head of medical at that time.
Q. Okay. How were you informed?

Page 448

A. I was asked to take on that responsibility by Dr. McDonald.
Q. Right. You didn't request a change, the company requested you to change?
A. That's correct.
MR. ALLEN: Thank you. Okay, sir, we're on my last document, I believe. It's 6128.
THE WITNESS: I'm sorry, I have not given my --
MR. ALLEN: Well, I think he had a copy of this already. That's a different one. Okay. Isn't that it?
MR. SEE: 6128.
MR. ALLEN: Can you give it to him? I don't think he has it.
I thought you had that already. I apologize, Mr. See, I thought you all used that yesterday.
MR. SEE: We're going to look and see if we have it.
MR. ALLEN: Sure. It's this one, the ludicrous. it could be

Page 513

MR. BOISE: You're not going to let --

MR. SEE: I know you wouldn't do it to anybody else's exhibit, would you?

MR. ALLEN: I wouldn't.

MR. SEE: There we are.

MR. BOISE: Who, me?

QUESTIONS BY MR. SEE:

Q. Dr. Beasley, let me just ask you a question or two about some of the exhibits that you've been asked about during your deposition.

First of all, if we could look at the Plaintiff's Exhibit 229. If you'll recall, and I want to look at Page 4 of that, if you recall that, this is the one that contains the statement no routine blood monitoring required. Do you see that?

A. Yes, I do.

Q. Dr. Beasley, as a physician with respect to the prescription of antipsychotic medications, does that have some particular meaning to you?

Page 514

MR. ALLEN: Objection, form, by the way.

MR. SEE: I'm sorry?

MR. ALLEN: Objection, form.

A. Yes, it does.

Q. Can you tell us what that is?

A. This would be in the area of antipsychotic prescribing, a statement that we would, that one would not need to routinely monitor white blood cell counts which is the case with one antipsychotic that's available on the market.

Q. All right. And is the monitoring of white blood cell count does that have anything to do with blood glucose or hyperglycemia or type two diabetes?

A. No, it does not.

Q. Dr. Beasley, do you recall questions put to you, I think it was with respect to one of the particular e-mails that made reference to two full-time people hired at Lilly to work on the Zyprexa and hyperglycemia issue?

A. Well, there were two full-time people assigned. And these were, these were people that were principally assigned in this area.

Page 515

Q. I just want to ask you about those people. Who were those people, particularly?

A. That would have been Dr. Cavazzoni and Dr. Missy Sowell.

Q. And those two individuals were assigned full time to do work on the hyperglycemia issue with respect to Zyprexa?

MR. ALLEN: Object to the form. And, Mr. See, I don't want to interrupt you ever and I don't want to object to any of your questions because that will destroy your flow.

If you will give me an objection to form to each one of your questions we can take care of it later so we don't have to interrupt you I'll give you that offer. Because the last question it's my belief it's leading. But I don't want to interrupt you every

Page 516

time.

If you want to give me a running objection to form I will not interrupt you.

MR. SEE: That's fine.

MR. ALLEN: Okay. Thank you.

QUESTIONS BY MR. SEE:

Q. Dr. Beasley, the question I want to put to you is who is Dr. Sowell that you made reference to?

A. Dr. Missy Sowell. She was a endocrinologist, diabetes and metabolism specialty physician holding both an M.D. and a Ph.D.

Q. Now, Dr. Beasley, in reference to the two people you've testified about who were assigned to work full time on the hyperglycemia issue were there additional resources other than those two people put to work on the hyperglycemia issue at Lilly?

A. There would have been statistical resources and system analyst resources.

Q. You were also asked questions

Page 517

about the meeting in Atlanta with the endocrinology outside consultants, do you recall that?
A. That's correct.
Q. And there was mention in that one e-mail with respect to the fact that those individuals had advised Lilly to look at continuous-type analysis of the Zyprexa data; do you recall that?
A. That's correct.
Q. Did Lilly take that advice?
A. To my understanding, yes. There were a number of activities undertaken during the fall and into the winter with medical supervision by, again, Dr. Cavazzoni involvement of interim statistical resources, I believe, Dr. Sowell was, probably, involved to some extent.
And then there were two separate outside consultants that were involved in analyses, Dr. David Allison, actually, earlier in the year, and then later Dr. John Buse.
Q. And to the best of your

Page 518

knowledge, Dr. Beasley, has Lilly continued with the project of the continuous-type analysis of the Zyprexa data with respect to blood glucose?
A. I'm not familiar with the specifics of subsequent analysis, but Lilly has certainly continued a number of projects and analyses in this area. It continues to be, obviously, an important area that is continuing to be studied and evaluated.
Q. You were asked, Dr. Beasley, about your change of responsibilities in moving over to a role regarding Cialis. Do you recall those questions?
A. Yes, I do.
Q. And do you have an understanding of what happened? That is, why you moved over to begin work on Cialis?
A. Yes. The medical director who had been responsible for the compound left the company, going to another company, and the molecule had had its submissions so it was in a critical regulatory phase of its development. And I was felt to have

Page 519

particular expertise in working both in the U.S., in Europe, and in Japan on the process of consulting with regulatory bodies around the submissions.
Q. All right.
A. So, it was a very good fit.
Q. Now you were asked some questions about what is marked as Plaintiff's Exhibit 1349, and in particular about Page 6 of that exhibit. I want to put that in front of you. That's the exhibit that shows the number of patients at that time in the Zyprexa clinical trials and the duration of exposure with respect to those patients. Do you recall those questions?
A. Yes, I do.
Q. And let me just ask. This is the exhibit that shows the number of Zyprexa patients that got, for example, more than one dose of the drug, exposure to the drug more than a month, then those who had exposure to the drug more than six months, and those who had exposure more than a year. Do you recall questions about that?

Page 520

A. That's correct.
Q. Now, Dr. Beasley, was safety data gathered from all of the patients in each of those groups?
A. Safety data was obtained for all individuals who were exposed to the drug.
Q. Are there recognized international standards, Dr. Beasley, with respect to the duration of exposure in drug studies like the clinical trials performed on Zyprexa?
A. There are. There are what are referred to as the CIOMS guidelines that are generally used and recognized by most regulatory agencies. And these, these are the guidelines that sort of dictate or indicate how many patients should be treated for how long before a new drug application can be submitted.
Q. Now with respect to Zyprexa, and again, referring, specifically, to the international guidelines for the duration of exposure for patients in the clinical trials, what can you tell us about how the Zyprexa

Page 521

clinical trials matched up with those guidelines?
A. Well, the guidelines suggest the number of patients that should be treated for one or more doses, and that is 1500, and for one or more doses with olanzapine or Zyprexa it was 3,139.
The guidelines, actually, recommend a range for six months or greater, and this is 300 to 600. And the number with olanzapine was 876. And the guidelines for one year is 100. And the number of Zyprexa olanzapine patients was 301.
MR. SEE: Just one moment, Dr. Beasley. We're just looking for an additional document.
MR. ALLEN: If I have a copy I'll give it to you.
MR. SEE: I think Michael has one right here.
MR. ALLEN: All right.
MR. SEE: Thanks a lot.
QUESTIONS BY MR. SEE:
THE WITNESS: Should I, are

Page 522

we finished with this document?
MR. SEE: I think we're finished with that one, Dr. Beasley, thanks.
QUESTIONS BY MR. SEE:
Q. Now I want to ask you about the, what's marked as Plaintiff's Exhibit 1605, and particularly Page 11 of that exhibit.
If you'll recall that's the exhibit that refers to study HGAJ and particularly the nonfasting glucose levels at any time. Do you recall those questions?
A. That's correct.
Q. Now you were, specifically, asked with respect to the Zyprexa patients about the percentage of patients who had a high glucose reading at any time during that study. Do you remember that?
A. Yes, I do.
Q. And that percent is what?
A. That is 2.6 percent.
Q. All right. Now, there's another value there for Zyprexa patients; is

Page 523

that correct?
A. Yes, there is.
Q. All right. Now, what was not asked of you, and I want to ask of you, is there a value for the Zyprexa patients in that study for moving from normal or high glucose to a low glucose level?
A. Yes, there is.
Q. Now you were already asked about that but I want to ask you about it. What percentage of Zyprexa patients does that show?
A. That is 7.7 percent.
Q. So does that mean that 7.7 percent of Zyprexa patients?
MR. SEE: Strike that. Let me ask it in another way.
QUESTIONS BY MR. SEE:
Q. With respect to the 7.7 percent for Zyprexa patients, can you tell us what does that signify?
A. Well, that signifies the number of individuals who at some time during up to six weeks of treatment with values

Page 524

being measured weekly had what was defined as a hypoglycemic value, a abnormally low value of glucose.
Q. Now can you make a comparison between the number of Zyprexa patients that went to low glucose as compared to the percentage that went to high glucose?
A. Well, it was 2.6 percent that went to high and 7.7 percent that went to low. That's the percent for low, or the lows are, probably, about 2.8 times as many patients as went to high.
Q. All right. And with that percentage of Zyprexa patients going to a low glucose level what does that tell us, if anything, about the significance of that, quote, at any time glucose measurement?
A. Well, that would suggest that it's very difficult to interpret these data as particularly meaningful. As I was suggesting, this is one analysis that we would take into consideration with the analysis of end point data, similar data at end point, and then mean change data. Which

Page 525

would, actually, be mean change to high, mean change to low, and mean change to end point. So we really consider five basic analysis in terms of coming to any final interpretation or conclusion.

Q. And overall, when all of the data is considered from that particular study, what did the data show with respect to glucose levels?

A. My recollection is that the interpretation was that there was no difference from haloperidol.

MR. SEE: All right. We're done with that one, Dr. Beasley. Thank you.

QUESTIONS BY MR. ALLEN:

Q. Now at the beginning of your deposition, Doctor, you were asked some questions about your training and qualifications, and your medical and scientific career, do you recall those?

A. Yes, I do.

Q. I want to just go back and fill in a couple of things. You told us that

Page 526

you got your undergraduate degree at Yale in psychology, do you recall that?

A. That's correct.

Q. You then went on to medical school?

A. Yes, I did.

Q. And remind us where that was?

A. That was at the University of Kentucky.

Q. And you graduated with your MD degree when?

A. 1983.

Q. In 1983 was Zyprexa an available drug at that time?

A. No, it didn't become available until 1996.

Q. Now, Dr. Beasley, there have been some questions during your deposition about patients who suffer from the mental disorder schizophrenia who also have a medical problem with high glucose levels or hyperglycemia. Do you recall being asked about patients like that?

A. Yes, I do.

Page 527

Q. Did you have experience in medical school with patients like that, Dr. Beasley?

A. Yes, actually I did.

Q. Could you tell us about that?

A. Well, I entered medical school knowing that I wanted to be a psychiatrist, that that was my intended specialty. And during the second semester of my first year in medical school had the opportunity to take, actually, some clinical electives. And one of these was in an out-patient facility that provided care to veterans suffering from severe mental illnesses.

And the way this, this course worked was I joined my proctor, my senior supervising physician, in observing interviews for a while. And then after that point, I was sent in to conduct interviews myself and come back and report to my supervisor.

Q. Was there one particular interview that made an impression on you?

Page 528

A. My very first interview. My, I was sent in to interview the patient. Of course, we started talking about has the patient had hallucinations or delusions? Those are hallmark symptoms of schizophrenia. Did not appear to have those but the patient at the time just did not seem right to me. Today, I would use technical terms that would say he had a fluctuating level of consciousness, he seemed to get sleepy, not attent to my questions and had poor attention.

Q. What did you do?

A. I went back to the supervisor and informed him of this finding.

Q. And then what happened?

A. The supervisor also interviewed him. Agreed with me that something might be going on with this patient of a, what we call an organic or medical nature, and he was transferred to the emergency room.

Q. And what was found there?

A. This patient had a glucose of

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IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: MDL-1596

ZYPREXA PRODUCTS

LIABILITY LITIGATION

THIS DOCUMENT RELATES TO:

ALL CASES

C O N F I D E N T I A L

- - -

January 11, 2007

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Videotape deposition of

ALAN BREIER, M.D.

- - -

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EXHIBIT C
Page 1 of 21

Q. And what's his position?
A. He is president of Lilly Research Laboratories.
Q. And to whom does he report?
A. He reports to Sydney Taurel.
Q. And Sydney Taurel is the Chief Executive Officer and Chairman of the Board of the company; is that correct?
A. Yes.
Q. Could you briefly describe your duties and responsibilities in the positions of Vice-president and Chief Medical Officer?
A. My responsibilities are to lead the medical organization.
Q. How many people are in the medical organization?
A. We have, approximately, I'm going to say, 2,000 people in the medical organization.
Q. Okay. I'm going to be asking a lot of questions about your activities regarding Zyprexa, but before I do that, I'd like to find out more about your background.

Am I correct that your received a Bachelor of Arts degree from the University of Toledo in Ohio in 1975?
A. That's correct.
Q. And you received a Doctor of Medicine degree in 1980 from the University of Cincinnati School of Medicine?
A. Correct.
Q. And then you were a resident in psychiatry from 1980 to 1984 at Yale University School of Medicine; is that correct?
A. Yes.
Q. And I know that you completed your residency in 1984, and that before you joined Lilly in 1997, you were at the University of Maryland and at the National Institute of Mental Health, sometimes referred to as NIMH, but I'm unclear as to what you were doing in that 13-year time period. Could you flesh it up?
A. Sure. When I left residency training at Yale, I joined the intramural program of NIMH. That was, primarily, for

further research training. I focused at that time on primarily schizophrenia research.
After completing a three-year research fellowship, I then assumed a position at the University of Maryland in the Department of Psychiatry and was an associate research professor there.
After completing that position, I returned to the NIMH in a more senior position, and I was there for, I believe, about four years, and then joined Eli Lilly and Company in 1997.
Q. Okay. So you started off at NIMH to do a three-year fellowship after your residency, then you were at University of Maryland as an associate research professor for again how long was it?
A. I believe that was about six years.
Q. And were you tenured?
A. Yes.
Q. And then you went back to NIMH for, it would have been, what, four more years?

A. Yes. And I just want to be absolutely precise. When I originally started at the University of Maryland, there were not tenure tracks, as I recall, for research professors, and I'm recalling that through that period of time that professors were then tenured.
Q. Okay. And were you tenured at the time you left University of Maryland to go to NIMH?
A. I believe so.
Q. Okay. And before joining Lilly, did you have any particular training or expertise in the diagnose and treatment of diabetes other than what is generally provided in medical school?
A. I did not.
Q. Okay. Am I correct that you had not conducted any research regarding diabetes before joining Lilly?
A. No, I did not.
Q. And you had not published any scientific articles regarding diabetes before joining Lilly; is that correct?

Page 94

analysis and then the needs, the clinical needs of an individual patient. The data is accessed by physicians in multiple different ways.

Q. But one of the ways is from the label that they get from the drug company, correct?

A. That's one.

Q. Okay. And, sir, when you were head of the Zyprexa Product Team, were you aware that FDA regulations require that the labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug and that a causal relationship need not have been proved? Were you aware of that, sir?

THE WITNESS: Could you repeat your question?

MR. SUGGS: Sure.

QUESTIONS BY MR. SUGGS:

Q. Were you aware, sir, back when you were the head of the Zyprexa Product Team that FDA regulations require that the

Page 95

labeling shall be revised to include a warning as soon as there's reasonable evidence of an association of a serious hazard with a drug and that a causal relationship need not have been proved?

THE WITNESS: Let me just understand. Are you describing criteria that would be used in order to determine where information would go in the label?

MR. SUGGS: No, sir. Well, in part. I'll represent to you, sir, that the FDA regulations do state that and require that the labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug, a causal relationship need not have been proved. I'll represent to you that's what the regulation states.

THE WITNESS: Um-hum.

QUESTIONS BY MR. SUGGS:

Page 96

Q. My question to you is, were you aware of that when you were head of the Zyprexa Product Team?

A. Yes.

Q. Okay. And in that context of that FDA regulation requirement, what did the term "association" mean to you when you were head of the Zyprexa Product Team?

MR. BOISE: Object to the form of the question.

A. Well, there's a number of different types of association. There's a temporal association, there's causal association. If we're talking about association that relates to labeling one must consider things like the consistency of the data, the strength of the data, the quality of the data.

So all of those factors are taken into account when determining information that should go into the label and then where in the label it belongs.

Q. Okay. You may have been responsive to this, but I'm not sure, so I want

Page 97

to probe this further.

A. Okay.

Q. In the context of that FDA regulation that I just talked about where the FDA does require the labeling shall be revised to include a warning as soon as there is, in the FDA regulations terms phrase, reasonable evidence of an association of a serious hazard, that's what the regulation says, what did "association" mean to you in that context?

MR. BOISE: Object to the form of the question.

THE WITNESS: And are we specifically talking about a warning? Is that what your question is?

MR. SUGGS: Yes.

A. Again, that would be -- a few of the things that would be very, very important would be the strength of the association, the quality of the data, the consistency of the data, if there is a causal relationship that would be important, the

type of event we're talking about in terms of its gravity and seriousness.

So, again, multiple factors are considered when determining where one proposed to put something in the label.

Q. Okay. Would you agree, sir, that reasonable evidence of an association could include a statistically significant finding in a clinical study that an adverse reaction occurs more frequently with a particular drug as compared to placebo or some other control group?

MR. BOISE: Object to the form of the question.

Q. That that could constitute reasonable evidence of association?

MR. BOISE: Object to the form.

A. You, again, would kind of need to look at the exact phenomenon you're talking about, and one would look for quality, consistency, validity of the signal. It's a little difficult to talk about this in the abstract, but typically one study and one

finding, if there's other data available that is perhaps contrary to that, one study would not suffice.

So one would need to look at the totality of the information in order to make their ultimate decisions.

Q. But you would agree that a finding of a statistically significant increased incidence of an adverse reaction in a clinical trial could constitute part of the evidence that would be assessed in making a determination as to whether there was reasonable evidence of an association, correct?

A. I can't agree with that statement as you just articulated because one would need to look at that particular clinical trial, the strength of the trial, the methodology, other data that might be available, mechanistic issues.

In other words, what I'm trying to indicate is that labeling is a very serious business. One needs to consider all of the relevant information, methodology,

other data, et cetera, before one can make an informed labeling decision.

Q. Would you agree, sir, that results of a controlled clinical trial is often regarded as the gold standard of scientific evidence?

A. I would not agree with that statement as you articulated because each clinical trial is subject to its own strengths and weaknesses. And there are some clinical trials that provide certain sorts of proof or evidence, and other sort of clinical trials that don't.

So one would have to actually look at the clinical trial in question. We call it kind of looking under the hood, really understanding the methodology, the patient characteristics, all of those factors before one could make an informed decision on results from that trial.

MR. SUGGS: Okay. Let me show you what's been previously marked as Plaintiff's Exhibit 8562.

(Whereupon, Plaintiff's

Exhibit(s) 8562, previously marked, was presented to the witness.)

MR. SUGGS: For the record this is a two-page -- take it back -- three-page document. It has a title at the top that says Zyprexa Business Processes.

QUESTIONS BY MR. SUGGS:

Q. Do you recognize this document, sir?

A. Let me take a moment to review it.

Q. Sure.

A. Okay.

Q. My question was, do you recognize the document?

A. I don't recognize this. Don't recall this specific document.

Q. Okay. I should note for the record also that when these documents are produced to us, Lilly also produces a computer database, and in some instances it shows a date, and in this particular instance, the

Lilly-produced database shows that this document was dated August 27, 2001.

Sir, below that centered heading there's a side heading entitled "Zyprexa Key Decision Team." Do you see that?

A. Yes.

Q. Was there, in fact, a Zyprexa Key Decision Team in 2001 as noted in this document?

A. Yes.

Q. Okay. And does the document accurately describe the voting members of that key decision team?

A. I'm refreshing my memory from this document, but I must say that I don't recall specifically the voting members of this committee, but I accept what is on this piece of paper.

Q. Do you recall when the Zyprexa Key Decision Team was formed?

A. No.

Q. Do you know whether it was in place when you took over as head of the Zyprexa Product Team?

A. I don't believe so.

Q. Okay. Did the Zyprexa product -- pardon me. Did the Zyprexa Key Decision Team exist within the Zyprexa Product Team during your tenure, pardon me, through August 2003 when you then moved on to be chief medical officer?

A. I don't recall.

Q. Okay. So the Zyprexa Key Decision Team did exist for some period of time within the Zyprexa Product Team, but you can't remember for sure exactly when it got started or how long it lasted; is that fair to say?

MR. BOISE: Object to the form.

A. That's correct.

Q. Okay. And the stated purpose, at least in this document, of the Zyprexa Key Decision Team is for efficient cross-representational critical decision making body for the Zyprexa Product Team. Did I read that correctly?

A. Yes.

Q. And did that accurately state the purpose of the Zyprexa Key Decision Team?

A. My recall of this particular committee is not very sharp. I'm reading this and you're reading it appropriately, but I don't have a good firsthand recall of the intricacies of this particular team.

Q. Let me ask you with respect to the types of decisions. The document lists the types of decisions to be made by the Zyprexa Key Decision Team, and they included, again, according to the document, clinical study priorities, label changes/modifications, publication priorities, key issues management, key marketplace decisions, IPP final submission Zyprexa marketing plan. Did I read that correctly?

A. You did.

Q. And did that accurately describe the types of decisions that were made by the key decision team?

A. I'll have to answer it the same way as I did before: I'm not recalling

this particular committee very sharply, but you're reading the document correctly.

Q. Okay. Do you have any reason to doubt that those were the types of decisions made by the Zyprexa Key Decision Team?

A. Well, I mean, I know how these kinds of decisions ultimately got made, and, I mean, I could speak to that.

Q. Okay. Well, the document indicates that down in the process section, the third paragraph within there, that "Decisions were made on the basis of a group vote. Alan Breier retains the right to make a final decision if he's opposed to the group vote."

Did that accurately reflect how decisions were made within that team?

A. I don't recall. It's very possible that this was a relatively short-lived committee and that could be why I'm not recalling it, but I don't have a recollection.

the determination as to whether or not a label change or modification would be proposed or recommended by the Zyprexa Product Team?

MR. BOISE: Object to the form.

A. Again, that would be a cross-functional group of scientists who were working with the data. If the analysis of the data indicated that this was something that warranted a label change and would change what we call our core label, we would then take that information to GPLC, the group we talked about earlier. GPLC would look at it, determine, yes, this should be added to core or no it shouldn't.

Q. Okay. Maybe I'm not being clear here or maybe I just need to explore this further.

Who within your Zyprexa Product Team made the decision as to whether or not a proposal would be made to the Global Product Labeling Committee to change or modify a label?

MR. BOISE: Object to the form.

A. We generally made those decisions in a fairly cross-functional format. We had safety physicians on the team, we had other experts on the team who would be working with other scientists. They would then analyze data. If they felt this was something that should go to the team, I would be brought into the discussion. We would analyze and look at the data carefully, and then we would make a determination, yes, this is something that needs to go to GPLC, let's get on the GPLC agenda.

Q. Let me ask the question this way. You know how Harry Truman had a sign on his desk that said "The buck stops here?"

A. Yes.

Q. With respect to labeling decisions within the Zyprexa Product Team and whether a labeling change should be taken to the Global Product Labeling Committee for review, where did the buck stop in the Zyprexa Product Team for that type of decision?

MR. BOISE: Object to the form.

A. On the Zyprexa Product Team, the buck would stop with me. That determination, again, would be predicated on a cross-functional group of scientists, content experts working on the data, and determining on the strength of the data we would then make a determination to go to GPLC.

Q. And would it be fair to say that while you were president -- pardon me -- while you were team leader of the Zyprexa Product Team, that you would have been aware of any proposal made by the product team to the Global Product Labeling Committee with respect to a label change?

A. Definitely.

Q. Okay. Would it also be fair to say that if a proposal was made by the product team to the Global Product Labeling Committee to change the Zyprexa label, not only would you have been aware of that proposal, but you would, in fact, have signed

off on that proposal going to the Global Product Labeling Committee, correct?

A. I would be knowledgeable about it and I would endorse it going forward.

Q. Okay. And would it be fair to say that if something was taken to the Global Product Labeling Committee by your team, you would have wanted to make sure, in your own mind, that before that was done that the proposal was appropriate?

A. We would strive to get it right.

Q. Okay. And you would want to make sure that the basis for that proposal was well thought out and well analyzed before it was taken to the Global Product Labeling Committee, correct?

A. Ideally that is absolutely correct.

Q. Can you think of any -- As you sit here today, can you think of any instance where that did not occur?

MR. BOISE: What didn't

Q. Okay. How -- and why is it that you were presuming that?
A. We're a very science-driven team. We looked at data a lot. We looked at signals. We had a process of continual iteration of data where a signal would pop up, we would reanalyze, we would look for better data. We would continually strive to understand what the studies were telling us. We did that with J, as well as other trials.
So I'm, again, I'm presuming that in the course of my activities, we probably reviewed this. And then as I was indicating before, went on to try to determine is this real or not, and through careful analysis determined that we did not feel this was a signal.
MR. SUGGS: Move to strike the nonresponsive portion.
QUESTIONS BY MR. SUGGS:
Q. When you referred in your answer to "J" did you mean that to be the HGAJ study?
A. Yes.

Q. Do you also presume that the other members of the?
MR. SUGGS: Strike that.
QUESTIONS BY MR. SUGGS:
Q. Do you also presume that the other medical members of the Zyprexa Product Team would have been familiar with the data from the HGAJ study, and in particular, this finding in June of 1995 that there was a statistically significant increased incidence of high glucose in the Zyprexa users?
MR. BOISE: 1999? The time period for that?
MR. SUGGS: Yes.
A. I can't speak for every physician or scientist on the team in terms of their knowledge of this particular finding because we had people working on, you know, vastly different themes. I would expect that scientists working, specifically, on this theme or on this particular trial would have been aware of it.
Q. Okay. Well, Dr. Beasley's already testified that he was aware of this

information. Would you have expected other physicians, such as Dr. Baker and Dr. Kinon, to have been aware of it as well?
MR. BOISE: Object to the form of the question.
A. I can't speak for Kinon or Baker, they were not on the Zyprexa Product Team.
Q. Okay. Would you have expected Mauricio Tohen to have been aware of that?
MR. BOISE: In 1999?
MR. SUGGS: Well, whenever he came on the Zyprexa Product Team.
A. I, again, I can't speak for Mauricio Tohen. He was our bipolar expert. He tended to work and spend most of his focus on our bipolar program. I'm not sure.
Q. Okay. By November of 1999, were you also aware that there had been hundreds of adverse reaction reports relating to elevated blood glucose and diabetes-related events?
MR. BOISE: Object to the

form of the question. Foundation.
A. I don't recall at that time the precise number, but I was aware that there were spontaneous adverse events of high glucose.
Q. And a large number of such reports?
MR. BOISE: Object to the form. Vague.
Q. Well, let me ask this. If, in fact, the evidence shows that as of September 1998 there were 200 adverse event reports tallied by Lilly relating to blood glucose elevations, would you have been aware of that?
A. Again, I'm not recalling the exact number. I was clearly aware that there were adverse events reported in the database, I just don't recall the number.
Q. And adverse events relating to blood glucose and diabetes?
A. Yes.
Q. Okay. And I'm assuming that you were aware in November of 1999 that Lilly

for the scope of future activities;" is that correct?

A. You read it correctly.

Q. And did the members of that executive steering committee that are listed there, which is composed of yourself and a number of others, did they stay involved in this process?

A. Yes. We had been working with a number of them before this and had a number of activities, scientific activities, going on.

The purpose of the steering committee was to update a broader group of what we were doing, get their input, and then suggestions for future directions. Because we had already had cross-functional interactions with some of the key people, we decided that we would continue on as we had before; in other words, I would take responsibility for bringing in key people at appropriate times as opposed to, say, having a biweekly meeting or something like that with these people on a formal basis.

So the spirit of that was continued on, but not as a regular meeting of those key individuals, although I took, again, responsibility to keep them informed and to continue to get their input.

Q. And when you described this situation at the beginning of your e-mail where "olanzapine-associated weight gain and possible hyperglycemia is a major threat to the long-term success of this greatly important molecule," for how long had that been regarded as a major threat within the company?

MR. BOISE: Object to the form of the question.

A. Well, the data on weight gain was in awareness from day one, so there was no question about that. As we went into the marketplace, it was very clear that this was a molecule that was having a very, very positive impact on this devastating illness, schizophrenia/bipolar.

There were at this time clinicians in the field asking more questions

about potential interventions for weight gain, et cetera. We reasoned if we were better able to understand it from a scientific perspective, offer more interventions, that would then allow more patients to take the medicine than were not being given the medicine because of the concerns around weight gain.

MR. SUGGS: Move to strike the nonresponsive portion.

QUESTIONS BY MR. SUGGS:

Q. For how long had weight gain and possible hyperglycemia been regarded by Lilly as a major threat to Zyprexa?

MR. BOISE: Object to the form of the question.

A. I'm going to have to answer it the same way I did before. We were very cognizant of weight gain from day one. It was very well described at that time, and those characteristics of weight gain did not change.

Q. Did you regard weight gain as a major threat to Zyprexa from day one?

MR. BOISE: Object to the form.

A. We acknowledged that weight gain was for some patients, particularly excessive weight gain, was an undesirable attribute of the drug.

Q. That's not my question. You used -- in your e-mail you describe olanzapine-associated weight gain and possible hyperglycemia as a major threat to the success of Zyprexa. My question is: For how long had you regarded that as a major threat?

A. And again, I'm putting the word "threat" into context, explaining it as those individuals who gained weight to an excessive amount, was a clear side effect of the drug.

MR. SUGGS: That's not my question, sir.

MR. BOISE: Just let him finish and then you can answer it.

QUESTIONS BY MR. SUGGS:

Q. You characterized that issue,

Page 162

either decreasing it or increasing it or whatever, but that they couldn't adjust the dose to deal with olanzapine weight change? Is that a fair restatement?

A. Yes.

Q. Okay. And then in parentheses you say, "Fact: OWC is not dose dependent." Correct?

A. You've read that correctly.

Q. So the fact was the same as the perception, correct?

A. Yes.

Q. Okay. Then you also note that physicians, in the following bullet point that "Physicians want more data." I'm assuming that was based on market research, correct?

A. Yes. Each one of the bullets under this section of market research would have been data brought into the company through surveys of physicians from the market research department.

Q. Okay. And then in your next bullet point you say, "Blanket detailing will

Page 163

be damaging since many physicians do not see OWC as an issue."

Did I read that correctly?

A. You did.

Q. We need some more translation there. Blanket detailing refers to going out and having your sales reps -- well, let me back up for a second.

We need to talk about detailing. In the pharmaceutical business, the process of a sales representative calling on physicians and discussing the product with the physician is often referred to as detailing, correct?

A. That's correct.

Q. Okay. In fact, sales representatives used to be referred to as detailmen, correct?

A. I'm not familiar with that term, but that's consistent with what you said.

Q. Okay. So when you're talking about blanket detailing here, what you're talking about, that phrase would mean having

Page 164

sales representatives from Lilly go out and talk to all physicians about a particular issue, correct?

MR. BOISE: Object to the form.

A. No. What this phrase means is having a unidimensional message. In other words, as opposed to presenting all relevant data or important relevant data would be to have a single isolated message.

Q. And what you say here is blanket detailing will be damaging since many physicians do not see olanzapine weight change as an issue, correct?

A. That's what it says.

Q. Okay. And how was it determined that many physicians do not see olanzapine weight change as an issue, do you know?

A. Well, again, this is market research, this isn't Lilly's opinion. This is the information coming into the company from prescribing physicians. What I interpret this to mean is to say that

Page 165

physicians that were in the survey, some of them were saying I'm interested in different information in a detail call. I'm not seeing weight gain as a problem in my patients, but I've got questions about other things. So don't give me a single message detail, but give me the information that's important to me.

I think each physician has, at various times, different questions and different needs for data, and that's what I interpret this bullet point to be referring to.

Q. Okay.

MR. SUGGS: I've been told that we have about five minutes left on this tape and it's now 12:30. You want to break for lunch?

MR. BOISE: Yeah.

THE VIDEOGRAPHER: Marks the end of tape two of the deposition of Alan Breier. We're off the record at 12:27.

(A lunch recess was taken by the

Page 182

frankly --
Q. Okay, then what do the boxes mean?
A. I don't know.
Q. Okay. And you won't accept my representation as to what Michele Sharp said those boxes mean?
A. I guess I have to defer to my counsel. I don't know.
MR. BOISE: If you're going to represent that that's what they said and he should assume that as part of his answer without accepting the baseline assumption, accepting your representation, then you can answer the question.
A. Then I accept that.
Q. Okay. And were you aware that that proposal was being made back in February of 2000?
A. I don't recall this specific proposal back in 2000.
Q. Okay. Not at all. Okay. Would it be fair to say

Page 183

that the way -- we talked earlier about the process by which proposals for labeling changes were made through the Zyprexa Product Team for submission to the Global Product Labeling Committee. Do you recall our earlier discussion this morning about that?
A. I do.
Q. Okay. And it's your testimony that you don't have any specific recollection of this proposal; is that correct?
A. That's correct. Proposal from the 2000 time frame.
Q. Okay. And would you agree that it would be fair to say that the procedures that you discussed this morning would apply to this particular submission?
MR. BOISE: Object to the form.
A. I don't recall this specific submission, so it's difficult for me to go beyond that in my answer.
Q. Nothing stands out in your mind that would say that the procedure that

Page 184

went through, this submission went through, was somehow out of the ordinary or treated differently than other situations from your team; is that correct?
A. Since I don't recall the submission, I can't attest to the process.
Q. Okay.
A. Excuse me. I can attest to an overall process by which we work with data like this, I just can't attest to this specific analysis.
Q. And we already talked about that general process earlier this morning, correct?
MR. BOISE: Object to the form.
A. And the general process that I was referring to was a iterative process, a series of analyses, sort of an evolution of looking at data, making sure it's correct, rechecking it, looking at it again, et cetera, until we're satisfied we have it right.
Q. If I could direct your

Page 185

attention to the middle box on the first page, it says "How has that proposal arisen?" It states, "Recent review of random glucose levels of patients in olanzapine clinical trials revealed that the incidence of treatment emergent hyperglycemia in olanzapine group, 3.6 percent, was higher than that in the placebo group, 1.05 percent."
Do you see that language?
A. I do.
Q. And the phrase "treatment-emergent hyperglycemia" refers to hyperglycemia occurring during the context or after a person's been exposed to the drug in a clinical trial; is that correct?
A. I would characterize it as data coming from a clinical trial.
Q. And these would be in people who did not have hyperglycemia before they started taking the drug, correct?
A. I don't know that that's the case.
Q. Well, then, what does the

Page 186

phrase "treatment emergent" mean?
A. "Treatment emergent" is a term that's used for an event that crosses a certain threshold. It doesn't refer to what the baseline was or the starting point.
Q. Well, doesn't the phrase "treatment emergent" indicate that the situation emerged during treatment?
A. Yes. But the reality of glucose, particularly random glucoses, is there's a lot of up and down. It's very possible that someone could have a high level at one point, say, a baseline, a low level later, a high level later on. So there's quite a bit of fluctuation with glucose.
So if you crossed a certain threshold at a certain point in time in a clinical trial, that would be considered a treatment-emergent event.
Q. Well, doesn't, in fact, the new statement that was proposed indicate that these were people whose random glucose was higher after they were treated than before they were treated?

Page 187

A. Well, what this -- in this particular instance, what it indicates was that the random glucoses at baseline were, say, 140, and then the event was captured at some point around 160.
Q. So their baseline blood glucose level was lower at the beginning than it was after they took the drug, correct?
A. On this one measure. But what I was trying to convey with random glucose --
Q. I'm sorry, what one measure?
A. With this one blood measure at baseline that would indicate that they were below 140 but the day before they could have been at 160.
So what I'm saying and trying to indicate is that particularly with random glucoses, there's a tremendous amount of variability. And I don't think that the baseline starting point for a definition of a treatment-emergent event is necessarily the critical component.
Q. Well, apparently, though,

Page 188

your product team and pharmacovigilance group thought this finding of treatment-emergent hyperglycemia in the olanzapine group warranted a revision to the label, correct?
A. I don't know all or who was involved in this particular analysis because, as I noted before, I don't have recollection of it, but whoever put this table together suggested that it go into the label.
Q. Well, we know that at least according to the first page of the document this was the proposal of the product team, correct?
A. That's what it says, and Pharmacovigilance.
Q. And Pharmacovigilance.
Now, when they refer to the treatment-emergent hyperglycemia in the olanzapine group being 3.6 percent and that the incidence of a placebo group was 1.05 percent, the rate of treatment-emergent hyperglycemia in the Zyprexa group was three and-a-half times higher than in the placebo group, correct?

Page 189

A. I would agree that 3.6 percent is three and-a-half times greater than 1.05 percent.
Q. And it's your testimony that you have no recollection of this submission being made to the Global Product Labeling Committee?
MR. BOISE: Objection. Asked and answered.
A. During the 2000 time frame, I do not have a recollection of this analysis or this document.
Q. Sir, in your November -- by the way, this label change was never made with this language, was it, sir?
A. I can attest that these data did not go into the label because we learned that these data were not reflective of the random glucose situation of this dataset.
MR. SUGGS: Objection, nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Your labeling never advised physicians of the proposal that was made

here, correct? Yes or no?
A. We did not advise clinicians of this particular finding because additional analyses were conducted that were more valid and clinically meaningful than these analyses, and it was the correct analyses that we submitted to the FDA and shared with clinicians.
MR. SUGGS: Sir, you're giving me spin which I'm going to move to strike as nonresponsive. I need a yes or no answer.
MR. BOISE: I object to your characterization, sir.
MR. SUGGS: I need a yes or no answer.
QUESTIONS BY MR. SUGGS:
Q. Did your company advise prescribing physicians with the language that was proposed there, yes or no?
MR. BOISE: Object to the form of the question. Asked and answered.
THE WITNESS: I want to be

very clear --
MR. SUGGS: Then say yes or no, sir.
THE WITNESS: I am not spinning any data during this proceedings nor have I at any other point.
QUESTIONS BY MR. SUGGS:
Q. Sir, can you give me a yes or no answer? Did the company tell doctors what was proposed in this label change or not? It's a simple yes or no question.
MR. BOISE: And he's answered your question.
MR. SUGGS: No, he has not. He has not.
I want a simple yes or no answer.
MR. BOISE: The record will reflect that he has answered it.
A. We don't share inaccurate data with clinicians.
Q. Sir, did you or did you not tell physicians of that label change that was

proposed there by the product team and pharmacovigilance, yes or no?
MR. BOISE: Objection, asked and answered.
A. We do not share inaccurate data with clinicians.
MR. SUGGS: Move to strike the nonresponsive portion.
QUESTIONS BY MR. SUGGS:
Q. Sir, did you tell physicians at any time that analysis of clinical trial data from Lilly's own studies showed that the existence of treatment-emergent hyperglycemia was three and-a-half times higher than in the placebo group?
MR. BOISE: Object to the form of the question.
Q. Yes or no?
A. We did not.
Q. Thank you.
By the way, these clinical trials that are referred to there in that middle section where it says "a recent review of random glucose levels of patients in

olanzapine clinical trials revealed that the incidence of treatment-emergent hyperglycemia was three and-a-half times higher than in the placebo group," what clinical trials were those, do you know?
MR. BOISE: Object to the form.
A. Again, I don't recall this specific analysis. My presumption would be that it would have well likely come from the integrated clinical trial dataset, which is a compilation of multiple trials.
Q. And do you know who did the analysis?
A. No.
Q. Do you know when they did the analysis?
A. This particular analysis?
Q. Yes.
A. Presumably the analysis were done prior to 2/21/2000.
Q. Do you know how they did the analysis?

Q. Okay. That seminar that's referred to there at Lilly at the end of 1999, did you attend that seminar?
A. Yes.
Q. Okay. And I assume Dr. Casey was, must have been invited to come and give a presentation, correct?
A. I invited him.
Q. Okay. And at that seminar, according to this document, "He," referring to Dr. Casey, "performed chart review of 136 veteran patients who had been exposed to olanzapine therapy for at least four months, average of 1.4 year. Of the 39 patients who had normal fasting glucose levels before olanzapine therapy, seven, or 18 percent, had fasting glucose levels of 126 milligrams per deciliter or higher during olanzapine therapy." And then in parentheses it says, "threshold that met the 1998 ADA diagnostic criteria for diabetes."
Do you see that language?
A. I do.
Q. And the ADA that's referred

to there is the American Diabetes Association, correct?
A. Yes.
Q. Okay. And so in this review of charts that Dr. Casey did of patients who had normal fasting glucose levels before they started using Zyprexa, 18 percent of them had fasting glucose levels that exceeded the criteria for diabetes after they had used it for at least four months; is that correct?
A. You are reading this correctly.
Q. Okay. Now, did Dr. Casey undertake that chart review on his own or was this part of a study that was being conducted by Lilly?
A. I don't know.
Q. Okay. When Dr. Casey came to Lilly and gave that presentation in which he said that 18 percent of people with normal blood levels had diabetic blood levels after using the drug for four months or more, did that come as a surprise to you at that point, or were you aware of his findings before he

came to give the seminar?
MR. BOISE: Object to the form of the question.
A. I don't recall if he and I talked about the data before he came or not.
Q. Do you recall who else was at that seminar where Dr. Casey said that 18 percent of the people who use Zyprexa after four months had diabetic blood levels?
A. I don't recall, sitting here at this moment, who else was at the seminar.
Q. Okay. The very term "seminar" makes me think, and I could be wrong, that there was a group of people there. Is that a fair assessment?
A. I think that's a fair characterization.
Q. And would you have expected the majority of people from the Zyprexa Product Team to be there?
A. I, again, don't recall who was in attendance. Typically, when we have a seminar with an outside speaker, we advertise it fairly broadly within the company. It's

an open-door policy, so those interested in this particular area were invited.
Q. Okay. And it's fair to say that, also, isn't it, sir, that Lilly never advised prescribing physicians in the labeling of Dr. Casey's findings, did it, sir?
MR. BOISE: Object to the form.
A. No, we didn't, because this gets to a very central point that we've been discussing today, and that gets to quality of data.
Q. Sir --
A. If I could just finish.
These are 39 patients, a retrospective analysis in which there are no controls, no understanding of baseline factors, inadequate amount of data to really understand even a full temporal association.
So these are the very kinds of data that, while it's important to look at all the data, and we were interested in looking at all the data, this is the type of

study alone that one cannot draw very many conclusions.

MR. SUGGS: Move to strike the nonresponsive portion of your answer after the word "no."

QUESTIONS BY MR. SUGGS:

Q. Sir, this proposal to change the label that was reviewed by the Global Products Labeling Committee did not go forward in February of 2000, correct?

MR. BOISE: Object to the form.

A. These data were not included in the label.

Q. Now, you did make a label change several months later in May of 2000, correct?

A. That's correct.

Q. And we've seen the document where that was done, Exhibit 4858. If you can find that in the pile. That was the May 9, 2000, letter?

A. Yes.

Q. And this May 9, 2000, letter

is from Gregory T. Brophy in the U.S. Regulatory Affairs Department in Eli Lilly to the FDA on May 9, 2000, correct?

A. Yes.

Q. And it informs the FDA that Lilly has already revised the package label for Zyprexa in three respects, correct?

A. Yes.

Q. And Dr. Brophy notes in his letter of May 9, "Effective immediately we will be implementing this change," correct?

It's on the second page, second to the last paragraph, last sentence.

A. Yes.

Q. And so this label change was made without prior FDA approval, correct?

A. That's correct.

Q. Okay. Now, one of the things that this label change did had to do with the neuroleptic malignant syndrome. And that has really nothing to do with the issue of diabetes. Would that be a fair characterization?

A. It's an important safety

phenomena. You're correct, it's not related to diabetes.

Q. Okay. And then another change that was made to the labeling was that there was an addition in the adverse reaction section of the labeling, in the post-introduction reports part of the label, inclusion of diabetic coma. So that that section then read, "Adverse events reported since market introduction which were temporally but not necessarily causally related to Zyprexa therapy include the following: Diabetic coma and priapism," correct?

A. Yes.

Q. And priapism is another condition that has nothing to do with diabetes, correct?

A. Correct.

Q. Okay. Priapism is involuntary sustained erection, correct?

A. Correct.

Q. Okay. And then the other change that was made was item No. 2 in the

adverse reaction section, there was some additional language added regarding the laboratory changes section and findings of data from the olanzapine clinical trial database with respect to random plasma glucose levels, correct?

A. Yes.

Q. And could you read that into the record, please?

A. The --

MR. BOISE: What, the entire section?

MR. SUGGS: Sure.

MR. BOISE: You can read. I can read.

MR. SUGGS: Well, the jury might want to hear it.

MR. BOISE: Why don't you read it in?

MR. SUGGS: No, I'd rather he read it in. Would you please read it into the record, sir?

MR. BOISE: Is it a question?

MR. SUGGS: It's a request.

Q. You had considerable skepticism expressed about the results of this analysis by other consultants to the company, did you not?

A. I would characterize that most people who saw the data found it very helpful. This was a unique dataset of over 6,000 patients in controlled trials. Just comparing it to the Casey report of a very small, retrospective, poorly-controlled dataset.

It were these kinds of studies, the Casey report, that were in the public domain that were not terribly informative. And we felt that we had a unique set of data, a one-of-a-kind in terms of quality and length, numbers of exposures.

And most of the input I received on this data was quite laudatory and positive. In fact, we not only submitted this data to the FDA, but we submitted it to regulatory bodies worldwide, and it's in the European label today. So those scientists looked at it and found it quite helpful and

meaningful.

MR. SUGGS: Move to strike as nonresponsive.

QUESTIONS BY MR. SUGGS:

Q. Do you recall that outside consultants to the company in a meeting of October 2000 informed the company that they were highly skeptical of these findings?

A. Not quite sure what you're referring to.

Q. All right. We'll come back to that.

If I could direct your attention to the following page. This is comments from another reviewer. And the first numbered comment there the reviewer says, "The authors do not adequately emphasize how crude their method is for finding an effect. Random glucose values represent an insensitive method for assessing glucose tolerance."

Do you see that language, sir?

A. Um-hum.

Q. And, in fact, at some point after this, Lilly switched from random glucose blood testing to fasting blood glucose testing, correct?

A. That's correct.

Q. And that's because, in fact, random glucose values are an insensitive method for assessing glucose tolerance, correct?

MR. BOISE: Object to the form of the question.

A. There are strengths and weaknesses to both approaches.

Q. If I could direct your attention to the second point there it states, "Most of the values were, probably, drawn during the first three months of each trial. It would be helpful to know the number of samples in each condition that were collected during the later stages of the trials."

And, sir, in fact, most of the values, the blood samples were drawn during the first three months of each trial;

isn't that correct?

A. I don't know if that's the case.

Q. If Dr. Kwong has testified that that's correct, would you have any basis to dispute that?

A. I would prefer to rely on my own answer here.

Q. And your own answer is you don't know?

A. I don't recall.

Q. Okay. The third point raised there by this reviewer was, "Many of the early studies of olanzapine were biased toward low doses of the drug. Since there's a consensus that most patients require 10-milligram or more of olanzapine, it would be helpful to know if there is a dosage effect on glucose tolerance."

Do you see that language?

A. Yes.

Q. And, in fact, many of the early studies of olanzapine did use low doses of the drug; is that correct?

died?
MR. BOISE: Object to the form of the question.
A. I don't know the number if you're referring to spontaneous adverse events. I just want to be certain in your question that you're not intimating a cause-and-effect relationship, because we do not have data on cause-and-effect nor does this label change suggest cause-and-effect.
Q. Sir, what I'm trying to get at here is we now have a black box warning for increased mortality in elderly patients with dementia-related psychosis, correct?
A. Yes.
Q. My question is, how many patients used Zyprexa for that purpose died?
MR. BOISE: Object to the form. Asked and answered.
A. Sitting here today, I cannot give you a precise number of --
Q. Which is why I asked if you could give me an approximation.
A. No, I can't.

Q. You have no idea whether we're talking about 2 people or 200?
A. Nope.
Q. When did this warning go on the label about increased mortality in elderly patients with dementia-related psychosis?
A. I believe it was 2005.
Q. Do you recall what month?
A. No.
Q. I believe you said that this launch meeting for primary care physicians where you were talking about the use of Zyprexa in Alzheimer's patients occurred in October of 2000; is that correct?
A. I believe that's correct. It was in 2000.
Q. Okay. And do you recall in that same month, October of 2000, that Lilly representatives met with a group of outside consultants in the field of diabetes to discuss the data that the company had put together?
A. We had a number of

consultations with external experts on diabetes. And I'm not clear which one you're referring to.
MR. SUGGS: Let me see if I can refresh your recollection. Let me show you what's been previously marked as Plaintiff's Exhibit 6998.
(Whereupon, Plaintiff's Exhibit(s) 6998, previously marked, was presented to the witness.)
MR. SUGGS: Which, for the record, is an October 9, 2000, e-mail from Robert Baker to Charles Beasley, Christopher Bomba, Alan Breier, Thomas Brodie, Patrizia Cavazzoni, James Gregory, John Holcombe, Jack Jordan, Suni Keeling, Bruce Kinon, Michael Murray, John Richards, Eugene Thiem, Mauricia Tohen and Paula Trzepacz.
QUESTIONS BY MR. SUGGS:
Q. If I could direct your attention, sir, to the first paragraph. It

states, "FYI: The Lilly diabetes/endocrine group held an academic advisory board meeting this weekend in Atlanta. They kindly allotted two hours for discussion of olanzapine's potential hyperglycemia risks, and Charles Beasley, Chris Bomba, Patrizia Cavazzoni, Suni Keeling and I attended. Unfortunately, this consultation reinforced my impression that hyperglycemia remains quite a threat for olanzapine and may merit increasing even further medical attention and marketing focus on the topic."
Do you see that language, sir?
A. I do.
Q. And does that refresh your recollection that members of your Zyprexa Product Team had a meeting with outside consultants in October of 2000?
MR. BOISE: Object to the form.
A. I recall this message, and I recall that consultation. Just to be accurate, at this time I believe Charles

Beasley was still on the product team. Patricia Cavazzoni clearly was on the product team. I'm not sure who Chris Bomba is. And I don't recall if Suni Keeling was on the product team or not.

Q. Was Jack Jordan on the product team?

A. No.

Q. Was Mauricio Tohen on the product team at that time?

A. Yes.

Q. So this e-mail's going to people who were on your product team and also other folks as well, correct?

A. Correct. You had just mentioned that members of my product team, and I just wanted to clarify that Chris Bomba and I'm not sure --

Q. My statement was correct, but there are other individuals besides people from your Zyprexa Product Team who this e-mail went to?

A. Oh, in terms of who it was sent to, yes, and also in terms of the

attendees.

Q. Okay. Do you know how it was that this meeting came about?

A. The meeting that I understand this is referring to is a standing group of advisors that advised the company primarily on the endocrinology portfolio.

Q. Okay. So when it refers here to the Lilly diabetes/endocrine group, that refers to that group in the company that would be dealing on a regular basis with the company's drugs intended for the treatment of diabetes, correct?

A. Correct. So the endocrinology consultants would be members, would be experts in the area of diabetology endocrinology.

Q. Okay. So the diabetes side of the company which deals with diabetes all the time has this group of outside consultants, outside experts that they deal with. And some of your folks dealing with Zyprexa went down there to attend the meeting and presented the data to them, correct?

A. That's correct.

Q. Okay. And the data they presented to them was essentially the same data that was reflected in your May 2000 label change and in the presentation to FDA in July of 2000 and in the paper that was submitted for publication to the "Journal of Biological Psychiatry." Isn't that correct, sir?

MR. BOISE: Object to the form of the question. Foundation. Compound.

A. What I recall is that the categorical glycemic data that we discussed earlier was presented. I believe also other data as well, including weight gain data and data of that nature.

Q. And, sir, have you reviewed this document since October of 2000?

A. Yes.

Q. When did you review it last?

A. Within the last month.

Q. Okay. In the second paragraph it states, "On the positive side,

like other endocrinologists, they were not impressed with the Newcomer findings."

What were the Newcomer findings, if you recall?

A. I don't recall.

Q. It goes on to say, "They were however concerned by our spontaneous AE reports, and quite impressed by the magnitude of weight gain on olanzapine and indications for glucose."

And when they're referring there to "spontaneous AE reports," am I correct that that stands for adverse event reports?

A. Yes.

Q. Okay. And these would be reports made to the company or to the FDA by either treating doctors or patients, or, frankly, could be anybody recording an adverse event that occurred to a patient while they were using the drug, correct?

A. Typically, the treating physician.

Q. Okay. And continuing on in

MR. SUGGS: Move to strike the nonresponsive portion.
QUESTIONS BY MR. SUGGS:
Q. You talked to Dr. Tollefson about this information you received, correct?
A. We talked nearly daily when we were both in the office. I can't recall sitting down with Dr. Tollefson and having an exact conversation about this topic. I assume we did because these are the kinds of things we talked about in our frequent communications.
Q. Okay. Directing your attention to the e-mail preceding the one from Mr. Baker, pardon me, the one from Mr. Brodie, the one at the bottom of Page 3 which starts off by saying, "FYI: My take was that this board of academic endocrinologists was impressed enough by the magnitude of weight gain and number of reports in the spontaneous adverse event database, that they were predisposed towards skepticism to any analysis that did not find higher hyperglycemia rates on olanzapine than

comparators."
I read that correctly, right?
A. Yes.
Q. And that's, essentially, the same kind of concern or lack of belief that was expressed by one of the reviewers of your paper. Do you recall that?
A. I recall that. But I again want to reiterate that we follow the data. If the data were there and demonstrated important relationships then we would communicate that information, we would follow the data.
I, just on this point alone, I'm recalling a letter to the editor by the neuropharm division of the FDA who analyzed data, not only from us but other sponsors, and came to the exact same conclusion, that there is not support from clinical trials of the kinds of associations that we're talking about here. So although it might be surprising, at the end of the day the data has to speak for itself.

MR. SUGGS: Move to strike everything in your answer after your first sentence "I recall that."
QUESTIONS BY MR. SUGGS:
Q. In fact, one of the reviewers said that the authors present a highly curious?
MR. SUGGS: Strike that.
QUESTIONS BY MR. SUGGS:
Q. One of the reviewers of your paper for publication that we looked at earlier, Exhibit 1440, said that "The authors present a highly curious dataset. Since their own work has shown that olanzapine is associated with a clinically and statistically pertinent increase in weight compared to both haloperidol and placebo, they seem to be suggesting that olanzapine exerts a sizable antidiabetic power."
That's what he said, correct?
A. That's what that one reviewer said.

Q. And your consultants in the meeting in October of 2000 were skeptical of your results as well, correct?
MR. BOISE: Object to the form. Go ahead.
A. Again, what I got from the consultant was, okay, those categorical analyses are interesting, let's keep looking at the data, and they were suggesting additional analyses.
It's not unusual in science to have surprising findings, to have findings that maybe are not predicted, but the scientific process is to continue to do the experiments, look at the data, analyze the data, and let the science lead the way. And that's precisely what we did on this topic.
Q. Can I direct your attention to Page 2. This is an e-mail in the same chain from Dr. Beasley to you with copies to Robert Baker, Paul Berg, Scott Clark, John Holcombe, Roland Powell, Alvin Rampey and Roy Tamura, correct?
A. Yes.

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Q. Sir, let me try for the fourth time, and I'd appreciate just a simple yes or no answer to what I think is a simple question.

Did Lilly tell physicians that weight gain with Zyprexa was manageable for most patients?

MR. BOISE: Object to the form of the question.

A. I don't recall that exact phrase.

Q. Okay. In other words, you don't know?

A. I know what we did in terms of communicating weight gain.

Q. If I could direct your attention back to Dr. Beasley's e-mail. Three lines up from the bottom he says, "There does not seem much to say about scientific analyses of weight gain. We know it's a weighty problem. When you translate 1 to 2 percent gain of 40 plus kilos into the absolute number based on 5 million patients, the number is 50 to 100,000. 100,000 people

putting on 90 pounds of weight is a lot."

Were you aware of that type of calculation before Dr. Beasley mentioned it in this e-mail to you?

A. I knew there was a distribution of weight gain. And knew, again we talked about the tails of a bell-shaped curve.

Q. And you recall this morning I asked you whether you were aware that Dr. Beasley had done calculations indicating that there were some people who gained 80 to 90 pounds of weight and you said you didn't recall that?

MR. BOISE: Object to the form.

A. I'd need to refresh that transcript.

Q. Okay. Well, does this refresh your recollection that Dr. Beasley, had, in fact, calculated on the order of 50 to 100,000 people gaining 90 pounds of weight while using Zyprexa?

A. I don't doubt the statistics.

It's again a 1 to 2 percent. And those would be the tails of that bell-shaped distribution.

And the Kinon publication, I think we presented the data quite clearly on not only the more likely weight gain but also extremes at both ends.

MR. SUGGS: Move to strike the nonresponsive portion.

QUESTIONS BY MR. SUGGS:

Q. Sir, if I could direct your attention to the following page. At the top of Page 3, Dr. Beasley writes, "On the diabetes side, the concern was about the use of categorical analyses."

Do you see that language?

A. Yes.

Q. And who was it that decided to do categorical analyses?

MR. BOISE: Object to the form of the question.

A. I don't know that I know who decided initially. For approaches to data of this nature, we would typically do it in a

cross-functional framework. We would consult endocrinologists in and outside the company, bring in our best people from stats and from neuroscience and create a delineated plan.

Q. Would that have originated within the Zyprexa Product Team, a decision to conduct categorical analyses of blood glucose?

A. I'm sure that Charles was involved in, Dr. Beasley were involved in those discussions.

Q. Okay. And back at this time in October of 2000 -- well, this analysis actually began in -- at least by February of 2000, as we saw earlier, correct?

MR. BOISE: Object to the form of the question.

A. Yes.

Q. Okay. And at that point in time there was nobody on the Zyprexa Product Team who was an expert in the field of diabetes, correct?

MR. BOISE: Object to the form.

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Page 350

hyperglycemia, et cetera.
QUESTIONS BY MR. SUGGS:
Q. Do you recall receiving this e-mail from Dr. Beasley back in February of 2001?
A. I do.
Q. And when was the last time you reviewed this document?
A. Um, I believe within the last month.
Q. And in this e-mail Dr. Beasley wrote starting in the third sentence, "Our continuous analyses show that olanzapine does result in statistically significant mean increases in random glucoses relative to placebo and haloperidol. No significant difference relative to Risperidone but power is small. Clozapine is associated with a larger olanzapine versus haloperidol and a significant increase compared to haloperidol. These increases are occurring as early as week one. May not represent a true deterioration in glycemic metabolism but

Page 351

simply an increase in food intake since these are random and not fasting glucoses. These changes are accounted for in part but not entirely by weight increase."
Do you see that language, sir?
A. Yes.
Q. And, sir, does that refresh your recollection that Dr. Beasley told you that the glucose elevations that they were seeing were partially accounted for by weight gain?
A. Again, we've looked at this very carefully and --
Q. Sir, my question is whether that refreshes your recollection that that's what Dr. Beasley told you?
A. You've read this e-mail correctly. He and I have had multiple different conversations on this topic.
Q. And that's my question, is whether he told you about that, whether this refreshes your recollection that he told you? And does it now refresh your recollection?

Page 352

MR. BOISE: Objection. He never said he -- object to the form.
A. You've read the e-mail correctly. The key point I think in this e-mail is the problem with continuous measures of random samples.
Q. Sir, let's get back for a second. Remember before I showed you that document, I asked you do you recall Dr. Beasley telling you that increases in glucose with Zyprexa users were accounted for in part but not entirely by weight increase and you said no. So I showed you the document. And now I've shown you that language.
And my question is: Does this now refresh your recollection that Dr. Beasley told you that? That's my question.
A. And I would say yes at this one point in time, but in order to give you fuller context to the question --
Q. Sir, I'm just asking for a direct answer to my question, and you have

Page 353

answered it, yes, this does refresh your recollection that Dr. Beasley told you that, correct?
A. To that narrow question yes.
Q. That's my question.
A. I do think, though, it's important to appreciate that what he points out here is very, very important in interpreting the continuous data, and that is the food effect of random samples, and that alone makes it nearly impossible to draw the conclusions around weight.
THE WITNESS: Move to strike your answer as not responsive.
QUESTIONS BY MR. SUGGS:
Q. Sir, can we get back to Exhibit 1111? That's the one in your left hand.
A. Yes.
Q. At the bottom of Page 4 is another heading that states "What We Don't Know." We already talked about part of that, the part that said you didn't know how to effectively deal with weight gain associated

Page 358

diabetes"?
A. No.
MR. BOISE: Objection, mischaracterizes the testimony.
A. That's really not the point. It's what the data says.
Q. You said "that would not be consistent with our approach." If it's not consistent with your approach, then it would be inappropriate, correct?
MR. BOISE: Objection, mischaracterizes the testimony.
A. Let me tell you what I do mean. When it says "lower the percentage of customers that directly link Zyprexa with diabetes," if there was a misunderstanding or a misperception about the data, then correcting that misperception would be appropriate.
There's not a baseline here upon which to kind of further interpret that statement. The goal would be to help prescribers have a realistic understanding of what the data said.

Page 359

Q. Sir, at least the language as stated in this document indicates that whoever wrote this, their desire was to get doctors so they didn't even think about diabetes with Zyprexa, and, in fact, took it out of the risk/benefit calculation; isn't that correct?
MR. BOISE: Object to the form. Compound.
A. No, that's completely inconsistent with our approach. We were very clear about the data. We were clear that there was a higher rate of diabetes in schizophrenic and bipolar patients. We had medical letters, slide sets, publications.
What I'm trying to address in this point is what is most critical is that prescribers have an accurate understanding of the information, and through multiple different approaches we strove to achieve that.
Q. Sir, you just denied that it was the approach of Lilly to have physicians take diabetes out of the risk/benefit

Page 360

calculation. Can I direct your attention to Page 2 of this document? And you see at the bottom of that page there's a Rationale For Position?
A. Um-hum.
Q. Can you read that aloud for the jury, please?
MR. BOISE: You can read it. He's done reading for you before, David. You can read it aloud.
MR. SUGGS: Can you read it aloud, please?
MR. BOISE: Are you able to read it aloud?
THE WITNESS: I can do that.
MR. BOISE: Why don't you ask him a question?
MR. SUGGS: I've asked him to please read it aloud for the jury, what that says.
MR. BOISE: He's not going to read. He's not here to read. It's not his document, it's not his writing.

Page 361

MR. SUGGS: I know you're embarrassed.
MR. BOISE: It's not embarrassed, Dave, it's not about embarrassed. It's not a question to ask a person. It's not his document.
QUESTIONS BY MR. SUGGS:
Q. Dr. Breier, are you refusing to read that language to the jury?
MR. BOISE: I'm telling you it's not an appropriate question and I'm objecting to it.
QUESTIONS BY MR. SUGGS:
Q. My question is, sir, would you please read that aloud for the jury, what this document says?
A. "Showing that diabetes is a common occurrence for all antipsychotics and not just Zyprexa will help reduce the perception that diabetes is linked specifically to Zyprexa, and in turn, will help to eliminate this risk from the risk/benefit equation."

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: MDL-1596

ZYPREXA PRODUCTS

LIABILITY LITIGATION

THIS DOCUMENT RELATES TO:

ALL CASES

CONFIDENTIAL

- - -

January 12, 2007

- - -

Videotape deposition of

ALAN BREIER, M.D.

VOLUME 2

- - -

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EXHIBIT D
Page 1 of 8

Page 403

original letter that went to Japanese physicians.
A. Yes, that is their practice.
Q. Okay. And the heading at the top of the letter says "Important" in the upper left-hand corner and then in big bold letters right at the top says "Emergency Safety Information," correct?
A. Yes.
Q. This is definitely designed to get the attention of physicians in Japan, correct?
A. Yes. That's the purpose of a communication to prescribers.
Q. And in fact, it did definitely get the attention of physicians in Japan, correct?
MR. BOISE: Object to the form.
A. Physicians in Japan were aware of this warning and of the data.
Q. And Zyprexa sales went dramatically down after physicians in Japan received this label; isn't that correct?

Page 404

A. I don't recall the sales trends after this was issued.
Q. Sir, don't you recall writing a memo about those sales trends to Mr. Lechleiter?
A. Sitting here today, I don't recall that.
Q. Okay. We'll go into that in some more detail later.
Let's talk about this "Dear Doctor Letter" or this Emergency Safety Information Letter that went out. This was done at the order of the Japanese regulatory authorities by Lilly, correct?
A. Yes.
Q. Thank you. This was not something Lilly wanted to do. Lilly was ordered to do this by the Japanese regulatory authorities, right?
MR. BOISE: Object to the form of the question.
A. The issue of wanting or not wanting is not relevant. The Japanese regulatory authorities directed us to send

Page 405

this letter out, and we complied with that direction.
Q. After first opposing it. You told the Japanese regulatory authorities that you didn't think it was necessary, correct?
A. We engaged the scientists of the Japanese regulatory agency on the merits of the cases that they were basing this on. We pointed out to them that those cases are confounded. What that means is that they had multiple other factors that could have contributed to these events.
We also brought to their attention a worldwide database that would suggest that some of what they were recommending was not supported by that worldwide database. So we had scientific exchanges with the regulatory group.
Q. You objected to having to do this, and the regulatory authorities listened to what you had to say and then directed you to issue this letter to physicians in Japan, correct?
A. On the merits of the small

Page 406

number of cases that they were citing, the fact that those cases were confounded and an extensive worldwide literature, we felt that this action was not warranted. They disagreed, and we complied with their direction.
Q. And at this point in time in Japan there had been nine serious cases including two cases of death with hyperglycemia, diabetic ketoacidosis, and diabetic coma that had been reported in Japan. Correct?
A. That is correct.
Q. And by this point in time in June of 2000 -- well, it says since the marketing of this product in June 2001, there had been those nine serious cases, correct?
A. At the time of this action, June -- or I'm sorry -- it appears that what this is saying is that -- my understanding is that from the time that this issue was introduced there had been nine cases.
Q. And worldwide, Lilly was

Page 427

referred to by metabolic issues is weight gain because it's under a section called Weight Gain and the available data on these newer drugs was, primarily, related to weight gain.

Q. Okay, those drugs also, though, have less reported adverse effects such as hyperglycemia and diabetes than Zyprexa or Clozaril or Risperdal or Seroquel; is that correct, sir?

MR. BOISE: Objection to the question.

MS. JOBES: Objection to the form, foundation.

MR. BOISE: Also compound.

A. That's incorrect.

Q. Okay. Lilly never informed physicians in the Zyprexa label that Zyprexa's weight gain is roughly twice that of Risperdal, did it?

MR. BOISE: Object to the form of the question.

A. The weight gain described in the label related to Zyprexa is very

Page 428

extensive. It's provided in a number of places in the label in great detail. The convention of labeling for weight gain and most side effects -- in fact, I can't think of an exception for any side effect -- would not include the safety information from another sponsor's drug. So, it would have been inappropriate to add safety information on another sponsor's drug in most instances.

Q. Sir, I'm not asking you for your opinion, I'm asking for fact. The Zyprexa label did not inform physicians that Zyprexa weight gain was roughly twice that of Risperdal, correct?

MR. BOISE: Object to the form of the question.

A. Again, the Zyprexa weight gain sections are quite extensive, they were so from day one. It would have not been appropriate to include weight gain from another atypical antipsychotic drug. And so as regarding to the label, you are correct. I think if there is something related to your question about

Page 429

communication of weight gain, there are appropriate venues where you can communicate not only one's own weight gain data on their own drug but weight gain associated with other drugs that might be important to prescribers in making a prescribing decision such as medical letters, publications, and those appropriate vehicles were used.

MR. SUGGS: Move to strike the nonresponsive portion which is everything other than "you are correct."

QUESTIONS BY MR. SUGGS:

Q. If I could direct your attention to the next section in this document that pertains to diabetes. And there are a number of bullet points below that heading. And in particular, I direct your attention to the third bullet point. You see where I'm indicating, sir?

A. Yes.

Q. Okay. And the first sentence there states, "Results of two Lilly epidemiology studies, analysis of AdvancePCS

Page 430

and GPRD databases, indicate that the risk of DM is increased in patients treated with antipsychotics including Zyprexa."

And the DM that's referred to there is diabetes mellitus, correct?

A. That is correct.

Q. Okay. So Lilly had conducted two epidemiological studies which showed that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa, correct?

A. You've read that sentence correctly.

Q. And Lilly did not include in the warning section or the precaution section of its labeling any language informing physicians of that fact --

MR. BOISE: Object to the form of the question.

Q. -- correct?

MR. BOISE: I'm sorry. Objection. Foundation.

A. Again, we need to go back to appropriate --

Page 431

Q. Sir, I need to have you answer my question as a matter of fact. I'm not asking for your opinion. I'm not asking for your spin. I just want you to confirm for the jury on this record that your labeling did not inform physicians that results of two Lilly epidemiological studies indicate that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa. It's a simple yes or no question. Did Lilly tell that to doctors or did they not?

MR. BOISE: Object to the form of the question. Compound. You've asked about four questions there. What is the simple question?

Q. My simple question, sir, is: It is true, is it not, that Lilly's label did not inform physicians in the precautions or warnings section in 2002 that "Results of two Lilly epidemiological studies indicate that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa"?

Page 432

A. I first want to take umbrage with your comment about spinning. And I assure you that I'm not spinning any answers, I'm answering as forthrightly as I possibly can.

Q. Then can you please give me a yes or no answer to that question, sir?

A. Yes.

The approach to labeling requires that you take into account the totality of the data --

MR. SUGGS: Excuse me, sir. Can you please answer the question simply and directly yes or no, and then after answering directly, if you feel the need to expand on your answer then by all means you can say whatever you want. I'm not going to try to cut you off at all. But please, sir, would you answer the question directly and then give whatever other verbiage you feel is appropriate. Okay? Let me restate the question.

Page 433

QUESTIONS BY MR. SUGGS:

Q. It is true, is it not, that Lilly's label in 2002 did not inform physicians in the warnings or the precautions section that results of two Lilly epidemiological studies showed that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa? Yes or no?

A. The answer is no. And the reason for that is because it would have been inappropriate to include such language based on the data that was available in 2002. These studies did not change the appropriateness of the label as of 2002.

They are used in labeling because we take a totality of all of the information when we examine our label. So these two studies did inform our thinking but reassured us that we were appropriately labeled in 2002.

MR. SUGGS: Move to strike the nonresponsive portion.

MR. BOISE: Okay, let's take

Page 434

five. Take a break.

MR. SUGGS: Okay.

THE VIDEOGRAPHER: Marks the end of tape No. 1 of the deposition of Dr. Breier. We're off the record at 10:45.

(At this time, there was a brief recess taken, after which the following proceedings were had:)

THE VIDEOGRAPHER: We are back on the record. This is the beginning of tape No. 2 of the deposition of Dr. Breier; it's 11:03.

QUESTIONS BY MR. SUGGS:

Q. Dr. Breier, I'd like to direct your attention back to Exhibit 4051. In the bullet point just below the one we were talking about it states "FDA FOI Database of reports of DM cases: Clozaril 542, Zyprexa 434, Risperdal 244, Seroquel 57."

We need to do some

E F G H I

correct?
A. Yes.
Q. Okay. So it was your expectation that if your sales force went out and promoted the use of Zyprexa within the new Japanese label and told physicians "don't give this to patients with diabetes, test people's blood glucose, and explain this issue sufficiently to the patient and family members," that that would, by design, dramatically reduce the number of adverse events, correct?
MR. BOISE: Object to the form.
A. That is correct. And the reason why is a very important point --
MR. SUGGS: Sir, I didn't ask for your opinion.
A. -- and that is because the data that we had at the time, including the TED analysis, indicated that the majority of cases or many of the cases that occur were, actually, latent diabetics at baseline prior to assignment or active diabetics

undiagnosed, and they then were emerging on treatment.
So because of the high rate of diabetes in this population and the fact that patients were going on to treatment already with either prediabetes or diabetes, then for many of these cases it was a matter of time, irrespective of what drug they were on, that their diabetes then would be diagnosed.
So with the contraindication at baseline, those cases that were now going into the different treatment arms would now be going to other agents, and here again, irrespective of drug, would be emerging as cases of diabetes. So I think this puts things into an important context.
MR. ALLEN: I object to everything after "that is correct" as nonresponsive.
MR. SUGGS: I was going to make the same objection.
QUESTIONS BY MR. SUGGS:
Q. You recall being informed --

MR. SUGGS: Well, let me back up for a second.
Let me show you what's been previously marked as Plaintiff's Exhibit 3211.
(Whereupon, Plaintiff's Exhibit(s) 3211, previously marked, was presented to the witness.)
MR. SUGGS: For the record, this is an e-mail from Vicki Poole Hoffmann to Kristine Healey with a copy to Robert Baker.
QUESTIONS BY MR. SUGGS:
Q. Do you know those individuals?
A. I have no recollection of Kristine Healey. I do know who Robert Baker is, and I'm not recalling who Vicki Poole Hoffmann is.
Q. Okay. In the first paragraph of Ms. Hoffman's e-mail, she states, "We are not sure that Zyprexa 'causes' hyperglycemia, because

of the high background rate in schizophrenics, and we have not yet said, specifically, that Zyprexa is or is not associated with hyperglycemia. Our strategy has been to say that if these agents are associated with hyperglycemia then all agents are associated with it at comparable rates."
Do you see that language, sir?
A. Yes.
Q. And that was, indeed, the Lilly strategy, was it not?
MR. BOISE: Object to the form of the question. Foundation.
A. I would disagree with the statement as worded. Again, Vicki Poole Hoffmann, I don't know who that is. I don't believe this is a person with medical background, certainly is not a physician, and that would not be a precise articulation of our understanding of the data.
Q. Sir, was it your understanding that Vicki Poole Hoffmann was in the Issues Management Department?

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Page 455

A. I'm just not recalling who that is.
Q. Do you recall being informed in June of 2002 that a clinical study by Lilly indicated that high nonfasting glucose in Zyprexa users was probably causally related?
MR. BOISE: Object to the form. Foundation.
THE WITNESS: I'm not understanding the question. Could you repeat it?
MR. SUGGS: Let me show you what's been previously marked as Plaintiff's Exhibit 7802.
(Whereupon, Plaintiff's Exhibit(s) 7802, previously marked, was presented to the witness.)
MR. SUGGS: Which, for the record, is a one-page document Listing of Treatment Emergent Abnormal Lab Findings in Olanzapine-Treated Patients. This

Page 456

is from study HGFU.
QUESTIONS BY MR. SUGGS:
Q. Are you familiar with study HGFU?
A. I'm recalling that to be a bipolar trial that looked at olanzapine plus mood stabilizers.
Q. And if you could direct your attention to the laboratory value for glucose nonfasting. It shows that 2.2 percent of the people who got olanzapine had high glucose and 0 percent had, of the placebo group, had high glucose; isn't that correct?
A. Yes. What I'm reading is 185 patients on olanzapine plus mood stabilizer, of the 185, four, or 2.2 percent, is on the glucose nonfasting high line. And that then looks like it's being contrasted with 97 patients with mood stabilizer plus placebo with zero cases or 0 percent.
Q. Um-hum. And to the right on that line there's some letters, A -- you see those letters A?
A. I do.

Page 457

Q. And if you could drop down to the bottom of the page there's a little legend describing what those letters mean. Could you read what it says for letter A aloud?
A. "Category: A equals event probably causally related."
Q. And did anyone inform you of that conclusion with respect to study HGFU?
MR. BOISE: Object to the form of the question. Foundation.
A. No. And I was, actually, quite aware of the data coming out of the FU trial, both efficacy and safety.
I'm not familiar with categorizations of this nature. I don't know who produced this single page. It was not the position that the data would be reflected as described in this particular table.
The data that I see on the page certainly would not support it if it were valid, and I don't know if it is or not.
So I must say I'm -- I can't comment too strongly to this particular

Page 458

one-pager, given I don't know who authored it, I don't know where it came from, I don't know if it was, for example, a rough draft or an early draft or produced by someone who was not fully cognizant of the data.
If we thought there was a new signal in FU, we all would have been working on it, we would have understood it, we would have communicated it to the FDA and we would have taken appropriate action.
MR. ALLEN: Object to everything after "no" as nonresponsive.
MR. SUGGS: Beat me to it.
QUESTIONS BY MR. SUGGS:
Q. Did you know a Dr. Simeon Taylor?
A. I have a recollection of that individual.
Q. And what's your recollection of that individual?
A. My recollection is that he was an endocrinologist who joined Lilly. Worked at Lilly, I'm recalling, for a

Page 479

Zyprexa, and other typical agents. Our message." And then there are seven items listed there, correct?
A. Yes.
Q. And at the core of your message was the position that the "Data do not support a causal link between Zyprexa and diabetes, and while the scientific literature is mixed there does not appear to be consistent differences among atypicals."
That would be item No. 4, correct?
MR. BOISE: Object to the form of the question.
A. You read item No. 4 correctly. That is reflective of the scientific information. You used the word "core." I don't know precisely what you meant by that. But this statement is here --
Q. Well, let me restate it. If you have a problem with that, let me state it this way: Included in your message was the Point No. 4 that "Data do not support a causal link between Zyprexa and diabetes;

Page 480

while the scientific literature is mixed there does not a appear to be significant differences among atypicals." Correct?
A. You read that correctly, and that is the best reflection of the totality of scientific information.
MR. SUGGS: Move to strike the nonresponsive portion.
QUESTIONS BY MR. SUGGS:
Q. When you stated there that there does not appear to be consistent differences among atypicals, that was referring to differences in rates of hyperglycemia and diabetes, correct?
MR. BOISE: Object to the form of the question.
A. That's my reading of that item.
Q. And on the second page under the heading Corporate Response Letter it states, "On July 11 customers will begin to receive the corporate response letter, Attachment 1, a letter targeted to clinicians, delivered by their Lilly sales

Page 481

representative. The letter is written on behalf of Lilly and signed by Doctor Alan Breier. Market research on the letter was conducted July 2-3 and was very positive."
And my question to you, sir, is Exhibit 9201 a copy of that letter that was referred to in Exhibit 995?
THE WITNESS: Take a look at this.
A. It appears to be the case.
Q. Okay. And to your understanding -- oh, by the way, this letter that is Exhibit 9201, is that something that was actually prepared by you or did someone else draft it?
MR. BOISE: Object to the form of the question.
A. I take accountability for the content of this letter. I've signed it. This was a communication that had input from others.
Q. Who? Which others?
A. I'm not recalling who, specifically, may have contributed. It's not

Page 482

unusual when we have a document that we circulate it for input and comments, and I'm quite certain that we did that with this.
Q. Did anyone from the marketing department review and comment?
A. Certainly we would have circulated it to members of marketing, particularly given the fact that it was going to be going to the sales force and then to physicians. But I'm not recalling precisely, precisely who.
Q. Would Cassandra Mehlman have reviewed this?
A. I'm not recalling that name. I have no idea.
Q. How about Jack Jordan or Mike Bandick?
A. I would assume that both of them would have reviewed it, again, given the fact that it was going to be going to the sales force to then to be circulated through that particular channel.
Q. Okay. How about Denice Torres?

A. Dr. Lechleiter was in charge of the product teams.
Q. And, in fact, I guess the best way to say it, since he's the one that appointed you to be the head of the Zyprexa Product Team, he was your boss?
A. I reported to Mr. van den Bergh, and Mr. van den Bergh reported to Dr. Lechleiter.
Q. And just for the record, Dr. Lechleiter is now the chief operating officer of the entire Lilly company?
A. That's correct.
Q. And I know without a doubt, because in my job, in any job, and the jury will understand, that when you're reporting to your superior concerning a trip to Japan, you're going to try to be as accurate and as truthful as you possibly can be so your superior will have true and accurate information upon which to make his or her decision that needs to be made, right?
MR. BOISE: Objection. Asked and answered.

A. We would convey our impressions as accurately as possible.
Q. And you told us at least one of the reasons you went to Japan was to assess how the affiliate was doing in Japan after the label change, right?
MR. BOISE: Objection. Asked and answered.
A. That's correct. We wanted to assess their implementation of the guidelines.
Q. Yes, sir. And if you look at Paragraph 1, and I will read it into evidence so it will be easier than making you read it. Here's the first paragraph of what you tell Dr. Lechleiter and Mr. Mayr, the head of global sales and marketing. You say this: "This is a summary of issues and proposed actions in follow-up to our previous update on Japan. It is clear that the impact of the label change in Japan has had a" very profound. We concluded, we, keep going on, you left out -- what word should have come after profound?

MR. BOISE: You left out a word before very.
MR. ALLEN: Yes, I did. Let me read it again.
QUESTIONS BY MR. ALLEN:
Q. "It is clear that the impact of the label change in Japan has been very profound. We concluded we have lost substantial ground and trust in our relationship with the MHLW."
That's the Japanese equivalent of the FDA, correct? Sir?
A. Yes.
Q. "Market research shows we have also lost quite a bit of credibility with prescribers and opinion leaders. Basically, because they felt left in the dark with what they perceived as the late sharing of safety information. As a result, there has been a 75 percent drop in new patients who are being put on the drug and a continuing fairly high drop-out rate. That's going to lead to a significant performance impact. Probably, over and above the

10 percent assumed on the sales line in the short term. Although we think we will be able to stem the tide and turn this around."
Did I read that correctly?
A. Yes.
Q. So you knew as a fact that a label change concerning diabetes, a warning concerning diabetes, as a fact, would have an impact on sales, correct?
MR. BOISE: Object to the form of the question.
A. What was, I think, a bit surprising was first the number of patients who were not put on the drug initially which, correct, had an impact on sales, but what's not conveyed in this e-mail was how rapidly the sales performance returned to normal and then actually went quite a bit beyond normal.
So our history is that it's very difficult to predict an impact of a label change and Japan is a good case in point.
MR. FIBICH: Objection. Nonresponsive.

E F G H I

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: ZYPREXA PRODUCTS LIABILITY LITIGATION
THIS DOCUMENT RELATES TO: ALL CASES
MDL-1596

SHAFIQA WARDAK	:	LOS ANGELES : COUNTY,
V.	:	CALIFORNIA
ELI LILLY, et al.	:	BC348211
JOEL ALGARIO	:	LOS ANGELES : COUNTY,
V.	:	CALIFORNIA
ELI LILLY, et al.	:	BC347855
PATRICIA GODLEY, et al.	:	LOS ANGELES : COUNTY,
V.	:	CALIFORNIA
ELI LILLY, et al.	:	BC347856

- - -

March 28, 2007

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C O N F I D E N T I A L

- - -

Videotape deposition of JOHN C. LECHLEITER, Ph.D.

- - -

GOLKOW TECHNOLOGIES, INC.
1880 John F. Kennedy Boulevard
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EXHIBIT E
Page 1 of 15

Page 38

Zyprexa has no connection with any consideration of the impact that would have on my compensation.

MR. ALLEN: I just need to object for the record.

BY MR. ALLEN:

Q. Doctor, now, I did take the liberty, so we wouldn't have to spend a lot of time on your background, we have introduced Exhibit Number 2, which has some of your work background with Eli Lilly. But just for the record today, you served as vice president for Lilly Research Laboratories from 1996 to 1998, during that time frame, correct?

MR. LEHNER: I'm sorry, Scott. Somebody just joined the phone.

MR. ALLEN: I want to say for the record, all this doesn't count against me, all this rigamarole.

MR. LEHNER: A few seconds here. Who just joined the phone, please?

MR. GREEN: This is Brian Green returning the call after reading and agreeing to the protective order.

MR. LEHNER: Thank you very much.

BY MR. ALLEN:

Q. Let me backtrack, Dr. Lechleiter. By the way, Dr. Lechleiter, for the record, I'm calling you Dr. Lechleiter because you are a doctor; is that correct?

A. I have a Ph.D. in organic chemistry.

Q. You have a Ph.D.

For the record, you're not a medical doctor, correct?

A. That's correct.

Q. You're not an expert in diabetes, for example; is that correct?

A. I'm not an expert in diabetes.

Q. You're not an expert in epidemiology?

A. I'm not an expert in epidemiology.

Q. You're not an expert in psychiatry?

A. I'm not an expert in psychiatry.

Q. You're not an expert more particularly on schizophrenia or bipolar mania, are you, sir?

A. That's correct. I'm not a medical expert in those areas.

Q. What you have to do is depend on the people at your company who you hold out as qualified in those areas to give you accurate reporting about what they found, is that true?

A. I depend on the people who work in my organization to have the expertise to do their jobs correctly and appropriately and to use good judgment and to follow the processes that we put in place to ensure that good work gets done.

Page 40

Page 41

Q. Not only --

So, when they prepare memos, e-mails, documents, you have to depend upon those documents and e-mails and reports to you or others in the company to be truthful and accurate, do you not, sir?

A. I have to depend on the judgment of the people who work in the company and who are expert in particular areas of science and medicine, for example, to use their good judgment and to reflect that in what they communicate to me.

Q. Often I've heard, and I'm sure you have as a leader here, the major --

By the way, is Eli Lilly -- I did not look this up, but I meant to, you can probably help the jury, is it a Fortune 100 company, is it a Fortune 200 company, or where does it fit in?

A. I believe we might be a Fortune 200 company, but I'm not

patent expire.
Q. Prozac was another Lilly blockbuster, was it not?
A. Prozac was an important product for Lilly and for millions and millions of patients. And it was also a drug whose sales in the course of its time on the market did exceed a billion dollars.
Q. In fact, Eli Lilly referred to Prozac as a blockbuster, did it not?
A. I don't recall that specifically.
Q. Okay.
Do you recall after the Court ruling, I believe it was in August of 2000, when Lilly's patent for Prozac was not upheld, that 2001 became year X?. You recall that, don't you?
A. I recall being aware of the appeal verdict in August of 2000 and having the knowledge at that time that within that year, we would lose the U.S. patent for Prozac, yes.

Q. That became year X?
A. That became year X. The term "year X" was coined much earlier than that as the company looked ahead to what was going to inevitably happen and to plan to bring forth from our research pipeline a group of new products which we successfully launched nine such new products in the years beginning in 2001 and following shortly thereafter.
Q. In year X, your company and its employees instructed the individuals who were responsible for selling and marketing Zyprexa to have year X for Zyprexa to become year exceptional, correct?
A. I don't --
MR. LEHNER: Object to the form. Go ahead.
THE WITNESS: I cannot answer that question. I don't know that to be true.
BY MR. ALLEN:
Q. Year X, which was 2001, your marketing for Eli Lilly's product Zyprexa was called limitless. Do you recall that marketing slogan, 2001 was a limitless year? Do you recall that?
A. No, I do not recall that.
Q. Back to Exhibit 1, sir. I forgot to ask. It's right here on the screen. Just for the record, it's the third bullet point on schizophrenia. "There is no cure for schizophrenia." "There is no cure for schizophrenia, antipsychotic medications have proven to reduce and control symptoms."
I assume that fact is correct as contained on your website?
A. There's no cure that we know of for schizophrenia. It's important that anyone with schizophrenia not only take the medication that's best for them, but to continue to take that medication. As far as we know, schizophrenia is a chronic disease. It never goes away. So, to treat the symptoms, some of these terrible symptoms I referred to earlier,

it's important that individuals continue to take their medication.
MR. ALLEN: I would just object to that and ask the question this way. And if I can get a direct answer to my question --
BY MR. ALLEN:
Q. Is it correct that there's no cure for schizophrenia as reflected on your website?
A. That is correct to the best of our knowledge.
Q. Thank you, sir.
MR. ALLEN: I'm going to hand you Exhibit 3, and this is a copy for your attorney.
- - -
(Whereupon, Deposition Exhibit Lechleiter-3, "Summary of Historical Analysis - Zyprexa" Slide set ZY203323915 - ZY203323921, was marked for identification.)

way related. I'm limited to time to four hours. His answers are taking way too long, and I'm asking for us to have yes or no answers to yes or no questions.
MR. LEHNER: That was not a yes or no question.
MR. ALLEN: Well, I'm going to object. His answer is nonresponsive.
BY MR. ALLEN:
Q. My question was, was it approved or not?
MR. LEHNER: That wasn't your question.
MR. ALLEN: Well, whether he agreed --
MR. LEHNER: You want to ask him a new question, go ahead.
MR. ALLEN: Let's go ahead.
BY MR. ALLEN:
Q. Sir, I'll short-circuit all of this. Zyprexa is not and has never been approved by the FDA for anxiety, has

it, sir?
A. I don't believe Zyprexa has been approved for anxiety, you're correct.
Q. You actually know it's not been approved?
A. Right. It's not currently in the approved label.
Q. You know for a fact that Zyprexa is not and has never been approved for depression, correct?
A. Zyprexa is not currently approved for depression.
Q. And has never been?
A. I want to make a caveat here. Zyprexa, the active ingredient in Zyprexa, which is called olanzapine, in combination with Prozac, this is a product that we have approved and registered at the FDA, it's called Symbyax, that fixed combination, one of the ingredients of which is olanzapine or Zyprexa, is approved for the treatment of bipolar depression, which is a form of

depression.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. The product, pharmaceutical product Zyprexa has been approved by the FDA?
A. It's approved by the FDA.
Q. That product has never been approved for depression; is that correct?
A. That product itself has never been approved for depression.
Q. Either depression or bipolar depression?
A. That product itself has not been approved for bipolar depression. I do want to note that that product in combination with fluoxetine or Prozac is approved for bipolar depression.
MR. SUGGS: Objection.
BY MR. ALLEN:
Q. Zyprexa has never been and is currently not -- or never been approved for dementia, correct?

A. Zyprexa has not been approved for dementia.
Q. And it's never been?
A. Zyprexa has never had an indication for dementia or the treatment of the psychosis associated with dementia nor for dementia.
Q. The FDA has never approved Zyprexa for Alzheimer's disease; correct?
A. The FDA has not approved Zyprexa for Alzheimer's disease.
Q. And it never has?
A. That's correct.
Q. Zyprexa has never been approved for autism, correct?
A. Correct.
Q. Is has never been approved for obsessive compulsive disorder or attention deficit disorder, correct?
A. Correct.
Q. Zyprexa is not indicated for and has never been approved by the FDA for sleep disturbances, correct?
A. Correct.

marked for identification.)

- - -

BY MR. ALLEN:

Q. Sir, I've handed you what's been marked as Deposition Exhibit Number 6. This is an on line document I got from the Wall Street Journal's web page concerning stock prices. Particularly I was looking at the stock price of Eli Lilly in the year 2000 from August 1st to October 10th. On August the 1st, Eli Lilly's stock price was somewhere near $110 per share. And before the end of August, it had dropped to $75 a share in August of 2000. What happened --

MR. LEHNER: Object to the form.

BY MR. ALLEN:

Q. -- to cause this stock price fall?

A. Stock price is generally responsive to -- can be responsive to external events. In this case, we were surprised to receive, I believe, in early

August, at about the time that you point to this stock price decline, word that was quite unexpected that a three-judge panel had reversed an earlier court's decision about the validity of our Prozac patent.

Q. Yes. And, in fact, Prozac had been the number one selling drug product for Eli Lilly up until August of 2000, had it not?

A. I'm not certain about that. It's possible that Zyprexa sales were larger than Prozac sales at that time. I'm not certain.

Q. Nevertheless, you know if you take the number of share prices or the share price, that Eli Lilly stock after Prozac lost its patent rights in August of 2000 lost $36 billion worth of equity. Did you know that?

MR. LEHNER: Object to the form.

THE WITNESS: Sir, it's not unusual when a company receives

this kind of news that tells investors that a key patent may be jeopardized or may be revoked sooner than the market had anticipated for the market to react this way based on their estimate of revenues, in this case, Prozac revenues, that would not be incurred.

MR. SUGGS: Objection, nonresponsive.

BY MR. ALLEN:

Q. My only question to you was, sir, the stock capitalization of Eli Lilly lost $36 billion in August of 2000 when this -- when your stock fell. Is that correct?

A. I don't have a basis for saying that. This simply shows me that the stock fell. I don't know what the valuation numbers were at that time.

- - -

(Whereupon, Deposition Exhibit Lechleiter-7 (Zyprexa MDL

Plaintiff's Exhibit No. 09070) "Eli Lilly & Company: Part A" (Gulati) 2002 ZY202166113 - ZY202166126, was marked for identification.)

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BY MR. ALLEN:

Q. I'm going to hand you what I marked as Exhibit Number 7. Particularly I'm going to point to Page 7 and part of Page 8, I've highlighted it for you, so we can know what we're going to talk about. I've given this to your lawyer before the deposition.

This is a report that was contained in Kellogg Graduate School of Management, Northwestern's University's graduate school, contained in your files and produced in this litigation. If we turn to Page 7, the highlighted language.

MR. SUGGS: Excuse me, can you also point out this is also Zyprexa MDL Plaintiff's Exhibit 9070.

Page 118

with the annual report?
A. Yes, I am.
Q. Publicly-held corporations such as Eli Lilly issue these every year?
A. Yes, we do.
Q. You issue it in the following year -- does your annual report come out in March or April?
A. It comes out in March generally.
Q. Is the one for 2006 out yet?
A. Yes, it is.
Q. When did it come out?
A. It would have come out about two to three weeks ago.
Q. I'm going to have to talk to somebody.
But anyhow, so, the 2000 annual report would have come out in March of 2001; is that correct?
A. That's right.
Q. Okay.
If we -- there's a lot I'd like to read, we don't have time, but if

Page 119

we look at the 2000 annual report, it says, "No company would relish losing the patent on its biggest product three years early. We certainly don't." You're talking about Prozac, are you not, what happened with Prozac? Doesn't it say that -- it's right there. Page 6. Right in the middle of the page it says, "What happened with Prozac?"
A. Yes. I'm sorry. I was looking to see if it was a continuation, but it's not. It starts right there.
Q. Yes, sir. I'm trying to be fair.
Now, it says, "What happened with Prozac?"
It says, "No company would relish losing the patent on its biggest product three years early. We certainly don't."
A. That's what it says.
Q. Now, you didn't expect this, to lose this patent. You were surprised to have lost this patent?

Page 120

A. Sir, we were surprised, but we were prepared.
Q. You were not only surprised, your report says you were "very surprised and disappointed by the judicial ruling." Is that correct?
A. That's correct.
Q. So, this loss of the Prozac patent that caused your company to lose over $36 billion in market cap came as a big surprise to Eli Lilly, did it not?
A. We were surprised at the ruling by the three judge panel.
Q. Yes, sir. I'm sorry. I didn't use the word -- I'm trying to find where I put it. Here it is. Y'all used the word. I didn't.
You not only were surprised, you were "very" surprised. Is that true?
A. Our analysis of the arguments that had held sway going into that appeal and the strength of those arguments led us to believe that the earlier decision would be upheld. So,

Page 121

naturally when the judges reversed that decision, we were surprised.
Q. Very surprised, right?
A. Sir, I said "surprised." It says "very surprised" here. I didn't write this piece, so it's difficult for me to characterize the distinction.
Q. Going on down, it's on the screen, sir, it says, what did y'all do? "We've significantly increased the size of our global sales force and will continue to do so in order to have the 'firepower' we need to successfully launch and sell the next wave of products from our pipeline."
Did you consider your global sales force fire power, sir?
MR. LEHNER: Object to the form.
THE WITNESS: Sir, our global sales force is the main way in which we engage our customers and help physicians make the right decisions for patients.

Page 122

BY MR. ALLEN:
Q. And what it says here is you "significantly increased the size" of the global sales force in response to Prozac losing its patent protection, correct?
A. That's not what that statement means. This refers to the fact that we had in our pipeline at that point in time, at the point at which this document was written, nine new molecules, new drugs that we intended to launch in the succeeding years, and that actually began in 2001. This refers to the commitment of resources that were going to be necessary to launch nine new products, which was more than anybody else in our industry launched during that time.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. Go ahead and skip to Page 9, and we'll talk about this blockbuster term that we discussed earlier which is

Page 123

used by your company regarding Zyprexa.
Page 9. We're on the topic of "So, what now?" That's on Page 8. Do you see where it says "So, what now?"
A. Yes. There's some kind of photograph, and I can't make that out. I can just see the words "So, what now" on this page.
Q. Yes, sir. And I don't have the photograph. This is the best copy I have available.
"So, what now?" Your company says, "Our newer products will stand as our front line against inevitable generic competition for Prozac. Introduced throughout the last half of the 1990s" -- that would be Prozac, right? I mean, excuse me, Zyprexa was introduced in the last half of the '90s, right?
A. Yes. Zyprexa would be one of several products introduced through the last half of the '90s.
Q. -- "they'll be the key to

Page 124

our ability to produce earnings growth during that time and resume our strong performance thereafter."
The number one product you list, it's number one, and not in the alphabet, it's number 26 in the alphabet, is Zyprexa; is that correct?
A. Zyprexa is next in the text here, yes.
Q. Yes. I take it it's because it's the number one product that y'all are going to have replace Prozac; correct?
MR. LEHNER: Object to the form.
BY MR. ALLEN:
Q. It's certainly not in alphabetical order, is it?
MR. LEHNER: Compound, object to the form.
THE WITNESS: I have no information, since I didn't put this report together, about why Zyprexa is listed first among this

Page 125

group of products. It includes Evista, insulins and Actos.
BY MR. ALLEN:
Q. Sure does. Actos, which starts with the A, is last, and Evista is in the middle.
Let's go to Zyprexa.
"Zyprexa is a genuine" -- can you read that word out loud for me, sir?
A. "Blockbuster."
Q. And so, "blockbuster" is not a term Scott Allen created. It's actually one that Eli Lilly uses itself in its annual reports, right?
A. "Blockbuster" is a term that is used generically and ubiquitously throughout our industry to denote a product, as I said earlier, in general that exceeds a billion dollars in sales.
Q. "Zyprexa is a genuine blockbuster, surpassing the $2 billion sales mark in 2000 and becoming Lilly's number-one-selling product in the fourth quarter. Just as Prozac changed the

Page 146

You're familiar with this, are you not, sir, this consensus statement? You know exactly what this is, don't you?

A. Yes, I've seen this document before.

Q. Sir, we obviously -- and you've read it before, have you not?

A. Yes, I have.

Q. I want to read certain selected portions and talk about it. It's on the board also if you need to, sir, you have it in front of you.

This consensus statement, by the way, was put out by the American Diabetes Association, the American Psychiatric Association, the American of Clinical Endocrinologists, and the North American Association for the Study of Obesity, correct?

A. That's what I read here, yes.

Q. Yes, sir.

Also you know that they had

Page 147

a panel of experts and Eli Lilly made presentations before this panel before this consensus statement was published, correct?

A. I believe that's correct.

Q. You also know that your company was given drafts of this consensus statement prior to the time of its publication, do you not?

A. I do recall that we saw a draft.

Q. Right.

In fact, your company was given the opportunity to make comments upon the draft before this consensus statement was published, correct?

A. I don't recall that specifically.

Q. Anyhow, so the jury knows, this consensus statement is something that you, Dr. Lechleiter, are personally intimately familiar with, correct?

MR. LEHNER: Object to the form.

Page 148

THE WITNESS: Sir, I'm familiar with the development of this document. I was familiar with the fact that there was a consensus conference. I was familiar with the fact that this represents -- this publication represented the outcome of that meeting. That's what I'm familiar with.

BY MR. ALLEN:

Q. And once this thing was published, the consensus statement, once it was published, you considered it a corporate crisis for Eli Lilly, correct?

A. I considered the conclusions reached in this consensus statement to be dead wrong.

Q. Yes, sir. Of course you're not an expert in diabetes, are you?

A. I'm not an expert in diabetes, but I think if you --

Q. You're not an expert in obesity, are you?

Page 149

A. I'd like to finish the answer to my question.

What you don't have attached here are some subsequent letters to the editor that appeared, and I think the comment I made about the conclusions we drew about this consensus recommendation or consensus conclusion were supported by other experts in the field who were expert in diabetes, including the FDA, the group at FDA that oversees the regulation of Zyprexa.

MR. ALLEN: Objection, nonresponsive.

BY MR. ALLEN:

Q. Sir, you understand the American Diabetes Association, the American Psychiatric Association and the American Association of Clinical Endocrinologists and the North American Association for the Study of Obesity is made up of individuals who do not manufacture nor sell antipsychotic medications. You understand that?

Page 266

A. I believe it would be Mr. Brodie.
Q. Mr. Brodie from the diabetes care side of the company says, "Subject: Re: Meeting with endocrinologic consultants." I'm sorry if I mangled that word.
He says, "Robert," he sent it to Robert Baker. The jury will know who Dr. Baker is. "Robert...clearly this group of Endocrinologists (who spoke up and I would rate those who did speak up as the leaders of the pack) are very concerned with the approach Lilly is taking towards the issue that Zyprexa leads to diabetes. I can only hope that you and all of the team who attended the North American Diabetes Advisory Board," that's NADAB, is it not?
A. I believe it is, yes.
Q. -- board "meeting are gaining the ear of senior leadership and articulating this finding. Although the board's recommendation is probably not

Page 267

the way Lilly typically does business, I do believe they made a very strong point that unless we come clean on this, it could get much more serious than we might anticipate."
Did I read that correctly?
A. You read that correctly.
Q. Now, you were senior leadership, were you not?
A. This was in 2000. Yes.
Q. And Tom Brodie says, the people who attended this meeting need to get the "ear of senior leadership." No one ever came to you and told you about what the endocrinologists said in 2000?
A. Sir, I wasn't the only member of senior leadership. We had a very talented, bright group of Lilly people, including physicians, who attended that meeting. Their job would have been to summarize and take appropriate notes on what was said at that meeting, to take that information to other people in the organization, to

Page 268

consider that information, and to put that in context, and this is the important point, with all of the other information we gathered. We cannot draw conclusions made from a presentation of data to a group of endocrinologists for a two-hour period and even suggest that that is the only view or the only evaluation we would take of the product, nor of any conclusions that we might draw about the product.
MR. SUGGS: Objection, nonresponsive.
BY MR. ALLEN:
Q. Sir, you didn't even come close to answering my question.
MR. LEHNER: Object to the characterization.
BY MR. ALLEN:
Q. You told me you were in senior leadership. We saw where Mr. Brodie recommended that the ear of senior leadership be gained based on this meeting. Isn't that what Mr. Brodie

Page 269

said?
A. Mr. Brodie had that opinion.
Q. Yes, sir.
And my only question to you was, did anybody ever come to you and report on the October 2000 meeting with endocrinologists? Yes, no or you don't know?
A. I believe your question was, did anyone ever report to senior leadership?
Q. Well, my question is now, sir, did anybody come and report on the meeting to you?
MR. LEHNER: Asked and answered.
THE WITNESS: Asked and answered.
BY MR. ALLEN:
Q. What's the answer?
A. No one reported specifically on the outcome of this meeting to me --
Q. At any time?
A. -- but I believe other

Page 274

document.
MR. ALLEN: Okay.
Well, I've highlighted for him what I'm going to ask him about in advance. It's right there in front of him.
BY MR. ALLEN:
Q. Sir, were reports --
A. I'm going to -- I'm sorry.
I'm taking the time to read the document.
MR. LEHNER: I don't think you heard me. I would like him to take the time to read the document.
MR. ALLEN: Okay.
I would like this timed, also.
MR. LEHNER: No. Because this document was not provided --
MR. ALLEN: Well, I'm going to time it --
MR. LEHNER: -- in advance.
MR. ALLEN: -- how long he reviews it.

Page 275

Let's go off the record while he's reviewing it so I can go to the men's room. Okay?
MR. LEHNER: You can do anything you want.
THE VIDEOTAPE TECHNICIAN: Off the record.
- - -
(Whereupon, a recess was taken from 12:26 p.m. until 12:32 p.m.)
- - -
THE VIDEOTAPE TECHNICIAN: We're back on the record. It is 12:32.
BY MR. ALLEN:
Q. Okay, sir.
Exhibit Number 20, policy committee Zyprexa safety overview. We've established you're on the policy committee, correct?
A. That's correct.
Q. Okay.
I don't have time to read

Page 276

the whole thing, and I'm not going to. I've highlighted it for you, did I not?
A. Yes. You've highlighted certain things in this two-page communication.
Q. Yes, yes, I certainly have.
A. Three-page.
Q. Yes, sir, I have.
"Introduction. A side effect that is associated with Zyprexa is weight gain and the sequelae of weight gain. Following is an overview of Zyprexa's metabolic profile, as well as a brief update on agranulocytosis.
"Clinical Data. Weight gain. Five atypical antipsychotic agents are associated with more weight gain than most traditional neuroleptic agents in the following order (most to least)."
Did I read that correctly?
A. You've read the statement correctly.
Q. Now, I would assume, since this is a policy committee on Zyprexa

Page 277

product safety, the individuals at this committee meeting are going to be reporting accurately and truthfully and being honest and forthright, correct?
A. I would believe that to be the case. I have no knowledge of who presented this information for the record.
Q. For the record, it appears a report was prepared on the results of the meeting, correct? For the record --
A. Sir, I can't tell whether this document was provided as a prelude to the meeting or whether it was a report following the meeting. It's not clear, nor is it clear who prepared this document.
Q. You would have been at the meeting, right?
A. I can't say for certain that I was. I don't recall what I was doing on that date listed on the cover here.
Q. Well, that's okay, sir.
The policy committee had

Page 278

this report. It says, "in the following order (most to least)." Clozaril is the most, Zyprexa is next, Zyprexa is more than Seroquel, and Seroquel is more than Risperdal. Do you see that?

A. I see what's written here.

Q. That's in the policy committee meeting. That's very similar to Table 2 of the consensus statement published in January of 2004, is it not, sir?

A. I don't think it's similar to Table 2. Table 2 doesn't have the same order shown here.

Q. We'll let others be the judge of that.

All right. The next bullet point. "Zyprexa weight gain is roughly twice that of Risperdal. (Average 7 kilograms versus 3-and-a-half kilograms)."

Did I read that correctly?

A. You've read what's here correctly.

Page 279

Q. All right.

And then it says, "Pfizer's Geodon and BMS's aripiprazole" -- now, that's Abilify, is it not?

A. I believe that's the product name.

Q. You know it's the product name, do you not, sir?

A. Aripiprazole, I think that is Abilify. Is that what you said?

Q. Don't you know it's Abilify?

A. Yes. I'm very sure of that.

Q. Okay.

"Pfizer's Geodon and BMS's" Abilify "appear to have less metabolic issues than other atypicals."

Did I read that correctly?

A. That's what's written there.

Q. So, internally at Eli Lilly in April of 2002, the policy committee was told that Zyprexa has more weight gain than Seroquel and Risperdal, that Zyprexa weight gain is twice that of Risperdal, and that the other products on

Page 280

the market, Abilify and Geodon, have less metabolic issues than the other atypicals, correct?

MR. LEHNER: Object. Mischaracterizes the document.

THE WITNESS: This is a set of statements made in this document. I don't know what the basis was for this. I don't know how they were developed. What I can say is that in our product label, we reported that in a long-term use of Zyprexa in controlled clinical trials, patients who gained weight averaged a weight gain of seven kilos, so, I do recognize that directly from our product label.

MR. SUGGS: Objection, nonresponsive.

MR. ALLEN: Objection, nonresponsive.

BY MR. ALLEN:

Q. Now, in these Zyprexa safety

Page 281

product overviews, skipping down, under "Diabetes (DM)," the second bullet point. "A recent Zyprexa clinical trial analysis indicates patients with baseline diabetes risk factors (obesity" -- let me stop there.

Is obesity a diabetes risk factor?

A. It's listed as such in this document.

Q. So, therefore, a product that causes obesity increases the risk of diabetes, true?

A. I'm not a diabetes expert. It lists obesity here as a risk factor for diabetes in this document.

Q. So, Zyprexa, assume with me, using your common sense as a Harvard graduate and as president and COO of Eli Lilly, assuming Zyprexa causes a patient to become obese, it would increase that patient's risk for diabetes, true?

A. That's not necessarily true.

Q. Okay, sir.

Q. Right.
"Results of two...epidemiological studies (analysis of AdvancePCS" -- what's AdvancePCS stand for, sir?
A. AdvancePCS is a pharmaceutical benefit manager that handles prescription execution for customers.
Q. So, you got their database. "(Analysis of AdvancePCS and GPRD," what's that?
A. I don't know what that refers to.
Q. "(Analysis of AdvancePCS and GPRD databases) indicate that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa." Did I read that correctly?
A. That's what that sentence states, and that was information that would have been gleaned from that particular type of an analysis, but it takes, I think, a composite of different

analyses to draw any conclusions, if you're trying to do that here.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. Sir, as of the time this policy committee on Zyprexa Safety Overview is written on April the 12th, 2002, when it is reflected --
MR. ALLEN: Tom, please. Tom, please.
BY MR. ALLEN:
Q. -- when it is reflected that results of two epidemiologic studies indicate that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa, your package insert or label on Zyprexa contained no warning on diabetes or hyperglycemia, did it, sir?
A. Sir, we continuously monitored the occurrence through our drug event reporting system of any reports of hyperglycemia or diabetes. We analyze

that data. We promptly submitted that data to the FDA. It was made very clear to us in advance of a label change that, in fact, impacted all of the products in this category in September 2003 that FDA was considering a composite of all kinds of data, including epidemiology studies, but also primary clinical trials.
We did a lot of work in this period to understand both weight gain and hyperglycemia, and I think this document in total, not just the sections you're citing, represent our good faith effort to understand this and to make sure that we were adequately communicating appropriate safety information to prescribing professionals.
MR. ALLEN: Objection, nonresponsive.
MR. SUGGS: Objection, nonresponsive.
BY MR. ALLEN:
Q. Just for the record, sir, just so we can get a clear, concise

record, remember you took an oath to say the truth, the whole truth and nothing but the truth? Remember that?
A. Yes, sir.
Q. You're a pharmaceutical manufacturer senior executive and their president and COO, correct?
A. Yes, I am.
Q. You know what short, concise and to the point means, do you not, sir?
A. Sir, I'm trying to give the shortest --
Q. Again, my question to you is, do you know what short, concise and to the point is?
A. Sir, I'm trying to give an answer that is responsive to your question that is as brief as possible.
Q. Let's look at this date. And as brief as possible, April the 12th, 2002, do you have that date in your head, sir?
A. Yes.
Q. Okay.

Page 290

As of that date, there was no warning in the Zyprexa label on diabetes and hyperglycemia, was there, sir?

MR. LEHNER: Object to form.

THE WITNESS: Hyperglycemia and diabetes were both in the label as adverse events from the day we launched the product.

MR. SUGGS: Objection, nonresponsive.

MR. ALLEN: Objection, nonresponsive.

BY MR. ALLEN:

Q. Sir, the FDA certainly differentiates between adverse reactions and warnings, does it not, sir?

A. Those are different sections within the label.

Q. Yes, sir. Right. And listen to my question.

As of April the 12th, 2002, the time of this policy committee meeting Zyprexa safety overview, there was no

Page 291

warning in the Zyprexa label on hyperglycemia and diabetes, was there, sir?

MR. LEHNER: Object to the form.

Go ahead. You can answer.

THE WITNESS: The Zyprexa product label fairly represented what we believed to be the best knowledge we have of the product and what FDA felt was the information most appropriate to communicate in the label.

MR. ALLEN: Objection, nonresponsive.

MR. SUGGS: Objection, nonresponsive.

BY MR. ALLEN:

Q. Sir, as of April the 12th, 2002, the policy committee meeting Zyprexa safety overview, there was no warning in the Zyprexa label as defined by the FDA, was there, sir?

A. I don't recall. I don't have the label in front of me. I do know that later in September, I believe, of 2003, there was a warning introduced in all manufacturers' labels that spoke specifically to the occurrence of diabetes and hyperglycemia and the fact that the FDA could not determine whether that was causally related to these products or not.

Page 292

MR. SUGGS: Objection, nonresponsive.

BY MR. ALLEN:

Q. Is that the best answer you can give a jury?

A. I don't have the label. If you want to show me the label from --

Q. The jury will see the label. And I'm asking you --

A. I believe the first warning that was introduced was the warning introduced in September 2003.

Q. Okay.

So, now, let's go back to my question. As of April the 12th, 2002,

Page 293

there was no warning in the Zyprexa product label, as that term is defined by the FDA, concerning hyperglycemia and diabetes, correct?

A. There was nothing of that nature in the section under warnings, but certainly diabetes and hyperglycemia were listed in the label and had been listed in the label as adverse events since the time we introduced the product.

MR. ALLEN: Objection, nonresponsive.

MR. SUGGS: Objection, nonresponsive.

BY MR. ALLEN:

Q. Sir, honestly, under oath to a jury and to a judge, you understand there's a difference between a warning under the FDA's definition and an adverse reaction, correct?

A. Yes, I do.

Q. You understand that differentiation is defined by law, correct?

the increased reporting of diabetes related to Zyprexa was the issue of weight gain, correct?

A. No. I would not concede that. I would say that individuals, whoever it was that prepared this report, looking at sheer raw numbers, that's what these 542, 434 are, just raw numbers, are speculating about why these numbers may be different. I can cite other reasons, and there are other reasons why they might be different, in addition to the ones cited, which include weight gain, illness severity and reporting bias.

Q. Go down under "Diabetic Ketoacidosis." You know what that is under C? Do you know what that is, diabetic ketoacidosis?

A. I know what that is.

Q. That's a deadly condition, is it not, related to diabetes?

MR. LEHNER: Object to the form.

THE WITNESS: DKA is a

potential serious complication of uncontrolled diabetes.

BY MR. ALLEN:

Q. You had a lot of information about DKA back in April of 2002. You were looking into that, weren't you, you, personally?

MR. LEHNER: Objection to the form.

THE WITNESS: Sir, I don't agree with your conclusion that we had a lot of information.

BY MR. ALLEN:

Q. Okay. Thank you. Diabetic --

A. And I don't -- I'm sorry. I want to answer the question.

And no, I was not looking into this personally.

Q. Okay.

Diabetic ketoacidosis, second bullet point. "FDA Freedom of Information Database cases of DKA (cases" and "total exposures):" Clozaril, 103

cases, total exposure not available; Zyprexa 132 cases, 3.7 million exposures.

Did I read that correctly?

A. That's what's written here.

Q. And of the gross number of cases of diabetic ketoacidosis as reported to the Zyprexa policy committee -- I mean, excuse me, Lilly's policy committee, Zyprexa had the most cases; is that correct?

A. Numerically, as it is shown here, Zyprexa had the most cases. It also is another situation where the absolute number that you cite cannot be taken without some additional context. There are many reasons and many explanations for why these numbers are different, and I think in looking at this information, as the FDA certainly did, and as Lilly did, I don't think one can draw clear conclusions.

MR. SUGGS: Objection to the nonresponsive portion.

BY MR. ALLEN:

Q. Of course, sir, I'm going to hand you -- April of 2002 was a busy month for your company, was it not? Wasn't it a busy month for your company --

MR. LEHNER: Object to the form.

BY MR. ALLEN:

Q. -- regarding Zyprexa?

MR. LEHNER: Object to the form.

THE WITNESS: I don't recall. That was five years ago.

- - -

(Whereupon, Deposition Exhibit Lechleiter-21 (Zyprexa MDL Plaintiffs' Exhibit No. 00320), "Appendix 6: Japanese Dear Doctor Letter" ZY 4051 1633 - ZY 4051 1638, was marked for identification.)

- - -

BY MR. ALLEN:

Q. Let me show you this. What

concerned how this would affect the stock price, correct?
MR. LEHNER: Object to form.
THE WITNESS: No. I was not concerned about how it would affect the stock price. I was concerned about how that label change would affect patients in Japan.
BY MR. ALLEN:
Q. Well, didn't it, in fact, affect patients in Japan in a favorable fashion?
A. I think it largely affected patients in an unfavorable fashion, because we know that many patients who were stable on Zyprexa were taken off therapy because of what we believe were unfounded fears of physicians following this label change.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. Doctor, you know, for a

person that's not a medical doctor, are you trying to suggest that you can judge medical care of doctors in Japan, whether it's good or bad, what doctors in Japan think about your product?
A. Sir --
MR. LEHNER: Objection to the form.
Go ahead.
THE WITNESS: -- I would never do that.
BY MR. ALLEN:
Q. Thank you.
A. I'm relying here on the input I received from very qualified medical doctors.
Q. And didn't you receive the input from qualified medical doctors that the patients in Japan had benefited by the label change?
MR. LEHNER: Object to the form.
THE WITNESS: I'm sorry. I don't understand your question.

MR. ALLEN: The tape is out. Let's take a break and we'll be back.
THE WITNESS: Okay.
THE VIDEOTAPE TECHNICIAN: This marks the end of Tape Number 3 in the deposition of Dr. John Lechleiter, 12:57.
- - -
(Whereupon, a recess was taken from 12:57 p.m. until 1:18 p.m.)
- - -
THE VIDEOTAPE TECHNICIAN: We're back on the record. This is the beginning of Videotape Number 4 of the deposition of Dr. John Lechleiter. It is 1:18.
BY MR. ALLEN:
Q. Dr. Lechleiter, Scott Allen. We're back on the record. I've discussed with counsel we have 48 more minutes, so, I ask you to bear with me.
- - -

(Whereupon, Deposition Exhibit Lechleiter-23, Letter 7-1-02 ZY203332491 - ZY203332493, was marked for identification.)
- - -
BY MR. ALLEN:
Q. I've handed you what's been marked as Exhibit 23. You're familiar with this exhibit, are you not, sir?
A. I recall having seen this document.
Q. Sir, this document is a letter that was written to you or a memo written to you on July the 1st, 2002 by two members of senior management at Eli Lilly, correct?
A. Yes. It was written to me by Mr. Bert van den Bergh and Dr. Alan Breier.
Q. For the jury, who is Mr. van den Bergh?
A. Mr. van den Bergh was -- is a Lilly executive. At the time, I believe he was responsible for a group of

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA	)	
	)	
Plaintiff,	)	
	)	
vs.	)	CASE NO.
	)	3AN-06-5630 CIV
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	

The videotaped deposition upon oral examination of DAVID THOMAS NOESGES, a witness produced and sworn before me, Carolyn L. Smith, CSR, RPR, Notary Public, in and for the County of Hamilton, State of Indiana, taken on behalf of Plaintiff, at the offices of Ice Miller, One American Square, Suite 3100, Indianapolis, Indiana, on January 11, 2008, at 9:31 a.m., pursuant to all applicable rules.

EXHIBIT F
Page 1 of 9

Page 114

Q Do you know who it was that concluded that it was essential to weaken this link in order to neutralize the diabetes/hyperglycemia issue?
A No, I don't. I can't tell who authored the document.
Q If I could direct your attention to the Summary at the bottom of page 3. It states, "Eli Lilly ... has a proud history in innovative diabetes research. The relationship between Zyprexa and diabetes, slash, hyperglycemia is a top priority for the company and has been studied extensively. The facts illustrate no difference in the incidence of treatment-emergent hyperglycemia and diabetes for patients Zyprexa, haloperidol, risperidone, ziprasidone, or divalproex. Neutralizing any concern from our customers will be essential to the future growth of Zyprexa in" the "marketplace."
Do you see that language, sir?
A Yes, sir, I do.
Q Was it your understanding that the goal of the company was to neutralize any concern that customers had about diabetes with Zyprexa?
A My understanding and my experience with what our goals with our customers were to ensure that they understood what our available data indicated

Page 115

through our clinical trials was the risk of diabetes associated with Zyprexa.
And that, in fact, in spite of some of the perceptions that there may be a direct link that our own data did not demonstrate a difference in the incidence of treatment-emergent hyperglycemia and diabetes in patients on Zyprexa relative to these other agents.
Q Sir, twice in this E-mail -- pardon me, in this memo the document talks about neutralizing concerns, does it not?
MR. BOISE: Look through the document and see.
QUESTIONS BY MR. SUGGS:
Q If you look at the first paragraph, I can point two out right away. The first is right under the discussion of Message Point #2. It states, quote, We believe it is essential to weaken this link in order to neutralize the diabetes/hyperglycemia issue, and the concluding sentence of the Summary which says, "Neutralizing any concern from our customers will be essential to the future growth of ZYPREXA in this marketplace."
The company obviously wanted to neutralize physicians' concerns about diabetes, correct?
MR. BOISE: Object to the form of the

Page 116

question.
THE WITNESS: Clearly, when I read this document what we are referring to because it talks initially about the competition having created perceptions around risk of hyperglycemia in Zyprexa and diabetes with Zyprexa, and what we are trying to do here is really articulate what our clinical trial data indicates around the real risk of diabetes for patients on Zyprexa. And that, in fact, throughout clinical trials we saw a comparable rate of diabetes and hyperglycemia among the psychotropic agents as identified in Message Point #1, that to understand the link between weight gain and hyperglycemia that -- although, weight gain can be a risk for hyperglycemia, that even among those patients with substantial weight gain a significant percentage of them had no glycemic abnormalities at all.
So the piece was designed to -- the characterization to neutralize is to offset some of the misperceptions in the market place.
Q This piece was designed to neutralize any concerns that physicians had about diabetes and Zyprexa, correct?
MR. BOISE: Objection, mischaracterizes his

Page 117

testimony.
QUESTIONS BY MR. SUGGS:
Q It's the Summary -- the bottom line Summary of this sales aid is, "Neutralizing any concern from our customers will be essential to the future growth of ZYPREXA in this marketplace."
MR. BOISE: Is your question it that what the words say?
QUESTIONS BY MR. SUGGS:
Q Is that the bottom line of the Summary?
MR. BOISE: Is that what the last line of the Summary says? Is that your question?
MR. SUGGS: My question stands.
MR. BOISE: Object to the form of the question, vague.
What do you mean by bottom line?
QUESTIONS BY MR. SUGGS:
Q Sir, do you know what the bottom line is?
A I assume, by "bottom line" you mean the last line in the Summary.
Q It happens to be the last sentence in that Summary; it also happens to be the fact with respect to the purpose and goal of this sell sheet was to neutralize any concern that physicians had about Zyprexa having a higher incidence of diabetes.

Page 118

MR. BOISE: Objection, move to strike the speech.
QUESTIONS BY MR. SUGGS:
Q Isn't it?
MR. BOISE: Object to the form of question.
THE WITNESS: No sir, that's not what I said.
QUESTIONS BY MR. SUGGS:
Q I know that's not what you said, but the fact of the matter is that the sell sheet was designed to neutralize concerns physicians had about Zyprexa having -- causing more diabetes than other drugs; isn't that correct?
MR. BOISE: Objection, asked and answered.
THE WITNESS: No, sir. The sell sheet was designed to communicate the results from our clinical trials and our analysis of what the risk of diabetes was associated with Zyprexa and other psychotropic agents.
QUESTIONS BY MR. SUGGS:
Q Sir, a sell sheet is designed to increase sales, correct?
MR. BOISE: Object to the form of the question.
(Conference room phone ringing.)
THE WITNESS: Sir, a sales sheet is a promotional document that is designed to communicate in a fair balanced matter consistent with the FDA regulations, both the benefits and the side effects of our product, and to increase the usage of our product for appropriate patients.
QUESTIONS BY MR. SUGGS:
Q To increase sales, correct?
MR. BOISE: Object to the form, asked and answered.
THE WITNESS: Sir, the purpose of our sell sheets is to communicate the benefits and risks of our product consistent with the promotional guidelines that we work under through our good promotional practices and to increase the sales of the product and the use of the product in the context of appropriate patients.
QUESTIONS BY MR. SUGGS:
Q The purpose of a sell sheet is to sell?
MR. BOISE: Object to the form, asked and answered.
QUESTIONS BY MR. SUGGS:
Q Right? That's why they call it a sell sheet, isn't it?
MR. BOISE: Object to the form.

Page 119

Page 120

THE WITNESS: Sir, the purpose of the sell sheet is to communicate to clinicians the risk and benefits of our products recognizing they are going to make the ultimate decision.
Certainly, a goal is to increase the sales of the product for what clinicians determine to be the appropriate patients for our product.
QUESTIONS BY MR. SUGGS:
Q I assume, sir, that you are aware of the consensus conference of the American Diabetes Association and the American Psychiatric Association in November of 2003, correct?
A Yes, sir, I am.
Q Okay. You came back to the U.S. to head up U.S. marketing in November of 2003?
A Yes, that's correct.
Q And in November of 2003 there was a consensus -- you know what, let me -- before I get into that, we have to mark this as the next exhibit.
Let me backtrack here and hand you what's been previously marked as Exhibit No. 5.
(Deposition Exhibit 5 marked for identification.)
MR. BOISE: He did not bring enough for the whole class, so I'll have to look over your shoulder.

Page 121

QUESTIONS BY MR. SUGGS:
Q If I could direct your attention to the last page. By the way, would you agree that this document -- would you characterize this document as a sell sheet or brochure or something different?
A I think both brochure and/or sell sheet would probably be a reasonable characterization of this.
Q If you look at the last page at the very bottom there is number 60, dash, OL26280.
Do you see that?
A Yes.
Q What does that refer to?
A That's a reference number so that we know what the document is.
Q And it indicates that the copyright for this would have been 2003, correct?
A Yes.
Q So it would appear that this sell sheet or brochure would have been later in time than Exhibit 4, correct?
A Which one was Exhibit 4?
Q That was the other color brochure or sell sheet that we were just talking about.
A It appears to be based on the copyright, yes.
Q Yep, about two years later, correct?

said it's a definition.
MR. SUGGS: It's a medical dictionary. I can't remember which one.
Q Would you accept that definition that indication is something that points to or suggests the proper treatment of a disease?
A I think you are clearly outside of my area of expertise. I would consult with --
Q Okay.
A -- my medical colleagues. If it was a clinical question, with my regulatory colleagues. If you are asking is that the FDA definition of indication, which is what's relevant for our package label, I don't know the answer to that.
Q Would you agree, sir, as someone in charge of marketing and sales that doctors look to the indication section of the label to see if the drug is appropriate to use for the proper treatment of the disease?
A Yes, I believe that's one source doctors may use to make that decision.
Q Okay. And the diseases for which the drug is indicated or appropriate to treat are listed in the indication section of the label, correct?
A The indication section of the label indicates --

those disease states are indication for which the drug has received FDA approval for promotion.
Q And Zyprexa was originally -- well, strike that.
As someone in charge of the marketing of Zyprexa and also responsible for sales of Zyprexa, you and the people who worked under you needed to be familiar with, conversant with what was contained in the label, correct?
A Yes.
Q And in 1996 -- well, let me put it this way:
Before 2000, Zyprexa was indicated for the management of psychotic disorders, correct?
MR. BOISE: Object to the form.
QUESTIONS BY MR. SUGGS:
Q Do you recall that?
MR. BOISE: Almost right.
THE WITNESS: I don't believe that is the exact indication. I would have to look at the package label to tell you what the exact indication was prior to that time frame.
QUESTIONS BY MR. SUGGS:
Q Okay. Do you recall that in 2000 the indication section of the label was changed to say that Zyprexa is indicated for the treatment of schizophrenia and Zyprexa is indicated for the

short-term treatment of acute manic episodes associated with Bipolar I disorder?
A Yes, I do.
Q Okay. You recall that in 2004 the indications were expanded to include treatment for the short-term treatment of acute mixed or manic episodes associated with Bipolar Disorder I and as maintenance treatment in bipolar disorder?
MR. BOISE: Object to the form, foundation.
THE WITNESS: Yes, I'm aware of the label change, but I would have to read from the label to know whether that's the exact language of the label in that time frame.
QUESTIONS BY MR. SUGGS:
Q Okay. You know, sir, that Zyprexa was never approved for the treatment of anxiety, correct?
A Yes, that's correct.
Q It was never approved for the treatment of irritability, correct?
A Zyprexa never had an indication for the treatment of irritability -- irritability, no.
Q Zyprexa was never approved for the treatment of disruptive sleep, correct?
A Zyprexa never had an indication for the treatment of disruptive sleep.

Q Zyprexa was never approved for the treatment of mood swings, correct?
A Zyprexa never had an indication for the treatment of mood swings, but certainly mood swings are an element of the symptoms of bipolar disorder.
Q Zyprexa never -- was never approved for the treatment of complicated mood symptoms?
A Again, we never had a specific indication for complicated mood symptoms, but those are symptoms consistent with -- with certainly the bipolar disorder indications for Zyprexa.
Q Move to strike the nonresponsive information.
Zyprexa was never approved for dementia associated with Alzheimer's, correct?
A No, sir, it was not.
Q I'm going to hand you what's been previously as Plaintiffs' Exhibit 4121.
For the record this exhibit is entitled "ZYPREXA - Primary Care Strategy and Implementation Overview."
The first section is entitled "Background." It states, Following several months of study by the LillyUSA Zyprexa Brand Team, the affiliate approved the recommendation that Lilly actively promote Zyprexa to selected current primary care prescriber

Page 170

2000.
What was the Sigma sales force, do you know?
A Sigma was a primary care sales force that among their responsibilities included Zyprexa promotion to primary care physicians.
Q It goes on to state, "It has gained over 12 share points since that time. As the current market leader in primary care, ZYPREXA will continue to revolutionize the way complicated mood disorders are treated by primary care physicians."
Do you see that language, sir?
A Yes, sir, I do.
Q And as we have talked about before, Zyprexa was not indicated for complicated mood disorders, was it, sir?
MR. BOISE: Object to the form of the question, mischaracterizes his prior testimony.
THE WITNESS: Zyprexa was indicated for schizophrenia and bipolar disorder.
QUESTIONS BY MR. SUGGS:
Q If I could direct your attention to page 5. And this is basically walking the sales rep through the use of a brochure, correct?
A Yes. This is a message example for sales representatives to use to help them in terms of how

Page 171

they communicate to physicians.
Q What we see here on this page in the upper right-hand corner and on the succeeding pages is an image of the brochure that was being used, correct?
A Yes.
Q And then the rest of the text on the page is a description provided by Lilly's marketing folks as to how to use that brochure, correct?
A Yes.
Q For example, on page 5 here, they show the front cover of the brochure -- and by the way, do you recall what this particular brochure was called?
A I don't know that it had a name.
Q Okay. But anyway we see the picture of the doctor and the patient on the first page. It looks like the patient is fording a river by stepping on various stones, correct? And the doctor is there to hold her hand as she gets over there, right?
A Yes, that appears to be what -- what the diagram depicts.
Q They have a suggested call opener there, correct?
A Yes.
MR. BOISE: Object to form.
THE WITNESS: Yes.

Page 172

QUESTIONS BY MR. SUGGS:
Q And what's a "call opener"?
A In this context the call opener is simply an introductory statement for the sales representative to make during the call to the doctor.
Q And the sales rep was to say, "Doctor, you treat patients who present with complicated mood symptoms. Many of these patients are struggling to gain control of symptoms like anxiety, irritability, disruptive sleep, and mood swings. I would like to talk about how ZYPREXA can help you help your patients gain control of these complicated mood symptoms," correct?
A Yes, sir, that's correct.
Q No mention of schizophrenia or the acute manic phase of Bipolar I disorder?
MR. BOISE: Object to the form of the question. Object to the form of the question.
THE WITNESS: There's no mention of that in this specific sentence, no.
QUESTIONS BY MR. SUGGS:
Q And Zyprexa was not approved for any of the symptoms that are listed in that call opener, was it, sir?
MR. BOISE: Object to the form of the

Page 173

question.
THE WITNESS: These symptoms are consistent with the symptoms of bipolar disorder as I read them.
QUESTIONS BY MR. SUGGS:
Q Sir, Zyprexa was not approved for the treatment of any of the symptoms that are listed in that call opener; isn't that correct, sir?
MR. BOISE: Object to the form of the question.
THE WITNESS: Zyprexa is indicated for schizophrenia and bipolar disorder.
QUESTIONS BY MR. SUGGS:
Q Not anxiety, irritability, disruptive sleep, or mood swings or complicated mood symptoms. It was indicated for schizophrenia and bipolar, correct?
MR. BOISE: Object to the form of the question.
THE WITNESS: Zyprexa is indicated for bipolar disorder whose symptoms include the symptoms that are described here in this call opener.
QUESTIONS BY MR. SUGGS:
Q Sir, one of the things that Lilly did was to have what they call "patient profiles."
Do you remember that?

Page 194

sales support personnel in LillyUSA and all sales activities that take place in the United States or with US Healthcare Professionals," correct?
A Yes, sir, that's correct.
Q And the policy statement was that, quote, It is the policy of LillyUSA that all sales personnel appropriately document sales calls with Healthcare Professionals in the call tracking system; is that correct?
A Yes, that's what it says.
Q What was the call tracking system?
A This is referring to basically the sales representatives' computer database that was available to them in this time frame, which would have been effective June 1st, is what this document is referring to -- to put their -- to document calls they were making on healthcare providers.
MR. BOISE: just so the record is clear it's June 1st, 2004.
Q And, in fact, this call system existed before 2004, correct?
A Yes, it did.
Q Okay. Can you describe for us, generally, what is involved in this call system or call note system?
A Depends on the time frame. While that system has

Page 195

been in place, the process of gathering call notes has changed over time.
Q Okay. Well, is it fair to say that the sales rep is expected to -- shortly after his calling on a particular physician is expected to go to a computer database and enter information about the particular sales call that he had?
A Yes, that's correct.
Q And all of that information is to go into a centralized database, correct?
A The sales representative inputs the data into their computer laptop which then is stored centrally, but I don't know the details of how -- how that information gets stored.
Q Okay. Again, I'm not asking for the details; but it's fair to say that there is a database of call notes that describes the -- or that lists the -- who the sales rep was, the doctors that they called on, the products that they discussed and what was said during the sales call, correct, or what information was presented at the sales call?
MR. BOISE: Object to the form of the question, compound.
THE WITNESS: No. It's important to note two things: One, it depends on the time frame, what

Page 196

got documented and, secondly, the call notes are not a comprehensive description. It won't describe everything that happened on the call or everything that was said on the call. To the contrary, it's more of a summary and notes taking process for the sales representatives to use for themselves.
QUESTIONS BY MR. SUGGS:
Q Understood; but -- and management can access the database quite easily, correct?
A Certainly the sales representative, sales managers can access their call notes.
Q If, for example, you wanted to go to get all of the call notes with respect to a particular sales representative, that could be easily retrieved from the call note system, correct?
MR. BOISE: Object to the form of the question.
THE WITNESS: I would have to work with our IT folks to get that, but I certainly could pull data from the call notes. Now, what I don't know is how far back the data goes at any time.
QUESTIONS BY MR. SUGGS:
Q I understand. There's a limitation on anything.
But I mean since whatever system is present now, you could certainly go to -- go to that

Page 197

database and make a query to pull up all of the call notes from Representative Harry Jones, for example?
A I'm assuming I would be able to. It's not something I have done in management. We don't routinely pull together data from the call notes.
Q Okay. And similarly if you wanted to get all of the call notes with respect to a particular doctor, the call note database would permit you do so, correct?
MR. BOISE: Object to the form.
THE WITNESS: Again, you are outside of my expertise in exactly what we can retrieve from the database.
QUESTIONS BY MR. SUGGS:
Q Okay. Directing your attention back to Exhibit 9.
A Yes.
Q There is a Definitions section there and sales call is defined as a face-to-face discussion about Lilly products between a healthcare professional and a Lilly sales representative, correct?
A Yes, it is.
Q And a call note is defined as a business record documented within a call system that accurately reflects all aspects of the sales call, correct?

A Yes.
Q Okay. And then below that there is a section entitled "Information and Procedures" and there's some bulleted points below that, correct?
A Yes.
Q The second bulleted point states, "The goal of the sales call is to appropriately influence a Healthcare Professional using the approved Lilly product information to allow him or her to choose the best therapy for his or her patients and ultimately to increase" the "sales of Lilly products," correct?
A Yes, that's correct.
Q And then on the following page there is a bullet point which states, "For each sales call and/or sample drop, the sales representative must accurately document the interaction in the Structured Call Note system in Premier."
Do you see that language?
A Yes, I do.
Q What is "Premier"?
A Looks like this was a typo here. It's probably referring to Premier Force which is the name of the sales representatives' computer database to enter calls, again, in this time frame, 2004.

Q And the structured call note system, was that a particular program within that Premier that is being referred to there?
A Yes.
Q And it goes on to say, "If applicable, unsolicited questions or medical letter requests must be documented within the SCN," or structured call note, "system according to policy, GPP 02-004 Unsolicited Questions on Off-Label Information or Unapproved Products."
Did I read that correctly?
A Yes, you did.
Q And that is the good promotional practice that we referred to earlier in Exhibit -- trying to find the number here. If you find it before I do, let me know.
A Exhibit 8.
Q Exhibit 8, very good. Thank you.
I would also like to show you some --
MR. BOISE: Dave, is there a question pending?
MR. SUGGS: I'm in the process of stating it.
MR. BOISE: Fair enough. Lots of shuffling of paper. I didn't know if I missed a question, if there was one.
MR. SUGGS: I was working on one.

MR. BOISE: Keep on working on it.
QUESTIONS BY MR. SUGGS:
Q I would like to show you some call notes that have been produced to us in the Alaska litigation, and I'll mark this next as Exhibit 10.
(Deposition Exhibit 10 marked for identification.)
QUESTIONS BY MR. SUGGS:
Q Which I'll represent to you is a page of call notes pulled from the sample that Lilly has produced to us in the Alaska litigation. And it would appear this particular page has call notes that were generated by Margaret Williams, several by her, and also by a Thea Jung.
Do you see that?
A Yes, I do.
Q It appears that this call note database has various fields that include the name of the sales rep, the call date, the call ID, the prescriber last name, the prescriber first name, the city in which the prescriber is, the state, and then it has action, reaction, follow up. And the rest of the information I think probably comes from this litigation.
Were you -- what's your understanding of what

the Action field was for?
A As I mentioned to you before, in this time frame this tool is really used for the reps to describe in shorthand notes to themselves as to the notes they wanted to record from their conversation with the doctor.
Q And then what is the Reaction supposed to be?
A The Reaction was designed to describe, kind of, a customer reaction to the calls. And my experience with these field notes is often it's not what you find in those fields. It all ends up really being shorthand notes to the representatives.
Q Is it the policy and practice of Lilly management to also review the call notes of the sales reps?
A No, we don't routinely review the call notes from the sales representatives.
Q Do you periodically do so?
A The district managers are able to access the call notes and if they choose to they can take a look at a call note or discuss it with a sales representative.
Q Do you know who Margaret Williams was?
A No, I do not know Margaret.
MR. SUGGS: Barry, can you tell me, is she the lady who is deceased?

around Zyprexa's usefulness in elderly patients.
QUESTIONS BY MR. SUGGS:
Q And, sir, Zyprexa was never approved for the treatment of hostility in elderly patients, was it, sir?
MR. BOISE: Object to the form.
THE WITNESS: Zyprexa does not have an indication for hostility in elderly patients.
QUESTIONS BY MR. SUGGS:
Q And Zyprexa was never indicated for the treatment of agitation in elderly patients, correct?
MR. BOISE: Object to the form, foundation.
THE WITNESS: Zyprexa does not have a specific indication for agitation in elderly patients.
QUESTIONS BY MR. SUGGS:
Q And, in fact, Zyprexa was never indicated or approved for the treatment of cognition or for improving cognition, correct?
MR. BOISE: Object to the form.
THE WITNESS: Improvement of cognition is certainly a symptom of schizophrenia as can be hostility and agitation, but there is not a specific indication for cognition.
QUESTIONS BY MR. SUGGS:
Q And, in fact, nowadays, at least since 2004,

there's been a black box warning against using Zyprexa for patients with dementia and Alzheimer's, correct?
MR. BOISE: Object to the form, foundation.
THE WITNESS: Your language is not in the specific label language that we currently have.
QUESTIONS BY MR. SUGGS:
Q I did not represent that it was.
There has been a black box warning in the Zyprexa label since 2004 with respect to the elderly, correct?
A Yes, that's correct.
Q That did not exist in 2002 when this call note was made, correct?
MR. BOISE: Object to the form, foundation.
THE WITNESS: No, I do not believe it did.
QUESTIONS BY MR. SUGGS:
Q Was Zyprexa indicated for the treatment of patients whose symptoms were aggravated by a SSRI?
MR. BOISE: Object to the form.
THE WITNESS: Zyprexa's indication, as we have discussed before, was for schizophrenia and bipolar disorder.
QUESTIONS BY MR. SUGGS:
Q Didn't sales reps in Alaska, in fact, promote

Zyprexa as being especially good for patients whose symptoms were aggravated by an SSRI?
MR. BOISE: Object to the form of the question, foundation.
THE WITNESS: Sir, what I can describe to you, as I have before, is what our marketing messages were on a given time frame, but I would have to know what time frame you were describing and then I could indicate to you what the company approved message was.
QUESTIONS BY MR. SUGGS:
Q Let me show you another set of call notes, which I'll mark as Exhibit 12.
(Deposition Exhibit 12 marked for identification.)
MR. SUGGS: Did I give you a copy?
MR. BOISE: Not yet.
MR. SUGGS: Sorry.
MR. BOISE: While you are shuffling, this has been marked as Exhibit 12, is a grouping of seven pages of call notes.
MR. SUGGS: Yes.
Q If I could direct your attention to the first call notes -- the first call note on the first page, these appear to be call notes from Margaret

Williams, dated May 17, 2002, with respect to a meeting with Dr. Kathryn Flores in Soldotna, Alaska, text which says in part, "Also got in a decent ZYP recap, reminded doc that ZYP is a great mood stabilizer, especially for patients whose symptoms were aggravated by an SSRI."
Do you see that language, sir?
A Yes, sir, I do.
Q Now, there were drugs that were approved as being mood stabilizers, correct?
A I would have to check the specific indications of Lithium and Depakote to know what the label language is around their indication.
Q Well, Depakote was a mood stabilizer.
Zyprexa was not indicated as a mood stabilizer, was it, sir?
MR. BOISE: Object to the form, foundation.
THE WITNESS: Again, I'm not a clinical expert, but my understanding of the term "mood stabilizer" refers to medicines that are indicated for treating bipolar disorder.
QUESTIONS BY MR. SUGGS:
Q Well, sir, as we have talked about before, in 2002 Zyprexa was only indicated for schizophrenia and the acute manic phase of Bipolar I disorder.

It was not approved as a mood stabilizer, was it, sir?
MR. BOISE: Object to the form, argumentative, asked and answered.
THE WITNESS: As I answered, I am not a clinical expert to be able to try to make that distinction; but my understanding is that a mood stabilizer is a way that clinicians and psychiatrists would describe a medicine that is used to treat bipolar disorder including bipolar mania.
QUESTIONS BY MR. SUGGS:
Q Well, the acute manic phase of Bipolar I disorder is something that lasts only for a couple of weeks, isn't it, sir?
MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: Again, clearly, I'm not a medical expert, but that's certainly not my understanding. A manic phase can last for variable times and stabilizing mood is a way that I have often heard clinicians describe treating any phase of bipolar disorder including the manic phase.
QUESTIONS BY MR. SUGGS:
Q Sir, the labeling for Zyprexa never stated that it

was good especially for patients whose symptoms were aggravated by an SSRI, did it, sir?
A No, sir, it did not.
Q If I could direct your attention to the call note that is second from the bottom, this is another Margaret Williams' call note dated June 6th, 2002.
Under the Action section it states, quote, Actually got in a decent ZYP detail for patients with unresolved symptoms, patients who fail on an SSRI, patients could be suffering from complicated mood order, perhaps bipolar, ZYP is an excellent mood stabilizer, very safe, easy to dose?
Do you see that language, sir?
A Yes, sir, I do.
Q Zyprexa was never indicated for patients who fail on an SSRI, was it?
MR. BOISE: Object to the form of the question.
THE WITNESS: No, sir, Zyprexa does not have a specific indication for patients who fail on an SSRI.
MR. SUGGS: I have no further questions at this time.
MR. BOISE: Why don't we take five minutes. I have five minutes of questions.

THE VIDEOGRAPHER: Off the record at 3:05.
(Recess.)
THE VIDEOGRAPHER: We are back on the record. It is 3:10.
EXAMINATION
QUESTIONS BY MR. BOISE:
Q Mr. Noesges, just a few questions for you.
You were asked about -- during your prior examination by Mr. Suggs, about what's been marked previously as Zyprexa MDL Plaintiff's Exhibit 1926, June 2002 document, Primary Care Sales Force Resource Guide.
Do you see that document in front of you?
A Yes, I do.
Q Does this represent the exclusive means of training a sales force concerning messaging in primary care?
A No, this document would be one aspect of many aspects of training. I think for -- anytime you see a training document like this, it needs to be put in the context of our typical training approach, which would be to provide a guide like this for sales representatives to read.
Then, typically, we follow up either with a conference call or a district sales meeting, at which time the district manager would review the

content of the guide and the direction of the sales message.
The representatives would typically practice that message, and then we have routine follow-up with our district sales managers, when sales representatives are actually making calls on physicians, for them to follow up and observe the sales representatives making calls, at which time they can provide them feedback and how well they deliver the message and how they respond to physicians' concerns.
Q Now, you were asked questions about a reference to, quote, complicated mood disorders. In particular, you were asked about questions on page 3 of the document on the right-hand column under ZYPREXA in Primary Care.
Do you see the reference to complicated mood disorders in that paragraph?
A Which paragraph are we looking at?
Q Under ZYPREXA in Primary Care, you were asked specifically about Zyprexa and complicated mood disorders which is halfway down that paragraph.
A Yes.
Q Is bipolar disorder a complicated mood disorder?
A Again, I'm not a medical expert and I rely on my

006548

SUPERIOR COURT FOR THE
STATE OF ALASKA
THIRD JUDICIAL DISTRICT OF ANCHORAGE

STATE OF ALASKA : Case Number
v. :
ELI LILLY & COMPANY : 3 AN 065630 CIV

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C O N F I D E N T I A L

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September 19, 2007

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Videotape deposition of SIDNEY TAUREL, held in the offices of Ice Miller, One American Square, Indianapolis, Indiana 46282-0200, commencing at 8:34 a.m., on the above date, before Linda L. Golkow, a Federally-Approved Registered Diplomate Reporter and Certified Shorthand Reporter.

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Page 58

(Whereupon, Deposition Exhibit Taurel-2, "Eli Lilly Said to Play Down Risk of Top Pill," (Berenson) New York Times, December 17, 2006 (4 pages), was marked for identification.)

- - -

BY MR. SUGGS:

Q. The headline states, "Eli Lilly Said to Play Down Risk of Top Pill."

The first two paragraphs of this article state, "The drug maker Eli Lilly has engaged in a decade-long effort to play down the health risks of Zyprexa, its best-selling medication for schizophrenia, according to hundreds of internal Lilly documents and e-mail messages among top company managers.

"The documents, given to The Times by a lawyer representing mentally ill patients, show that Lilly executives kept important information from doctors about Zyprexa's links to obesity and its

Page 59

tendency to raise blood sugar - both known risk factors for diabetes."

Do you see that language, sir?

THE WITNESS: I see it, yes.

BY MR. SUGGS:

Q. And did --

I'm assuming that when that article was published, it was probably noticed by the members of the board of directors, correct?

MS. GUSSACK: Objection, no foundation.

BY MR. SUGGS:

Q. You may answer.

A. I believe that they paid attention to it. It was a very important article obviously.

Q. Okay.

Did the board of directors or its public policy and compliance committee investigate those allegations that I just read?

MS. GUSSACK: Objection.

Page 60

THE WITNESS: Could you repeat the question.

MR. SUGGS: Sure. Could you read it back to him.

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(Whereupon, the requested portion of the notes of testimony was read by the court reporter.)

- - -

THE WITNESS: We informed immediately the board of our response to this -- to these allegations. As we informed them, those allegations are based on a select small number of documents and do not reflect the conduct of the company.

BY MR. SUGGS:

Q. That really, I don't think, was responsive to my question.

My question was, did the board of directors or its public policy and compliance committee investigate those allegations?

Page 61

MS. GUSSACK: Objection.

THE WITNESS: No, they did not do an investigation because they trust and they rely on the report that -- and the compliance systems that we have in place and have been following this issue for a long time. And we're satisfied that all of the information that we have had over the years on Zyprexa has been appropriately reflected in our label and shared with doctors.

BY MR. SUGGS:

Q. Did you provide members of the board or its public policy and compliance committee copies of any of the documents that were referenced in this article?

MS. GUSSACK: Objection.

THE WITNESS: This article did not specify specific documents. So, we couldn't share those.

Q. Those 2,000 additional sales reps, part of their function was to promote Zyprexa, correct?
MS. GUSSACK: Objection.
THE WITNESS: Not necessarily. Many of those, I believe, were outside of the United States, and I'm not sure in 2000 -- I know that in 2000, the product was not yet available in every country. So, some of these sales reps would have been promoting Zyprexa, but I don't know how many.
BY MR. SUGGS:
Q. But clearly you invested in the years before 2000 in the marketing capability of Zyprexa, correct?
A. We invested in both our R&D and marketing capabilities in general to handle both existing and products to come. With eight new products especially in some new therapeutic areas for us, it was important for us to increase the

number of sales representatives. For example, in 2000, we launched a product called Xigris. That was in a totally new area for us, so, we needed a completely discrete, separate sales force for that product, which we created in several countries around the world.
Q. If I can direct your attention back to the previous page in the right-hand column, the second paragraph under the heading "Strong product line fuels growth."
In particular, the last three or four lines of that paragraph, it states, "In 2000, our sales of Zyprexa were $2.3 billion, a 25 percent increase. During the fourth quarter, this neuroscience blockbuster surpassed Prozac as our top-selling product." Do you see that language?
A. Uh-huh.
Q. That is an accurate statement, is it not?
A. Yes.

Q. So, at least by -- by the way, this 2000 Annual Report would have actually been issued sometime in 2001, correct?
A. Correct.
Q. So, by 2001, clearly, Zyprexa was your biggest selling product and had sales in excess of $2 billion a year, correct?
MS. GUSSACK: Objection.
THE WITNESS: You said in 2000?
BY MR. SUGGS:
Q. Yes.
A. The answer is no. Prozac was still bigger.
Q. Well, your 2000 -- the report that we just read here said, "In 2000, our sales of Zyprexa were $2.3 billion, a 25 percent increase. During the fourth quarter" --
A. Ah.
Q. -- "this neuroscience blockbuster surpassed Prozac as our

top-selling product."
A. You said during the year 2000. I think for the full year, Prozac was still bigger.
Q. Okay.
From that point forward, was Zyprexa your top-selling product?
MS. GUSSACK: Objection.
THE WITNESS: I don't know the answer to that, but certainly after 2001, as the sales of Prozac came down, it also lost its flagship position in our product portfolio.
BY MR. SUGGS:
Q. Okay.
It's fair to say that by around this time, 2000/2001, Lilly was counting heavily on Zyprexa to help it bridge the gap in the shortfall of corporate revenue that would be created by generic competition for Prozac, correct?
MS. GUSSACK: Objection.

THE WITNESS: Zyprexa was one of the very many action -- drivers of growth that we had and, again, the response to the Prozac patent expiration was -- included both the launch of new products, which we were just starting to put on the market, and development of new indications and line extensions for existing products. We also took under license a couple of products such as Actos and Cialis, which have since then been launched.

BY MR. SUGGS:

Q. But of all those different products that you were talking about, just Zyprexa was the one that was producing the most revenue, correct, of all of them?

MS. GUSSACK: Objection.

THE WITNESS: Several products that I've just quoted were not yet launched, but they

were a very important part of how our investors were looking at Lilly. What's important is not just make up for the revenue of a lost -- of a product which had just lost its patent, it's also to have a very promising pipeline of new compounds to be launched.

BY MR. SUGGS:

Q. Sir, I don't think your answer was responsive to my question. I'm going to ask the court reporter to please read my prior question back.

- - -

(Whereupon, the requested portion of the notes of testimony was read by the court reporter.)

- - -

THE WITNESS: I think I was responsive in that I told you that some of these products were not launched. So, evidently the sales of Zyprexa, even if it had been $1, would have been higher than

the sale of the product which had not been launched.

BY MR. SUGGS:

Q. Well, and of all the products that the company had on the market, in 2001, Zyprexa was bringing in more revenue than anyone else, correct?

MS. GUSSACK: Objection.

THE WITNESS: I think I've answered.

BY MR. SUGGS:

Q. The answer to that is yes, correct?

MS. GUSSACK: Objection.

THE WITNESS: Zyprexa in 2000 was our second product. In 2001, after the patent expiration of Prozac, became the number one product.

BY MR. SUGGS:

Q. Okay.

When did you personally first become aware that hyperglycemia and diabetes were potential safety problems

associated with Zyprexa?

MS. GUSSACK: Objection.

THE WITNESS: I knew from the time we launched Zyprexa that there were incidences of weight gain which are associated with Zyprexa and that adverse events had been observed in some patients taking Zyprexa, adverse events including hyperglycemia and very, very few cases of diabetes. All of these were reflected in our label when we launched the product.

MR. ALLEN: Objection, nonresponsive.

MR. SUGGS: I join in the objection.

BY MR. SUGGS:

Q. Who was it that brought you information about the safety of Zyprexa back at the time it was launched?

MS. GUSSACK: Objection.

THE WITNESS: Before a

product is launched, we have -- even before we submit for registration, we have a review of all of the information on the product.

BY MR. SUGGS:

Q. My question is really more specific than that. I'm asking what individual or individuals did you rely on back in 1996, in that era, to give you information about the safety of Zyprexa?

A. I would rely on the person who had the overall responsibility for Zyprexa. In that time, I believe it was Dr. Tollefson, to give me all of the information regarding Zyprexa on both its efficacy and safety.

Q. For how long did you continue to rely on Dr. Tollefson to provide you that information?

A. For however long he was in the job. I don't remember exactly when he switched to a different job.

MS. GUSSACK: David, I'm

sorry, before we move on, can we take a break now or in a few minutes?

MR. SUGGS: Sure.

MS. GUSSACK: We've been going for about an hour. Is this a good time?

MR. SUGGS: Sure.

THE VIDEOTAPE TECHNICIAN: Off the record at 9:35.

- - -

(Whereupon, a recess was taken from 9:35 a.m. until 9:53 a.m.)

- - -

THE VIDEOTAPE TECHNICIAN: Back on the record. This is the beginning of Videotape Number 2, the deposition of Sidney Taurel. It is 9:53.

BY MR. SUGGS:

Q. Mr. Taurel, when did -- well, strike that.

Did Dr. Tollefson tell you

that in December of 1995, before Zyprexa even went on the market, that an advisory board of outside consultants hired by Lilly had told him and Dr. Beasley that the weight gain associated with the use of Zyprexa might result in increased risks of hyperglycemia and diabetes?

MS. GUSSACK: Objection, no foundation.

BY MR. SUGGS:

Q. Did Dr. Tollefson tell you about that?

A. I do not recall.

Q. Okay.

Were you informed by Dr. Tollefson or anyone else that in the summer of 1995, before Lilly even submitted its NDA to FDA for review, that computer analyses of some of Lilly's clinical trials showed an increased incidence of high blood glucose in Zyprexa users?

MS. GUSSACK: Objection.

BY MR. SUGGS:

Q. Were you informed of that?

A. I was not informed of the specifics of individual trials or data. What I was informed of was the overall clinical safety and efficacy profile of Zyprexa before we submitted, as I mentioned earlier.

Q. Were you informed by Dr. Tollefson or others that beginning in 1998, articles were published in the medical literature by independent researchers noting that patients using Zyprexa were developing hyperglycemia and diabetes?

MS. GUSSACK: Objection.

THE WITNESS: I have been kept informed through regular briefings of new important data as it came out. I do not recall a specific briefing on any specific data by Dr. Tollefson.

BY MR. SUGGS:

Q. If you had been informed that scientific articles were appearing

beginning in 1998 linking Zyprexa with hyperglycemia and diabetes, is that the type of information that you would have passed on to the board of directors or not?

MS. GUSSACK: Objection.

THE WITNESS: I think you're making a hypothetical case here. What I do do and ask is to rely on the internal processes that we have to ensure that we take into account all of the data, the totality of the body of data that we have at any point in time on our products, and reflect those in both our communications with regulatory bodies, including the FDA, and as appropriate, communications to physicians.

BY MR. SUGGS:

Q. Sir, that wasn't the thrust of my question. My question is what information you provided to the board of directors. And my question specifically

was, if it was brought to your attention in December of 1998 that there were published medical articles showing that patients who use Zyprexa were developing hyperglycemia and diabetes, is that type of information something that would have been provided to Lilly's board of directors?

MS. GUSSACK: Objection. Did you say 1978?

MR. SUGGS: I said 1998.

THE WITNESS: We provide to our board of directors conclusions of analyses done on all of our products, not specific one-off pieces of data. I would not even know about them myself.

BY MR. SUGGS:

Q. So, it's your testimony that you would not have been made aware of articles in the medical literature in 1998 indicating that Zyprexa patients were developing hyperglycemia and diabetes?

MS. GUSSACK: Objection, mischaracterizes --

BY MR. SUGGS:

Q. That was not brought to your attention?

MS. GUSSACK: Objection, mischaracterizes the testimony.

BY MR. SUGGS:

Q. You may answer.

A. I got regular briefings on all of the body of evidence that we had and continue to have on our key products, including Zyprexa. I am not in a position in my job to know every article which is being published.

Q. Who was it that gave you regular briefings on Zyprexa back in the late 1990s/2000 time frame?

A. I do not recall the time at which Dr. Breier replaced Dr. Tollefson. So, it was first Dr. Tollefson and then Dr. Breier.

Q. Okay.

Did you continue to rely on

Dr. Breier to keep you regularly informed of Zyprexa, say, up to the present day?

MS. GUSSACK: Objection.

THE WITNESS: Dr. Breier no longer has responsibility for Zyprexa. So, the answer is no.

BY MR. SUGGS:

Q. Okay.

I believe he was head of the Zyprexa product team until sometime in 1994 or late -- strike that. I misspoke.

I believe that Dr. Breier had -- was head of the Zyprexa product team until sometime in late in 2003 and then became the chief medical officer. Is that accurate?

A. That's his current title. I don't recall exactly at what time he took that job.

Q. Okay.

Was he the one who kept you regularly informed of Zyprexa matters until the time he left his position as head of Zyprexa product team and moved

There's no such thing as a special warnings section or special precaution. The regulators know -- have a different nomenclature, but that information was passed on to the FDA.

MR. SUGGS: Move to strike the nonresponsive portion of your answer.

BY MR. SUGGS:

Q. By at least the fall of 1999, Zyprexa was facing attacks by competitors who were asserting that Zyprexa had a higher incidence of hyperglycemia and diabetes than other antipsychotic drugs because Zyprexa caused more weight gain; isn't that correct?

MS. GUSSACK: Objection.

THE WITNESS: I cannot speak specifically to the time frame that you are talking about. It is clear that competitors have talked extensively about what they see as

the risks associated with Zyprexa and sometimes going beyond -- often going beyond what the data shows.

MR. SUGGS: Move to strike the nonresponsive portion.

BY MR. SUGGS:

Q. Were you aware that in 1999 Lilly formed an executive steering committee to deal with olanzapine-associated weight gain and hyperglycemia?

MS. GUSSACK: Objection.

THE WITNESS: Can you repeat the question.

- - -

(Whereupon, the requested portion of the notes of testimony was read by the court reporter.)

- - -

THE WITNESS: I believe that around the time when we heard from the market that there was concern about the issue of weight gain and

potential association with hyperglycemia, we wanted to go to the bottom of that issue and that several people were involved, a cross-functional team was involved in looking at all of the data.

BY MR. SUGGS:

Q. I'm going to hand you what has previously marked as Exhibit 8262. For the record, this is a chain of e-mails. The one I will be asking you questions about is on the bottom of the first page. It's from Alan Breier to more than a dozen people dated November 9, 1999.

A. (Witness reviewing document.)

Q. Have you ever seen this document before, Mr. Taurel?

A. Not at the time, no.

Q. I'm sorry, not at --

A. Not at 1999. I'm not on the list here of recipients.

Q. Have you seen this document

since that time?

MS. GUSSACK: Objection, privileged. Instruction not to answer.

MR. SUGGS: My question is simply whether he's seen the document since 1999.

THE WITNESS: I've seen it in the context of privileged information from my lawyer.

BY MR. SUGGS:

Q. Okay.

The author of the e-mail that I directed your attention to is Mr. Alan Breier. We've talked about him before. At the time, he was head of the Zyprexa product team, correct?

A. Again, I do not recall exactly when the switch was made from Dr. Tollefson to Dr. Breier.

Q. Okay.

I notice that Steven Paul is one of the addressees of the e-mail. He was a senior executive within the company

success depends very much on the reputation that we have, which is based on the application of our policies, the ethics with which we conduct our business and so on.

Q. I couldn't agree with you more, sir.

Dr. Breier goes on in his e-mail to state, "In addition, it could be argued that Eli Lilly, with its strengths in neuroscience, metabolism, endocrinology and diabetology is better positioned than any other institution to elucidate the mechanisms and developed treatments for this side effect." Do you see that language, sir?

A. Yes.

Q. Lilly had been very closely involved, very deeply involved in the manufacture and sale of anti-diabetic drugs for decades at this point, correct?

A. Correct.

Q. Lilly had within its stable of employees a number of physicians and

other scientists who were deeply knowledgeable about diabetes and the risks of that disease, correct?

A. Correct.

Q. Dr. Breier goes on to say, "Thus, we have formed a cross-functional action team to meet these challenges. Success of this effort will contribute to securing the future of olanzapine and the financial health of our company, and likely spur the development of next generation antipsychotic drugs (i.e. olanzapine without the weight gain) and drugs for obesity."

Did I read that correctly?

A. You read that correctly.

Q. You were informed of that cross-functional action team, correct?

MS. GUSSACK: Objection.

THE WITNESS: No. As I mentioned earlier, I was not aware of that specific cross-functional action team. I was aware that we were, in general, investigating

this issue and putting all our resources to make sure we understood it well.

BY MR. SUGGS:

Q. How was it that you were made aware of that activity? Was that again through Dr. Tollefson at the time?

MS. GUSSACK: Objection.

THE WITNESS: Again, I do not remember who was in charge of the product at that time, in other words, when it went from Dr. Tollefson to Dr. Breier, but we could very well have had some review of the product at the policy committee, or I may have been briefed by a person reporting to me on this. But I was aware in general that we are trying to understand, putting to bear our resources in both the diabetology field and the psychiatry field. We wanted to understand and elucidate this issue.

BY MR. SUGGS:

Q. Okay.

I believe you testified previously that you were indeed aware that your competitors were essentially attacking Zyprexa in the marketplace and saying that the weight gain associated with Zyprexa would lead to the development of hyperglycemia and diabetes, correct?

MS. GUSSACK: Objection.

BY MR. SUGGS:

Q. You were aware that your competitors were alleging that, correct?

MS. GUSSACK: Objection.

THE WITNESS: I was aware that our competitors were focusing a lot of their detailing efforts on attacking Zyprexa, and, yes, alleging that the weight gain that we did see and reported was causing potentially both hyperglycemia and diabetes.

BY MR. SUGGS:

previously been marked as Exhibit 9281.
For the record, Exhibit 9281 is a February 6, 2004 e-mail from Alan Breier to US Medical. And in particular, sir, I'm going to direct your attention to the language in Dr. Breier's e-mail under the bolded heading "Principles."
A. (Witness reviewing document.)
Q. Have you seen this document before, sir?
A. I've been shown this document by counsel.
Q. Okay.
Did you receive a copy of it back in 2004?
A. No.
Q. In that section that I pointed your attention to regarding principles, Dr. Breier starts off by saying, "Making medicine for people facing illness is a much different and higher calling than making consumer products for other markets. We do not

sell soap! It therefore requires a different and higher code for conducting our business."
Do you agree with that, sir?
A. Very much so.
Q. Okay.
If you drop your attention down to about the third line from the bottom, Dr. Breier has a sentence which starts off, "we are particularly challenged." Do you see that?
A. Yes.
Q. It says, "We are particularly challenged when it comes to presenting our data in a completely objective, unbiased manner because of our passion for our molecules and the belief that 'spinning' data is sometimes necessary to gain a competitive advantage. If we do not abandon the 'spinning' mentality, we will not restore confidence in our medical research and rebuild the public trust our industry compromised." Do you see that language?

A. I do.
Q. Sir, you don't abandon something that you're not already doing, correct?
MS. GUSSACK: Objection.
THE WITNESS: I'm not Dr. Breier, and therefore, I cannot speak for him and what he meant here. But I do note that he refers in the last part of this sentence to the industry, rebuilding "the public trust our industry has compromised." And I believe that here he's talking to our colleague in medical, bringing her to a higher calling and a higher standard of performance than the industry has the image of having. That's why the principles of medical research were adopted. They are very ethical principles, and they were put in a very strong document.
Secondly, this is why Eli

Lilly was the first company to create the registry of clinical trials and be totally transparent as to the medical research that we do. So, I believe that this is what Dr. Breier has in mind here when he's saying this.
MR. SUGGS: Move to strike as nonresponsive. Would you read back my prior question.
- - -
(Whereupon, the requested portion of the notes of testimony was read by the court reporter.)
- - -
MS. GUSSACK: Objection.
THE WITNESS: I think I've responded that I cannot take a word out of context without trying to understand what Dr. Breier here is saying. So, I've given my answer as to my interpretation --
BY MR. SUGGS:
Q. Do you know that the word --

A. -- of what Dr. Breier is saying.
Q. What does the word "abandon" mean to you, sir?
A. It means to leave behind.
Q. It means to stop doing something that you're already doing, right?
MS. GUSSACK: Objection.
THE WITNESS: Again, in this context, I believe that Dr. Breier is talking about the public trust in the pharmaceutical industry, which is -- which has been damaged over the last decade or so with allegations that the industry is not sufficiently objective in presenting data. And he's calling his colleagues in medical to a higher level of standard that would address that public trust perception.
BY MR. SUGGS:
Q. Dr. Breier, you said the

word "abandon" means to leave behind. What Dr. Breier was talking about leaving behind was spinning of data, correct?
MS. GUSSACK: Objection.
BY MR. SUGGS:
Q. Isn't that the subject of his e-mail there?
A. I think I've given my answer that this needs to be interpreted in the context of this whole message. For example, he's saying that the patient should be the raison d'etre. It should be -- "the patient is our primary customer." What is good for patients is good for business. I think he is here reaffirming very strong principles that would ensure that Eli Lilly is at the forefront of transparency and ethics in our industry and help, therefore, address this public image that the industry is suffering from.
MR. SUGGS: Move to strike as nonresponsive.
BY MR. SUGGS:

Q. What doctor e-mail -- strike that.
What Dr. Breier was talking about in this e-mail was abandoning or leaving behind the spinning of data in order to gain a competitive advantage. Isn't that the subject of his e-mail there?
MS. GUSSACK: Objection.
THE WITNESS: I do not agree. The subject of his e-mail is to talk to all medical colleagues about the principle -- ethical principle of medical research. And part of his message relates to issues of public trust that the industry is suffering from.
BY MR. SUGGS:
Q. Sir, in fact, Eli Lilly itself was regarded by your customers, by payors and doctors who used your product as spinning the data about Zyprexa. Isn't that true, sir?

MS. GUSSACK: Objection.
THE WITNESS: No.
BY MR. SUGGS:
Q. Let me hand you what's been previously marked as Exhibit 3223. For the record, Exhibit 3223 is an e-mail from Jerry Clewell to Virginia Stauffer with copies to a bunch of people, probably, I'm guessing, two dozen people. My first question -- by the way, the e-mail is dated January 14, 2004, and the subject is "Re: Annals of Pharmacotherapy Recent articles of interest 2004."
Sir, do you recognize any of the names of the individuals on that e-mail?
A. (Reviewing document.)
One or two. I do not know who Virginia Stauffer is, and know who Jerry Clewell is, and I don't know most of the people who are cc'd.
Q. Which names do you recognize?
A. There is -- Bruce Kinon is a

approximately five percent in normal volunteers, then it would be false to tell doctors that weight gain with Zyprexa was manageable for most patients; isn't that correct?

MS. GUSSACK: Objection.

THE WITNESS: I do not know the exact message which was given to physicians. This program was helpful. It was something that met a need that they had, because for many patients under Zyprexa, they saw weight gain. So, this was helping them deal with the potential issue. And even if that premise is true, it only helps five percent of the patients, it's very important.

BY MR. SUGGS:

Q. But, sir, your company was telling Doctors that Zyprexa weight gain was manageable for most patients; isn't that correct?

MS. GUSSACK: Objection.

THE WITNESS: I do not know that.

BY MR. SUGGS:

Q. Isn't that exactly what this document says?

MS. GUSSACK: Objection. Do you want him to review the entire document?

BY MR. SUGGS:

Q. No. I want him to look back at the position section that's on Page 2 that we already talked about before where it states "Our Position." "Weight gain can occur with Zyprexa as with other antipsychotics and mood stabilizers. For most patients, this can be managed allowing them to receive the overwhelming benefits Zyprexa offers." That was your position, wasn't it, sir?

A. Well, this is a planning document, as I see the title. What we said to the doctors in visits to them was in accordance with the label. It is -- all the messages to physicians go through

a very involved process of medical, regulatory and legal review. So, there's a distinction between what you see in a planning document and actually what we say to physicians.

Q. Well, sir, we have many other documents that indicate exactly what was told to physicians by sales reps.

MS. GUSSACK: Objection. Is that a question?

BY MR. SUGGS:

Q. Are you familiar with what the sales reps went out and told doctors?

A. No, not in detail.

Q. Are you going to deny that doctors were told that weight gain was manageable for most patients?

MS. GUSSACK: Objection.

THE WITNESS: I have no knowledge of exactly what went on in every detail with doctors. What I do know is that the job of our sales reps is to present

objective clinically meaningful information on both efficacy and side effects of our drugs. And I trust that they have done that with Zyprexa, as with every other drug.

MR. SUGGS: Move to strike the nonresponsive portion of your answer.

BY MR. SUGGS:

Q. Were you informed that in early 2002, Lilly's medical department concluded that the incidence of treatment emergent hyperglycemia was about three-and-a-half times higher in Zyprexa users as compared to placebo?

A. No.

Q. I'm going to hand you what's been previously marked as Plaintiff's Exhibit 990.

For the record, this is a document, the first page of which says, "Attachment E," and above that it says, "Confidential, Do Not Forward - To be

Page 186

give you as unbiased and straightforward view of the science as they possibly can, correct?

MS. GUSSACK: Objection as to form.

THE WITNESS: We consult with these consultants, with these opinion leaders, to get their views on our data, on new products and other things.

BY MR. SUGGS:

Q. And you expect them to give you the best possible expertise they can, correct?

MS. GUSSACK: Objection as to form.

THE WITNESS: Yes, we expect them to use their knowledge and expertise in their advice to us.

BY MR. SUGGS:

Q. And you don't want them to be tailoring their advice to you based on what they may perceive as the company position, correct?

Page 187

MS. GUSSACK: Objection.

BY MR. SUGGS:

Q. You want their bald, unvarnished truthful assessment of the matter, right? That's why you have them, right?

A. Yes.

Q. Okay.

Did anyone inform you, as Dr. Baker notes here, that they, referring to that advisory board, were concerned by your spontaneous adverse event reports and quite impressed by the magnitude of weight gain on olanzapine and implications for glucose? Did anybody ever tell you that back in 2000?

A. No. As I mentioned, I was not aware of a specific meeting, but I'm not surprised that this meeting took place. I think at that time we were doing everything we could to elucidate the issue of whether there was an association of olanzapine with hyperglycemia, and, therefore, it made

Page 188

sense to get the opinion of specialists in diabetes and not just talk to psychiatrists.

MR. SUGGS: I move to strike the nonresponsive portion of your answer.

BY MR. SUGGS:

Q. Directing your attention to a couple of lines down in Dr. Baker's e-mail, he says, "Citing methodological questions, at least the vocal members were not reassured adequately by our analyses, such as the finding that relative risk was not higher than comparative drugs. Disconcertingly, one member compared our approach to Warner-Lambert's reported argument that Rezulin did not cause more hepatic problems than other drugs in its class." Do you see that language, sir?

A. I do.

Q. Rezulin is an anti-diabetic drug, correct?

A. Yes.

Page 189

Q. You were aware that Warner-Lambert was claiming for a while that Rezulin did not cause more liver problems than other drugs in its class, correct?

MS. GUSSACK: Objection.

THE WITNESS: I do not have specific knowledge of that.

BY MR. SUGGS:

Q. Okay.

Were you ever informed by anyone that this outside group of experts "were not reassured adequately by our analyses"?

A. No. What I see in this message and series of messages, in fact, is scientific exchange where you have data and you have various ways to look at the data, you have suggestions to what other information, what other analyses to do, and I believe that informed our actions.

Q. I direct your attention to the next exhibit, which is Exhibit 1453.

Page 202

Q. Were you ever advised of that recommendation of the advisory board?
MS. GUSSACK: Objection.
THE WITNESS: Again, I was not aware there was a meeting of the advisory board and, therefore, I could not be aware of that specific recommendation. But they are referring here to the issue of impaired glucose tolerance, and I believe that we conducted something called clamp studies, don't ask me more details about that because I'm not a physician, but this was geared at understanding whether there was a direct correlation between impaired glucose tolerance and Zyprexa. And those studies were conducted later on and did not show the correlation.
MR. SUGGS: Move to strike as nonresponsive.

Page 203

BY MR. SUGGS:
Q. They were clearly saying, "Don't get too aggressive about denial, blaming it on schizophrenia, or claiming no worse than other agents until we are sure of the facts," correct?
A. That's what it says here.
Q. Now, this meeting occurred in October of 2000 about two months after the Federal Appeals Court had denied your patent in that litigation, correct?
A. Which patent?
Q. The Zyprexa patent.
MR. ALLEN: Prozac.
MS. GUSSACK: Objection.
BY MR. SUGGS:
Q. I'm sorry. I misspoke.
This meeting in October of 2000 occurred several months after the Federal Appeals Court held that the Zy -- pardon me, that the Prozac patent was to expire in 2001, correct?
A. Yes.
Q. Okay.

Page 204

That legal decision had a profound impact on Lilly's financial well-being, didn't it, sir?
MS. GUSSACK: Objection.
THE WITNESS: I think we talked about that earlier. It's a decision for which we had been prepared and which led us to the development of several new products and licensing of others and so on.
BY MR. SUGGS:
Q. Sir, do you recall that the day that that Federal Court ruling was announced publicly that Lilly's stock plunged by almost one-third in a day, wiping out over $36 billion in equity?
A. I sure do. I still have the scar tissue.
Q. I'll bet you do.

MR. SUGGS: I'll show -- have marked as Taurel Exhibit 4 --
MS. GUSSACK: After this

Page 205

exhibit, David, would it be appropriate for a lunch break?
MR. SUGGS: Sure.
- - -
(Whereupon, Deposition Exhibit Taurel-4, Wall Street Journal Online Excerpt (1 page), was marked for identification.)
- - -
BY MR. SUGGS:
Q. I went on Wall Street Journal online and had a chart drawn of Lilly's stock between the dates of August 1, 2000 and August 10, 2000, August 10, 2000 being the date of the outside advisory board meeting that we had referred to in the prior exhibits. And it indicates that there was a quite dramatic drop in the stock price in early August there on the day of the announcement from, it looks like something -- the stock value is something over $105 per share, dropping down to about $75 per share. Is that accurate?

Page 210

very loose term, global management team. To what are you referring?

MR. SUGGS: I'm going to hand you a document. We actually have to put a sticker on this one. This will be Taurel number 5.

- - -

(Whereupon, Deposition Exhibit Taurel-5, Presentation excerpt ZY206198660, was marked for identification.)

- - -

BY MR. SUGGS:

Q. For the record, this is a document produced by Lilly that bears the Bates Number ZY206198660. It's a one-page document. And the first paragraph says, "Chairman Sidney Taurel presented the company's 2002 priorities to the global management team on December 14, stressing their importance as Lilly works to become 'the pharmaceutical growth company of the decade.'" Does that help at all in --

Page 211

A. Yes. This refers to all the people who have the title of manager and above inside the company. And typically once a year I would discuss in a video or even a live conference the company's priorities for next year.

Q. Okay.

And I presume this probably would have been given, your presentation, sometime in December of 2001; is that correct?

MS. GUSSACK: Objection.

THE WITNESS: Yes. This says December 14.

BY MR. SUGGS:

Q. The people who would have heard this presentation would have been dozens or hundreds of people?

MS. GUSSACK: Objection to the form.

BY MR. SUGGS:

Q. How big was the global management, the group that you would have presented this to?

Page 212

A. I believe there are about 5,000 people more or less who are at the management level. Whether all of them listened in to this isn't clear. Typically I make the presentation to a live audience of a few hundred, and then the rest is broadcast in various locations.

Q. Okay.

So, this message -- the message that you delivered there would have been broadly spread throughout the corporation; correct?

A. Yes.

Q. Okay.

According to this document, "Taurel emphasized that to weather Year X," which we've talked about before, "and outgrow its competition, Lilly must," and there's a list of bulleted up items, correct?

A. Yes.

Q. Very first thing is "Maximize sales of Zyprexa" correct?

Page 213

A. Yes. I note that it is a truncated first bullet point.

Q. I would agree. You'd have to ask your lawyer why that was.

A. I am pretty sure that this would have included other products which had been launched since the mid '90s.

Q. Is that speculation on your part?

A. Oh, I'm pretty sure that would be, because this was very much a part of the Year X strategy which I mentioned earlier. We recognize the other bullet points, strengthen our pipeline, maximizing partnering effectiveness if we could license products, and maximize all of our existing products, Zyprexa, Gemzar, Actos, Humalog --

Q. Since --

A. Evista.

Q. Since that section of the document has been redacted by Lilly's counsel, I'll object to any question --

Page 218

Q. Directing your attention to the text in the first page of this exhibit, it says, "Zyprexa was first launched in late 1996. The estimated R&D spend to first launch was $195 million. Since then, Lilly has spent approximately $750 million plus on R&D for Zyprexa's multiple indications.

"On a cumulative IBT basis, Zyprexa will bring in approximately $16.1 billion in IBT through 2004."

Do you see that language?

A. I do see that language, yes.

Q. Is it your understanding that that would be a correct statement?

A. I have no basis to say yes or no.

Q. Okay.

A. I don't know where this document comes from, who wrote it, and one figure which surprises me a lot is the $195 million R&D spend to first launch. Typically, it costs much more than that to bring products to market.

Page 219

Q. If you wanted to find out -- well, strike that.

Who would you regard as the most knowledgeable person in the corporation to find out whether these figures are accurate or not?

MS. GUSSACK: Objection.

BY MR. SUGGS:

Q. Who would you rely on?

A. I would have to work through my line management, the people who report directly to me. In this case, that would be the CFO who, in turn, would look to within his organization, I guess the controller, who would, in turn, look to somebody else until they find someone who is really in charge and working with Zyprexa. I have no idea who that might be.

Q. Continuing on in the text of this document, it goes on to state, "Sales and IBT have greatly exceeded the pre- launch PMC valuations for Psychosis and Schizophrenia combined. Through 2004, Sales and IBT will be approximately $14.3 billion and $9.2 billion, respectively, above the initial PMC valuations." Do you see that language?

Page 220

A. Yes.

Q. Now seeing that phrase "PMC valuations" in that context, does that help you understand what they're referring to there?

A. No.

Q. Very first sentence of the next paragraph starts off by saying, "Zyprexa clearly exceeded all expectations." Do you see that?

A. Yes.

Q. That's a fair statement, is it not?

MS. GUSSACK: Objection.

THE WITNESS: I think the success of Zyprexa, once it was launched and the way it was embraced by physicians, was above our expectations. Indeed, the experience that we heard from

Page 221

patients and physicians alike were that the product really transformed the lives of patients with schizophrenia.

MR. SUGGS: Move to strike the nonresponsive portion.

BY MR. SUGGS:

Q. If I can direct your attention to the following page. It bears the title at the top, "Zyprexa - Revenue and Cost Summary Estimated 1981 through 2002 and Forecasted 2003 through 2004." And the numbers that are expressed there in that chart are in the millions. And do you see that towards the bottom of the chart, the second to last entry there is the total IBT impact?

A. Yes.

Q. Would that be your understanding that the number there states the income before taxes for that particular year?

A. The income before taxes of what?

A. Yes.
Q. Were you informed that that was the instruction that was being given to your sales force?
MS. GUSSACK: Objection. I'm going ask that the witness be allowed to review the document before he answers questions about the document.
MR. SUGGS: I'm only asking about that one piece of language.
MS. GUSSACK: I understand.
BY MR. SUGGS:
Q. Sir, were you informed that the sales force was instructed that diabetes was a highly competitive driven issue and that "Therefore, we will NOT proactively address the diabetes concern, but rather only when it arises from an MD"? Did you or did you not become aware that that instruction was given to your sales force?
MS. GUSSACK: I'm going to object and also ask that the

witness be given an opportunity to review the document.
BY MR. SUGGS:
Q. Can you answer that question, Mr. Taurel?
A. Not without reading the document.
Q. It is your testimony to the jury that you have to read this entire document in order to answer the question that I posed to you? Is that correct?
MS. GUSSACK: Objection. Mr. Suggs, you already made an agreement with the witness that if he simply said that he wanted to review the document before he answered your question, you would give him the opportunity.
MR. SUGGS: I'm going to give him that time. I just want the jury to understand --
MS. GUSSACK: So, he's not going to answer any more questions --

MR. SUGGS: I want the jury to understand that this witness is telling the jury that he has to read this entire document in order to answer that question.
MS. GUSSACK: He's not going to answer any more questions that you pose until he reviews the document pursuant to an agreement that you offered and he accepted.
MR. SUGGS: Fine. Go ahead. Start reading.
MS. GUSSACK: So, your testimony on the issue isn't really relevant.
MR. SUGGS: Start reading. You are wasting time, Counsel.
(Witness reviewing document.)
THE WITNESS: So, what is your question?
BY MR. SUGGS:
Q. My question, sir, was, were you informed that the sales force was

instructed that diabetes was a highly competitive driven issue and, "Therefore, we will NOT proactively address the diabetes concern, but rather only when it arises from an MD"?
A. I was not specifically informed of what is in this document. What I know is the context of how we were discussing with physicians. The context is that there was a lot of noise in the marketplace raised by our competitors alleging that there was a correlation between the use of Zyprexa and diabetes. And our instructions to our sales reps was to put this issue in perspective.
MR. SUGGS: Move to strike as nonresponsive.
BY MR. SUGGS:
Q. Sir, do you recall that the sales force was instructed that "Patients treated with Zyprexa, risperidone, haloperidol, divalproex, and ziprasidone in clinical trials had comparable rates of diabetes and hyperglycemia"?

Page 242

Psychiatric Association, the American Association of Clinical Endocrinologists and the North American Association For the Study of Obesity, correct?
A. Yes. I'm aware of the process they use, which was to bring together experts from those groups, and they spent two days discussing the data on Zyprexa.
Q. In fact --
A. I'm sorry, on antipsychotics.
Q. In fact, employees of Lilly attended and made presentations at that conference; correct?
A. I believe that's correct.
Q. Also, outside consultants to Lilly appeared and presented material to that conference, correct?
A. I don't know.
MS. GUSSACK: Objection and no foundation.
BY MR. SUGGS:
Q. Do you know Dr. John Buse?

Page 243

A. I don't.
Q. Do you know Dr. David Allison?
A. No.
Q. Do you know any of the presenters that are listed on the last page in the left-hand column other than the Lilly employees?
MS. GUSSACK: What page are you on, David?
THE WITNESS: Among the presenters?
BY MR. SUGGS:
Q. Yes.
A. No. I just recognize one name here, and it is Patrizia Cavazzoni, who is a Lilly employee. I don't know if there are other Lilly employees or consultants to Lilly.
Q. Sir, this consensus statement by those medical organizations that we talked about before concluded that "Clozapine and olanzapine are associated with the greatest weight gain

Page 244

and highest occurrence of diabetes and dyslipidemia," correct?
MS. GUSSACK: Objection as to form.
THE WITNESS: Can you point me to the --
BY MR. SUGGS:
Q. Sure. The summary section, sir, on Page 5, right-hand column, the second full paragraph, four lines down. "Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia." Did I read that correctly, sir?
A. Yes.
Q. It goes on to state, "Risperidone and quetiapine appear to have intermediate effects." Did I read that correctly?
A. Yes.
Q. And it goes on to say -- I can never pronounce this correctly -- "Arip --
A. Aripiprozole.

Page 245

Q. Thanks. "Aripiprozole and ziprasidone are associated with little or no significant weight gain, diabetes or dyslipidemia, although they have not been used as extensively as the other agents." Did I read that correctly?
A. That's what's written here, yes.
Q. That was the conclusion of those medical organizations, correct?
A. That was the conclusion of the group of people that they gathered during two days on this issue, yes.
Q. Sir, even after that consensus statement came out, Lilly continued to maintain that the data showed that the rates of diabetes were comparable between the various agents, correct?
MS. GUSSACK: Objection.
THE WITNESS: I would point out that after this article was written, a number of letters to the editor were sent by various

Page 246

physicians and also by the FDA reporting on different conclusions based on either their clinical experience in the case of individual physicians or the weight of all the data that the FDA spent months reviewing, which was much more than -- much more time and analysis than was devoted by this group of people.

MR. SUGGS: Move to strike as nonresponsive. Would you read the question back to him, please.

- - -

(Whereupon, the requested portion of the notes of testimony was read by the court reporter.)

- - -

THE WITNESS: We believe -- we believed that the weight of evidence at that time, as confirmed by the decision of the FDA not to differentiate between products was that at that time

Page 247

based on the information available, there was no strong basis for the conclusion of the so-called consensus group.

MR. SUGGS: Move to strike your answer as nonresponsive.

Could you please listen to the question when I have the court reporter read it back and answer the question I have asked.

- - -

(Whereupon, the requested portion of the notes of testimony was read by the court reporter.)

- - -

MR. SUGGS: The answer is either a yes or a no or a you don't know.

MS. GUSSACK: I believe the witness has answered the question already.

THE WITNESS: Lilly continued to take its guidance from the decision of the FDA.

Page 248

MR. SUGGS: Move to strike as nonresponsive.

Sir, could you please just answer this question directly.

BY MR. SUGGS:

Q. Did Lilly continue to maintain that there were comparable rates of diabetes between the various antipsychotics even after the consensus development statement came out? It's a yes, no or you don't know. Which is it?

MS. GUSSACK: Objection, asked and answered. You may answer.

THE WITNESS: I would say again that we are bound in our activities to take our guidance from the FDA. The FDA had access not only to all the data that we have access to, but also the data that was supplied by other manufacturers of antipsychotics, and also the data that they get from spontaneous reporting of

Page 249

events in the marketplace. We believe that this was the broadest database possible to reach conclusions, and, therefore, we relied on that conclusion and not on the conclusion that the group of people who worked for two days on this issue arrived at.

BY MR. SUGGS:

Q. Sir, you still have not answered my question.

MR. ALLEN: Objection, nonresponsive.

THE WITNESS: We have taken our guidance from the FDA.

BY MR. SUGGS:

Q. Sir, I'm asking about the statements that Lilly has continued to make. I'm not asking where it came from or anything else. I'm just asking, isn't it true that even after the consensus statement came out with those conclusions that we stated before, Lilly has consistently maintained that the rates of

diabetes among the various antipsychotic agents are comparable? It's either a yes or a no. You've explained all the background behind your answer before, but you haven't answered the question directly yet.

A. Okay.

Q. Did you or did you not continue to make those statements?

MS. GUSSACK: Objection, asked and answered.

THE WITNESS: I don't know for sure, but whatever we did was, I'm sure, informed by the best science available.

BY MR. SUGGS:

Q. So, your answer is you don't know?

A. Correct.

Q. Okay.

Did anyone inform you that taking the position that there was no differential risk of diabetes among the atypicals in spite of the differences in

weight gain was making the company look foolish?

MS. GUSSACK: Objection, no foundation.

THE WITNESS: Can you repeat that question.

MR. SUGGS: Sure. Could you read it back.

- - -

(Whereupon, the requested portion of the notes of testimony was read by the court reporter.)

- - -

MS. GUSSACK: Objection as to form.

BY MR. SUGGS:

Q. Either someone advised you of that or did not.

A. I object to the premise that we were looking foolish when we were following the FDA class label.

MR. SUGGS: Move to strike as nonresponsive.

BY MR. SUGGS:

Q. Sir, I'm going to hand you what's been previously marked as Exhibit 3192, which, for the record, is an e-mail from Vicki Poole Hoffmann to Thomas Hardy, Sara Kollack, copies to Michael Baker and Michael Overdorf. I believe you previously testified that you know Dr. Baker.

A. Correct.

Q. Do you know any of the other individuals?

A. Michael Overdorf.

Q. Who is Michael Overdorf?

A. Right now I think he's somewhere in the UK. He's an employee of the company in the marketing area.

Q. I'll note for the record that this e-mail is dated March 10, 2004, and I would direct your attention to the second paragraph that starts off "I think," and in particular, the language at the beginning which states, "I think we should delete most of the third paragraph and all of the fourth as they

are defensive and attempt to show that there is no differential risk of" diabetes mellitus or "DM among atypicals in spite of the differences in weight gain. Our advisors have told us that this position is making us look foolish." Do you see that language, sir?

A. I do.

Q. It's your testimony that no one ever told you that Lilly's advisors told the company that that position was making Lilly look foolish?

MS. GUSSACK: Objection.

THE WITNESS: That's what this said in this e-mail. I have no basis to assess that this is what our advisors, indeed, told us, and no one has told me that specifically.

BY MR. SUGGS:

Q. I'm going to hand you another Wall Street Journal chart. I went on the Internet apparently on September 14 and had the Wall Street

Journal stock charting program draw a chart of Lilly's stock performance as compared to the Dow Jones Industrial five years back from November -- or September 14. So, it would have been from September 2002 through September of 2007, and we'll mark this as Exhibit 7.

- - -

(Whereupon, Deposition Exhibit Taurel-7, Wall Street Journal On-line excerpt (1 page), was marked for identification.)

- - -

BY MR. SUGGS:

Q. Would you agree with me, sir, that this chart indicates that starting around a couple of months into 2004, the Dow Jones Industrial Average continued on an upward slope, and that at that point there is the beginning of a fairly wide divergence between the Dow Jones Average and the Lilly stock value?

A. Yes.

Q. Okay.

The timing of that happens to be around the same time that Lilly made its label change in -- well, strike that.

Were you informed that the "Dear Doctor" letter of the Zyprexa label change went out in March of 2004?

A. The label change of what -- I'm sorry.

Q. There was a "Dear Doctor" letter regarding the Zyprexa label change which included warning language regarding hyperglycemia that went out in March of 2004. Were you aware of that, sir?

MS. GUSSACK: Objection as to form.

THE WITNESS: I do not recall. I know that there was a change in September '03, I believe. Early '04 I recall CVAE "Dear Doctor" letter and changing the label.

BY MR. SUGGS:

Q. Did no one inform you that

Lilly did not send out a "Dear Doctor" letter warning -- or advising physicians of the change in the warning regarding hyperglycemia until March of 2004?

MS. GUSSACK: Objection.

THE WITNESS: I do not recall that.

BY MR. SUGGS:

Q. This divergence here would have also been a couple of months or so after the publication of the consensus statement; is that correct?

A. Well, what I know, and it is not in this chart, is that the whole pharmaceutical industry stock prices have been affected negatively by a variety of factors. We track how our stock price behaves in relation to the rest of the industry. And the percentage of the total market capitalization of the industry that we represent today is very similar to what it was in 2004/2003/2001. So, this is a -- you would see the same curve for the average of the

pharmaceutical industry. There are many factors which affect this performance.

Q. You would agree that the change in the performance or the divergence did occur within months after the consensus statement was published and also at around the same time that the March 2004 "Dear Doctor" letter went out, correct?

MS. GUSSACK: Objection as to lack of foundation and as to form.

THE WITNESS: This chart doesn't tell me exactly when. When was the consensus statement again?

BY MR. SUGGS:

Q. Consensus statement was published in February of 2004 in Diabetes Care.

A. Well, this chart is not very clear, but it looks like it is more towards the middle of 2004 and more in 2005 that the stock price of Lilly

Page 258

declined. So, it does not -- the answer to your question is, therefore, no.
Q. Okay.
I want to switch gears for a while to talk about what Lilly was warning foreign doctors about as compared to what was it was telling US doctors about. Would it be fair to say that the U.S. market for Zyprexa was the most profitable market as compared to the rest of the world?
A. The U.S. market is the largest market for pharmaceutical products, that's correct, yes.
Q. Prior to 2003, there was no mention in the U.S. label in the Warnings section regarding hyperglycemia or diabetes, correct?
A. I believe that's correct. Those observations that we had in our clinical trials were elsewhere in the label.
Q. And you do recall that there was mention of hyperglycemia and diabetes

Page 259

in the European label before that time, correct?
MS. GUSSACK: Objection.
THE WITNESS: I don't believe that's correct.
BY MR. SUGGS:
Q. Do you recall that in April of 2002, the Japanese regulatory authority required Lilly to issue a warning about diabetes occurring with Zyprexa?
MS. GUSSACK: Objection as to form.
THE WITNESS: I believe that the Japanese authorities mandated a black box warning or their version thereof mentioning instances of ketoacidosis. This is data that we shared with the FDA and the regulatory authorities in Europe and elsewhere. And they concluded that since the few cases on which this black box warning was based were compounded by other

Page 260

factors, there was no reason to change the label outside of Japan.
MR. SUGGS: Move to strike the nonresponsive portion.
BY MR. SUGGS:
Q. Sir, I'm going to hand you what has been previously marked as Exhibit 320, which I will represent to you is a translation of the Japanese "Dear Doctor" letter. I believe the translation or the document was certainly produced to us by Lilly. Have you seen this document before?
A. No. But I'm aware of the change in label which occurred in '02 in Japan.
Q. According to this document, which is dated April of 2002, there were three major elements to the warning over in Japan, correct?
A. Say that again. I'm sorry.
Q. According to this document and the numbered items in the box that you see there, there were three major

Page 261

elements to the warning in Japan, correct?
A. Yes.
Q. The first was: "Do not administer to patients with diabetes... and those who have a history of diabetes..." correct?
A. Yes.
Q. The second part was "During administration of this product" -- I'm just reading what's written here -- "observe sufficiently with such as measurement of blood glucose." Correct?
A. Right.
Q. Was it your understanding that patients were supposed to have their blood glucose measured while they were on Zyprexa, at least the ones over in Japan?
MS. GUSSACK: Objection.
THE WITNESS: It is not clear from what this translation says.
BY MR. SUGGS:
Q. Okay.

Page 266

understanding of what was being referred to there?
MS. GUSSACK: Objection as to form.
THE WITNESS: I believe I would not have had any reaction until I read the whole preread, which I'm trying to do now.
(Witness reviewing document.)
THE WITNESS: Now I understand the context.
BY MR. SUGGS:
Q. When you got this preread stating "A side effect that is associated with Zyprexa is weight gain and the sequelae of weight gain," what did you understand those sequelae to be?
A. My understanding of what Dr. Breier was trying to convey in this document is all of the information that is available regarding metabolic effects of antipsychotics and Zyprexa in particular. We are very keen on

Page 267

understanding and elucidating that issue, and his report here is a comprehensive review of everything that was known by at least Eli Lilly on this.
Q. Sir, my question still stands, and I don't think you've answered it. You agree with me that sequelae is an aftereffect or secondary result. This refers to the sequelae of weight gain. My question to you is, what was your understanding of what those sequelae of weight gain were?
A. Again, we -- I think we're trying to understand the overall metabolic impact, if any, of Zyprexa.
Q. Sir, I'm not asking you for the process.
MS. GUSSACK: Excuse me, Mr. Suggs. Can you finish your answer, please.
THE WITNESS: I think the rest of the document elucidates what Dr. Breier means by sequelae. He's talking about whether there

Page 268

is any correlation with weight gain, with diabetes, with diabetic ketoacidosis, and discusses all of the data that is there. And then he has a number of action steps to elucidate it further and to share all of that information with the general public.
BY MR. SUGGS:
Q. Diabetes was clearly a sequelae of weight gain, correct?
MS. GUSSACK: Objection as to form.
THE WITNESS: No, no. I wouldn't say that. Because that would imply that everybody who gains weight will become diabetic.
BY MR. SUGGS:
Q. He doesn't imply that at all.
A. Sequelae?
Q. Saying that diabetes is a sequelae of weight gain is not saying that everybody who is overweight is going

Page 269

to get diabetes?
MS. GUSSACK: Objection. Is there a question?
BY MR. SUGGS:
Q. Sir, what was your understanding when you saw the phrase there "sequelae of weight gain"? What did that mean to you?
A. It didn't mean anything until I read the rest of the document.
Q. Let's talk about the rest of the document.
A. Okay.
Q. Under the weight gain section, it states, "Five atypical antipsychotic agents are associated with more weight gain than most traditional neuroleptic agents in the following order," "Clozaril greater than Zyprexa, greater than Seroquel, greater than Risperdal," correct?
A. Yes.
Q. As we saw in one of the first documents we looked at in your

Page 290

product within the label, and point out how to specifically address concerns about hyperglycemia and the potential use of the product in patients with diabetes." Do you see that language, sir?

A. Yes.

Q. Were you aware of that?

A. Not specifically.

Q. If I could direct your attention to the very last page. Four lines up from the bottom of the last paragraph there's a sentence that starts off "There appears." Do you see that?

A. I'm sorry, the last paragraph or --

Q. Well, the second to last paragraph, the big one there.

A. Starting with "There is a need"?

Q. Starting with "There appears." Are you on the last page?

A. I'm sorry. Yes.

Q. Okay.

Page 291

Do you see where I'm referring to, "There appears"?

A. Yes.

Q. Dr. Breier and Mr. VanDenBergh state, "There appears to be a decrease of hyperglycemic AEs since the label changes." Were you aware of that, sir?

A. No.

Q. He goes on to state, "Again, we will make every effort through promotional efforts and physician-to-physician and medical communications to ensure that we promote the use of the drug within the label, which would by design dramatically reduce the number of events." Do you see that language, sir?

A. Yes.

Q. Did Dr. Breier or Mr. VanDenBergh or Mr. Mayr or Dr. Lechleiter ever inform you of the conclusion of Dr. Breier, that if they promoted the use of the drug within the label in Japan with

Page 292

the language that was in the label there, that that would by design dramatically reduce the number of adverse events?

A. No. This is the first time I see this document, so I would need to really understand the whole context of what Mr. VanDenBergh and Dr. Breier are saying. But, again, as I mentioned earlier, what I do know is that the acceptance of the product in Japan after a period of negative impact started to improve significantly.

MR. SUGGS: Move to strike as nonresponsive.

BY MR. SUGGS:

Q. It's your testimony that you were not made aware that Dr. Breier had concluded that if the product was promoted in Japan in accordance with the label there, that that would by design dramatically reduce the number of adverse events, correct?

MS. GUSSACK: Objection as to form.

Page 293

THE WITNESS: The --

BY MR. SUGGS:

Q. I think you were starting to answer, that is correct?

A. That is correct. Yes. It's not -- I do not get involved in individual trip reports or individual country and product-specific marketing programs.

Q. Did anyone in Lilly ever recommend that the label in the United States be changed to reflect the same type of warnings that were being given in Japan in 2002?

MS. GUSSACK: Objection as to form and vagueness.

THE WITNESS: I know that we shared the data that had caused the change in the label in Japan. We shared the data with both the FDA and regulatory authorities in Europe. Our conclusion, as well as theirs, was that the few cases on which this decision was made

Page 294

were mostly confounded. I think eight or nine cases, if I'm not mistaken, had a number of factors which could explain the adverse events.

MR. SUGGS: Move to strike as nonresponsive.

BY MR. SUGGS:

Q. Sir, my question is whether any individual within Lilly ever recommended or suggested to the corporation that Lilly change the label in the United States to reflect the warnings that were present on the Japanese label after April of 2002?

MS. GUSSACK: Objection as to form.

BY MR. SUGGS:

Q. It's a simple yes or no or you don't know?

A. I do not know. I would doubt it very much, given the fact that as a company, and in agreement with regulatory authorities outside of Japan,

Page 295

it was pretty clear that this data was not conclusive and did not justify a change in label.

MR. SUGGS: Move to strike the nonresponsive portion.

BY MR. SUGGS:

Q. Sir, do you recall that in March of 2007, the FDA informed the company that it was concerned about the adequacy of the Zyprexa label?

A. I'm aware we received a letter -- an approvable letter for Symbyax from the FDA which had some comments about their concerns on the label.

MR. SUGGS: I'm going to hand you what we'll mark as Taurel Exhibit 9.

- - -

(Whereupon, Deposition Exhibit Taurel-9, Letter 3-28-07 (35 pages), was marked for identification.)

- - -

Page 296

MS. GUSSACK: While you're doing that, Mr. Suggs, I'm going to ask you to allow -- to take these questions slowly so that we can make sure that we are observing the agreement that we have established.

MR. SUGGS: Sure.

MS. GUSSACK: I'm sorry, exhibit number --

MR. SUGGS: 9 --

BY MR. SUGGS:

Q. -- which I'll describe for the record as a letter from FDA to Eli Lilly with attachments. It has several, what appear to be fax imprint dates at the top of the pages, the earliest of which is March 28, 2007. It also bears the date of March 28, 2007 with a stamp for G. Brophy. I don't see any other dates on here. I'll also represent this document does not have a Lilly Bates Number on it.

MR. SUGGS: I believe, Nina,

Page 297

this is a copy that you produced to Judge Weinstein in the MDL, and this is a copy of that.

MS. GUSSACK: Thank you.

BY MR. SUGGS:

Q. Mr. Taurel, is this letter that I've handed you as Exhibit 9 the letter that you were referring to?

A. Yes, approvable letter for Symbyax.

Q. It refers to -- by the way, is Mr. Brophy, is he in the regulatory affairs of Eli Lilly?

A. Yes, Dr. Brophy, yes.

Q. This refers to a supplemental new drug application regarding a drug product called Symbyax, correct?

A. Yes.

Q. Symbyax is a combination of both olanzapine and fluoxetine, correct?

A. Correct.

Q. Olanzapine is the generic name for Zyprexa, and fluoxetine is the

Page 306

A. I do.
Q. So there again, with respect to those people who had borderline to high levels at the outset, their rate or incidence of going above 200 milligrams per deciliter was, again, about ten times higher than those folks who were exposed to placebo, correct?
MS. GUSSACK: Objection as to form.
THE WITNESS: I note the next sentence says, "This latter finding was based on a small number of patients in the OFC program, and for this reason, we would like to see such data for the entire olanzapine program."
So, my understanding is that --
BY MR. SUGGS:
Q. Sir, you need to answer the question first.
MS. GUSSACK: Could you finish your statement first.
THE WITNESS: Could you

Page 307

repeat --
MS. GUSSACK: I'm sorry. Could you finish your statement?
THE WITNESS: And my understanding is that we have engaged since that time with the FDA on addressing some of the suggestions and concerns that they have expressed in this letter.
BY MR. SUGGS:
Q. Mr. Taurel, I need to have you answer the question. And my question is that this letter indicates that there is data showing that people who were exposed to combination drug who had borderline to high levels of blood sugar at the outset of treatment had an incidence of -- 46 percent of those folks went on to have blood levels above 200 as compared to only 5 percent of the placebo-treated patients, correct?
A. That's what this says, yes.
Q. And 46 percent is about ten times higher than 5 percent, correct?

Page 308

MS. GUSSACK: Objection.
THE WITNESS: No. It's incorrect. It is about 9.2 percent times --
BY MR. SUGGS:
Q. That's fine. It is over 9 times higher, correct?
A. Yes. But as the next sentence indicates, this finding is based on a very small number of patients. So, the FDA is telling us this is not significant; however, there's here potentially a signal that we want to investigate.
Q. These studies that had been done, do you know when they were done, what year?
A. No, I don't.
Q. Do you know who was responsible within the corporation for conducting those studies?
MS. GUSSACK: Objection as to form and vagueness. Which study?

Page 309

BY MR. SUGGS:
Q. The studies from which this data comes.
A. This data seems to come from the OFC submission, and the OFC or Symbyax submission would have been put together by the Symbyax team. I don't know exactly who are the people on that team.
Q. The FDA goes on to note: "We were troubled that this important finding was not included in your proposed label." Do you see that language?
A. Yes.
Q. When Mr. Paul or Dr. Paul informed the policy committee of this letter, did he also tell the policy committee that the FDA was troubled that this important finding was not included in your proposed label?
A. As I told you, I do not recall exactly how I came to know about this or I do not recall exactly the words that Dr. Paul used. My understanding is

Page 310

that following this letter, we had communications with the FDA. In fact, they were suggesting I think in the letter that we should discuss with them how to address their concerns, which we did immediately, and we put a very strong team of people and the resources necessary to address those issues.

MR. SUGGS: Move to strike the answer as nonresponsive.

BY MR. SUGGS:

Q. Directing your attention to -- well, do you see towards the bottom of the page there's a heading entitled "Post Marketing Commitments"?

A. Yes.

Q. In the paragraph just above that, it states, "Our overall goal is to improve labeling with regard to these findings so that clinicians will be better informed on what the risks are for their patients. They cannot make reasonable treatment decisions until they have such information. We do not feel

Page 311

that current labeling for either Symbyax or Zyprexa provides sufficient information on these risks, and we fully intend to insure that these labels are enhanced with the best available information to characterize these risks." Do you see that language, sir?

A. Yes.

Q. Did Dr. Paul inform the members of the policy committee of that language at that meeting that you would have had shortly after this letter was received by the company?

A. I will repeat that I do not recall the exact words used by Dr. Paul, but that I know that following the receipt of this letter, we immediately put a team of people together to engage the FDA in responding to their concerns and doing the analysis that they wanted us to do and which we wanted to do.

MR. SUGGS: Move to strike as nonresponsive.

BY MR. SUGGS:

Page 312

Q. Sir, to this day, Lilly has not warned physicians in the Zyprexa labeling of the findings that were noted there in the second paragraph of FDA's letter, correct?

MS. GUSSACK: Objection, and I'm going to ask Mr. Taurel not to answer that question. And consistent with the agreement between counsel, there have been ongoing discussions with FDA that Mr. Taurel is not going to speak to those communications or --

MR. SUGGS: I'm not talking about discussions. My question is --

MS. GUSSACK: -- actions as a result beyond the ex-approvable letter.

BY MR. SUGGS:

Q. I'm not asking for any communications.

Sir, as we sit here today on September 19, 2007, the Zyprexa label

Page 313

does not reflect the data that is in the second paragraph of the FDA's letter indicating a ten-fold increased incidence of hyperglycemia in people exposed to that combination drug, correct?

MS. GUSSACK: Objection both as to form and to foundation. If you are asking the specific question, Dave, because I want to make sure that we're being faithful to the agreement -- if you're asking the question does the label that's in existence today include this data, that's a question that he can answer.

MR. SUGGS: That's exactly what my question was.

THE WITNESS: Can you ask the question again.

MS. GUSSACK: If he knows.

BY MR. SUGGS:

Q. As we sit here today on September 19, the Zyprexa label does not warn physicians of the data that's

it's on the board, sir? I'm going to help you out. We're going to go straight to it. We're going to go to indications.
A. All right.
Q. Indications are schizophrenia, bipolar mania, right?
A. Right. I don't remember exactly when the bipolar mania --
Q. I understand. This isn't a test. If you need me to help you, I'll help you. Okay?
MS. GUSSACK: Oh my God, an objection must lie there.
BY MR. ALLEN:
Q. I'll help you. All right.
So, when you, when Zyprexa lost its patent protection -- excuse me.
When Prozac lost its patent protection, you were telling the shareholders Zyprexa exemplifies our growth opportunities and Zyprexa was indicated for two things, schizophrenia and bipolar mania, correct?
A. Correct.

Q. As a matter of fact, in that same letter, you said, "In 2000, our sales of Zyprexa were $2.3 billion, a 25 percent increase. During the fourth quarter, this neuroscience blockbuster surpassed Prozac as our top-selling product." Right?
A. Right.
Q. And then not to beat a dead horse, I hope, you skip over here to Page 9 of that annual report. It has a little heading. I don't have a color copy. It says, "So, what now," and it says, "Our newer products will stand as our front line against inevitable generic competition for Prozac. Introduced throughout the last half of the 1990s, they'll be the key" -- don't you use the word "the key," sir? That's your word, right?
A. Yes.
Q. "They'll be the key to our ability to produce earnings growth during that time and resume our strong

performance thereafter." Did I read that correctly?
A. Yes, sir.
Q. Okay.
So, the front line against the generic competition for Prozac are the products that were introduced during the last half of the '90s, and that would include, and the first one listed in the annual report is Zyprexa, correct?
A. Correct.
Q. By the way, I saw there, you've led an interesting life. You were born in Morocco; is that right?
A. Yes.
Q. Spanish citizen?
A. Yes.
Q. I think you've gone to school in France, and your family is from Spain, and you've practiced and done your career all over the world, isn't that right?
A. I've lived in several countries, yes.

Q. I was born and raised in Galveston Texas, and I spent my entire life in about a 300 mile square area. Okay? So, I'm going to try to use some of the words, just common sense words and see if I understand what you're writing here in this report. Okay? Do you understand me?
What you're saying here is that the key to protecting our earnings is to get growth in our products that we developed in the last half of the '90s, right?
A. No --
MS. GUSSACK: Objection as to form.
THE WITNESS: That's not the word I used. You said "protect" our earnings, and I'm saying "produce earnings growth."
BY MR. ALLEN:
Q. That's even better. You did better than I did. You were going to produce earnings growth from these

Page 334

products that you developed in the '90s?
A. Following a decline which we had in 2002 due to the Prozac patent expiration.
Q. Well, in fact, you don't list the drugs in any type of alphabetical order, you introduce -- the first drug you talk about is Zyprexa, right? Is that correct?
A. Yes.
Q. Down here you said, "Introduced as a therapy for schizophrenia in 1996, Zyprexa was approved in the U.S. last year for additional indications of acute mania associated with bipolar disorder and the maintenance of treatment response in schizophrenia." Did I read that correctly?
A. You did.
Q. So, what you're saying is what we just discussed, the two indications, and the only two FDA-approved indications for Zyprexa at

Page 335

the time Prozac went off patent were schizophrenia and bipolar mania, right?
MS. GUSSACK: Objection to the form.
THE WITNESS: Schizophrenia had actually two different indications. It was first schizophrenia short term therapy and then the maintenance of treatment response in schizophrenia.
BY MR. ALLEN:
Q. Right. Two disease states. Two diagnoses, schizophrenia and bipolar mania, right?
MS. GUSSACK: Objection as to form.
THE WITNESS: Again, yes.
BY MR. ALLEN:
Q. Thank you, sir.
It says, "We're exploring broader uses for Zyprexa in schizophrenia and other key segments of the antipsychotic market, including bipolar

Page 336

depression and the psychotic or behavioral disturbances that accompany dementia." Did I read that right?
A. You did.
Q. Now, I know it's clear as a bell and you know you can tell me right now, Zyprexa has never been approved for the treatment of dementia either in the past or as we sit here today, has it?
A. No. But at the time I was writing this, we were doing clinical trials, and we had already, I believe, one first clinical trial which was positive. And, therefore, we're pursuing the clinical development of Zyprexa in various new indications, and I believe that we did get approval for other indications which are referred to here.
MR. ALLEN: I need to object as nonresponsive.
BY MR. ALLEN:
Q. I wasn't quibbling with you. Maybe you misunderstood my question. I only asked about dementia, and I just

Page 337

want you and I to agree that Zyprexa has never been approved for dementia, correct?
A. That is correct.
Q. That's all I was asking. That's all I was asking.
A. All I was saying is that at that time, we were doing the clinical trials to get to the FDA, if those were positive, to get an approval for the treatment of dementia.
Q. Right.
A. And the nature of pharmaceutical R&D is that some hypotheses are sometimes confirmed, and others are not.
Q. Yes, sir. You and I are agreeing on that.
A. Good.
Q. Sometimes things work out, and sometimes things don't work out, right, sir?
A. It is the nature of pharmaceutical R&D, yes.

Page 350

A. No.
Q. Has Zyprexa ever been approved for attention deficit disorder or hyperactivity disorder?
A. No.
Q. Has Zyprexa ever been approved for the management of social phobias?
A. No, there's no indication.
Q. Sir?
A. There's not an indication.
Q. If there's no indication approved by the FDA, a drug company can't promote the drug for that, right?
A. Right.
Q. Thank you. That's all I need to know.
Has Zyprexa ever been approved for sleep or sleep disorders, for the treatment of sleep, insomnia, sleep or sleep disorders?
A. Not for a specific treatment of sleep disorders, but a bipolar patient may have sleep disorders, may have a

Page 351

problem with sleeping, and, therefore, this is one of the symptoms that you would find in the approved indication. And the same about -- I'm not a psychiatrist, but I believe the same applies to many of the symptoms that you just talked about.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. You made a very good point, Mr. Taurel, and I had it in my notes. Just so it's real clear, you are not a doctor?
A. That's right.
Q. You have no medical training?
A. No, I don't.
Q. You are not a scientist. I think in one of your answers to Mr. Suggs earlier today, you made a particular point and said to him, and I'm paraphrasing, you'd have to talk to the science end, not the business end.

Page 352

A. Right. I have a general understanding of the areas of medicine where our products are used because I have been in this business for 36 years.
Q. Yes, sir. I got a general understanding as a lawyer, but it wouldn't qualify me to be a doctor now, would it?
A. No. I don't claim to be qualified to be a doctor.
Q. Right. That's why I'm trying to get to just so you and I are communicating. You're not a doctor, are you?
A. No.
Q. You can't make diagnoses, can you?
A. No.
Q. You can't treat people, can you?
A. No.
Q. You wouldn't claim to be an expert in science or technology, would you?

Page 353

A. No.
Q. In fact, you described yourself on the record to Mr. Suggs as you're on the business end of the company, right?
A. Well, I run the whole company.
Q. Yes, sir, you're the big shot, right?
MS. GUSSACK: Objection as to form.
THE WITNESS: That's not what I'm saying. What I'm saying is I have responsibility to supervise all the functions of the company, including the R&D function.
BY MR. ALLEN:
Q. Right.
Now, back to what my question was. Zyprexa was not indicated --
Have you ever heard of Ambien? Have you ever heard of the drug

Page 354

Ambien?
A. Yes.
Q. And Lunesta, I've seen advertisements on TV. You've seen those advertisements, haven't you?
A. Yes.
Q. Those are called direct-to-consumer advertisements, right?
A. Right.
Q. Which you're only allowed to do in the United States and New Zealand, correct?
MS. GUSSACK: Objection to the form.
BY MR. ALLEN:
Q. I think that's right.
A. I think so, maybe some other countries like Singapore.
Q. United States, New Zealand and Singapore can get direct-to-consumer.
Anyhow, you know there are specific drugs that treat sleep and are approved by the FDA for that, Lunesta, Ambien? You're familiar with that?

Page 355

A. Yes.
Q. My point to you is Zyprexa was not approved for sleep, right?
A. There's a difference. I believe these products are approved for insomnia, seen as a disease. Sleep disturbance as part of a symptom of bipolar mania, for example, is a different matter.
Q. Yes, sir. I'm not quibbling. I just asked you a direct question.
Has Zyprexa been approved by the FDA for sleep disturbances or sleep disorders or insomnia?
MS. GUSSACK: Objection to the form.
BY MR. ALLEN:
Q. Yes or no?
A. It has not been approved for insomnia. It has not approved -- it has been approved for schizophrenia and bipolar mania.
Q. Which are two diagnoses, are

Page 356

they not?
A. They are.
Q. Right. Those are diagnoses that, in fact, are defined, I believe, in a book called a DSM. Are you familiar with that?
A. Not specifically.
Q. That's because you're not a doctor, right?
MS. GUSSACK: Objection as to form.
BY MR. ALLEN:
Q. Right? Are you familiar with the DSM-III or DSM-IV manuals?
A. I thought this was a scale, not a book, but I may be wrong.
Q. You are wrong. That's okay. That's because you're not a doctor. So, you're not familiar with the DSM-III or DSM-IV, right?
MS. GUSSACK: Objection as to form.
BY MR. ALLEN:
Q. Right?

Page 357

A. I'm generally familiar that these are scales that are being used to measure symptoms of psychiatric diseases.
Q. DSM-III and DSM-IV?
A. Yes.
Q. Okay.
Now, let me ask just some general questions. By the way, has Zyprexa ever been approved for complex mood disorder?
A. Zyprexa has been approved for schizophrenia and bipolar mania. Those are complex or psychiatric indications, and they do involve mood disorders, disturbance of the mood.
Q. But you have to have --
The diagnosis has to be made by the doctor, schizophrenia or bipolar mania, right?
MS. GUSSACK: Objection as to form.
THE WITNESS: For what?
BY MR. ALLEN:
Q. I don't know. I'd rather

that's what I said.
Q. I'm not -- I'm just putting this into context, simple questions and simple answers.
MS. GUSSACK: Objection.
THE WITNESS: Yes. But you are putting all the emphasis on only Zyprexa. And as I told you several times, we had five new products that we had launched over the previous five years which were growing the company, and we were working on another eight products that were going to be launched. All of that was part of our answer to the so-called Year X challenge.
MR. ALLEN: I need to object to that as nonresponsive to any pending question, and there's a time that you can give those answers and then I can cross-examine you, but I've only got limited time.
BY MR. ALLEN:

Q. All right. Now, I take it then in October of 2000, when it said "Zyprexa PCP launch meeting," you were aware Zyprexa was being launched to the primary care physicians in October of 2000?
A. Yes.
Q. And this was part of the Zyprexa growth strategy, was it not?
A. Yes.
Q. Just for the record, there was no change in the indications for Zyprexa between August of 2000 and October of 2000, was there?
A. I believe this decision followed the approval of the drug for bipolar mania, which took place earlier. And the decision to go into the primary care market was made, in fact, prior to August, prior to the decision that you mentioned of Prozac. It has nothing to do with it. It was following the earlier approval of the product for the indication of bipolar mania.

MR. ALLEN: I need to object to that as nonresponsive.
BY MR. ALLEN:
Q. My only question was, there had been no change in the indications of Zyprexa between August of 2000 and October of 2000; is that correct? Still indicated for the same thing, schizophrenia and bipolar mania, right?
A. That is correct. The only decision --
Q. Thank you --
A. Excuse me. The decision for us to go into the primary care physician is not a decision that can be implemented in two or three months. We need to hire the sales reps, and it takes time. Therefore, it was not driven by anything happening between August to October, but, rather, by the approval earlier, I think in March or so, of the bipolar mania indication.
Q. Sir, I haven't even made any implication one way or the other. You

are answering something and giving a speech about a question I didn't ask.
MS. GUSSACK: Objection.
BY MR. ALLEN:
Q. With all due respect, I think you're being overly defensive, but let's just move on.
A. In my view, you were making an implication.
MS. GUSSACK: Objection. Given the limited amount of time, Mr. Allen, if we could minimize the commentary and focus on the questions.
MR. ALLEN: I would agree. That's what I'm trying to do, is minimize the commentary and focus on the question.
MS. GUSSACK: I was referring to your commentary. Let's not be confused. What's your question?
MR. ALLEN: I'm focusing on his.

Page 390

Q. Well, I think he was hired by y'all to do this, but it doesn't matter, this is y'all's tape you gave the sales reps. We'll quibble about that later.

"Our intent is to spark a memory or two, and strengthen your selling efforts." Now, is that generally what you want to do when you're training sales reps, is to spark their memories about your meetings on what they were trained so it will help them sell the product?

MS. GUSSACK: Objection to the form.

BY MR. ALLEN:

Q. Is that what you were trying to do for sales reps?

A. We bring sales reps to meetings of that type to inform and educate them about everything that we know about a product, about how to communicate with physicians about that product.

Page 391

Q. So, you're training, and you did better than I did, to educate them, to train them and to tell them how to communicate with physicians, right?

MS. GUSSACK: Objection, mischaracterizes his testimony.

BY MR. ALLEN:

Q. Right?

A. We tell them everything that we know about the product and information on the label and so on so that they can appropriately communicate with physicians.

Q. Okay. Why don't we go back to Page 4, and let's see what Dr. Breier said at this meeting.

THE VIDEOTAPE TECHNICIAN: Excuse me. We have two minutes left.

MR. ALLEN: Why don't we change tapes.

THE VIDEOTAPE TECHNICIAN: End of Tape 5 to the deposition. We are off the record at 4:28.

Page 392

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(Whereupon, a recess was taken from 4:28 p.m. until 5:35 p.m.)

- - -

THE VIDEOTAPE TECHNICIAN: We're back on the record. It is 4:35. This is the beginning of tape 6 of the deposition of Sidney Taurel.

BY MR. ALLEN:

Q. Mr. Taurel, we're back on the record, and we're going over this -- Mr. Taurel, we're back on the record, and we're going to go over this audio transcript of what the Zyprexa product team leader said at the primary care launch in Orlando to the sales reps. Dr. Breier, you personally know Dr. Breier, do you not?

A. I do.

Q. As the medical director of the entire company now, how often do you interact with Dr. Breier?

Page 393

A. Oh, I see him every three months when we have the meetings of the senior management council, and beyond that, periodically. I don't know how many times.

Q. I'm just assuming that he could not have been promoted to the medical director of the entire company unless you approved it. Did you have to approve that promotion?

MS. GUSSACK: Objection as to form.

THE WITNESS: I do approve promotions to vice president level.

BY MR. ALLEN:

Q. He's on the vice president level?

A. Yes.

Q. So, when he is promoted to his current position from his position when he was product team leader for Zyprexa, you had to approve that promotion?

Page 394

A. That's correct.
Q. Let's see what he said to the sales reps back in Orlando in the fall of 2000. Now, putting this in context again, Mr. Taurel, this was when Zyprexa was representing one of your growth opportunities, right, for your business, correct?
A. Zyprexa was and is an important product for the company.
Q. Well, but, we saw --
You specifically said in the 2000 annual report Zyprexa represented a growth opportunity for your company?
A. That's correct.
Q. Now, we're not going to read everything he says. Let's go down here where he says to the sales reps "Now, why don't we go on and talk about some specifics around Zyprexa, and sort of what the future looks like. And I said that Zyprexa is a very, very special molecule.
"Let's go to the first one:

Page 395

growing sales in the elderly. How many people, in their own lives and their own families, have been touched by Alzheimer's disease. Parents, grandparents, uncles, aunts, best friends. Yeah, so have I. Is there a more tragic illness? That illness takes what we all consider to be human and begins to erode that, month after month after month in a very progressive way. And the need for better treatment in Alzheimer's and other elderly conditions is so paramount and so key, and what you're going to see, and you'll see it with your own eyes, is that Zyprexa is an optimally suited molecule for this disorder."
Did I read that correctly?
A. That's what's written here.
Q. Was Zyprexa approved for the treatment of the elderly and Alzheimer's in October of 2000 when Dr. Breier was telling the sales reps this?
A. I do not believe that Dr.

Page 396

Breier is saying it was approved, neither is he telling them to talk about this indication. He was talking about planning for the development of that indication through clinical trials.
Q. Well, no. He told the sales reps, you'll see it with your own eyes. Were the sales reps involved in the clinical trials?
A. No. But he -- he's referring to the fact that doctors on their own are using antipsychotics in psychosis and dementia. There's nothing which is indicated for that disease. And those are very difficult patients, and so doctors are using products off label in that indication.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. Now, Dr. Breier is talking to the sales reps and he says, "Zyprexa is an optimally suited molecule." When something is optimally suited, that means

Page 397

it's the very best, doesn't it, optimal, the very best?
MS. GUSSACK: Objection as to form.
THE WITNESS: I believe taken in context, which is a large sales meeting where Dr. Breier is conveying his enthusiasm for the product that he's responsible for, he's talking about the characteristics of the molecule which might make it a good agent for Alzheimer's. And indeed we were at that point doing clinical trials to find out whether the characteristic that he's referring to and ideally suited and optimally suited were going to be indeed proven in clinical trials.
BY MR. ALLEN:
Q. Well, does he say anything about it's going to be proven in clinical trials, or is he talking directly to the sales representatives at the time of the

the rest as well.
Q. Well, we don't have time. We'll just get back to the -- you want to see evidence of whether what the sales reps were being told about the elderly. I think that's what you asked for.
Do you remember a person called Martha? Do you remember a person called Martha, sir? Do you know who that is?
A. No.
Q. Do you know that patient profiles were used by your sales teams to promote Zyprexa?
A. Not at the time.
Q. Have you learned that since then?
A. Yes.
Q. When did you learn that patient profiles were used to promote Zyprexa?
MS. GUSSACK: Objection, privileged.
BY MR. ALLEN:

Q. Let me ask it again. Did you learn it --
Did you learn that patient profiles were used to promote Zyprexa by the sales force in September of 2007? Is that when you learned it?
A. Yes.
MS. GUSSACK: Objection. I instruct the witness not to answer because it implicates confidential attorney-client communications.
BY MR. ALLEN:
Q. When he learned it, the month is --
Sir, did you know -- let me ask this.
Did you know --
Prior to September of 2007, did you know that Eli Lilly used patient profiles to promote Zyprexa?
MS. GUSSACK: If that doesn't call for privileged communications with counsel, you may answer.

MR. ALLEN: Did he know?
BY MR. ALLEN:
Q. Did you know prior to September of 2007 that Eli Lilly used patient profiles to promote Zyprexa?
MS. GUSSACK: I'm instructing the witness not to answer to the extent that it involves any client --
MR. ALLEN: Communications.
MS. GUSSACK: -- client communications, correct.
MR. ALLEN: I'm not asking.
BY MR. ALLEN:
Q. I'm asking your knowledge.
Let me rephrase the question. I'm taking the deposition on September 19, 2007. As of August 31st, 2007, did you know that Eli Lilly used patient profiles to promote Zyprexa as of August 31st?
MS. GUSSACK: As a general matter? Perhaps that would help clarify.

BY MR. ALLEN:
Q. As a general matter.
A. We describe patients with a description of their symptoms, and so it is a normal practice to describe patients and how they present to physicians for Zyprexa and for any of our other products.
MR. ALLEN: That didn't answer my question in any regard, so I object to it as nonresponsive. But I'm going to move on.
BY MR. ALLEN:
Q. The evidence will show that a patient profile y'all used to promote Zyprexa was Martha. Now, here's what Mr. Bandick said. "What's the first thing you notice about Martha? She's old. That does two things. First, it reinforces Zyprexa as a nursing home drug. Our mission is to build" --
A. I'm sorry. Where are you?
Q. Page 13, the bottom. Right

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: MDL-1596

ZYPREXA PRODUCTS

LIABILITY LITIGATION

THIS DOCUMENT RELATES TO:

ALL CASES

C O N F I D E N T I A L

- - -

November 6, 2006

- - -

Videotape deposition of

GARY TOLLEFSON, M.D.

- - -

GOLKOW LITIGATION TECHNOLOGIES
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EXHIBIT H
Page 1 of 17

.05, then it's regarded generally and generally accepted by people in the field that that is statistically significant, correct?

A. Correct.

Q. And in this instance, the P value is less than .05; it was .03, correct?

A. True. But I think as you know with your background of statistics, this has not been subject to multiple comparisons. These are -- I mean you're showing me 12 pages of P values here, and I don't know if the appropriate corrections were done or not. But I concur that it says less than .031 for this particular analysis.

MR. SUGGS: Move to strike the nonresponsive portion of your answer.

(Whereupon, Deposition Exhibit(s) 1604, previously marked, was presented to the witness.)

MR. SUGGS: I'd like to show you another similar exhibit which

has been previously marked Plaintiff's Exhibit 1604.

MR. LEHNER: We've been going about almost an hour, 25. Are you going to spend a long time on this one?

MR. SUGGS: It shouldn't take too long. Why don't we finish this one and then we'll take a break.

THE VIDEOGRAPHER: Five minutes left on the tape.

MR. LEHNER: Five minutes left on the tape.

MR. SUGGS: Pardon me?

MR. ALLEN: You've got five minutes left on the tape.

MR. SUGGS: We'll get done then.

QUESTIONS BY MR. SUGGS:

Q. Exhibit 1604 is dated July 5, 1995, and purports to be a computer printout of Abnormal Lab Values For HGAJ All Phases. Do you recognize this document, sir?

A. It looks familiar for the

formatting, yes.

Q. And does it appear to be, in fact, as I said, a printout of Abnormal Lab Values for the HGAJ Study All Phases?

A. Yes. It looks to be one HGAJ which was one of the studies in the new drug application.

Q. Okay. In fact, HGAJ, as you said before, was the largest study, correct?

A. Slightly over half the patients, yes.

Q. Okay. If I could direct your attention to Page 2, towards the bottom of the page, there is a table on that page that shows what the low limits and high limits are of the various tests that are being done, correct?

A. Correct.

Q. Okay. And at the very bottom, or not the very bottom, but second to last is a listing for nonfasting glucose, correct?

A. Yes.

Q. And it shows in the

international system the low limits and high limits, correct?

A. Correct.

Q. The low limit being 2.4975 millimoles per liter and the high limit being 13.875 millimoles per liter, correct?

A. Yes.

Q. And that can be translated to -- well, that's the system, convention that used over in Europe, correct?

A. I believe it's used internationally but, yes, it's used in Europe.

Q. Okay. But here in the United States people tend to use another measuring system of blood glucose that is advocated by the American Diabetic Association, correct?

A. Right.

Q. And to convert the international system to the ADA system you multiply by 18, correct?

A. I don't have the algorithim so I can't answer that.

Q. If I represent that to you

Page 86

would you have any dispute with that?
A. Just that I don't know.
Q. Okay. Would you agree with me, sir, that if you take the upper limit as shown here of 13.875 millimoles per liter that translates to 247 in the ADA system?
MR. LEHNER: Object to the form.
A. Yes.
Q. Pardon?
A. Yes, I would agree.
Q. Okay. If I could direct your attention, sir -- by the way, when it says that this is referring to all phases, what would that mean?
A. That would be both the blinded phase and then any open label extension that might have been available for humanitarian purposes to allow responders with schizophrenia to continue on treatment.
Q. Okay. So this would be a -- it would be fair to say that the data in this document includes more data and a greater pooling of data and information than what we

Page 87

saw in the exhibit just before this, Exhibit 1605; is that correct?
A. Yeah, probably had significantly more exposures for the olanzapine assignments.
Q. Okay. If I could direct your attention to Page 5. And again, they're numbered in the bottom right-hand corner as you hold it up in portrait?
A. Um-hum.
Q. There is at the top of that page the Data for Glucose Nonfasting; is that correct?
A. Correct.
Q. And it shows that in the Haldol group there were only two folks who had high glucose. And in the olanzapine group there were 27 who had high glucose, correct?
A. Yeah, these are unadjusted numbers.
Q. Okay. And there is no P value that's shown here on this computer printout; is that correct?

Page 88

A. Correct.
Q. However, I'm sure, sir, that you're familiar enough with statistics that you can just eyeball those numbers and see that even taking into account the smaller size of the Haldol group that that kind of difference between two out of 628 versus 27 out of 1536, that that would indeed be statistically significant; isn't that correct, sir?
A. I wouldn't make that assumption. That's why we, actually, run the statistics. I think that I would suspect here that the olanzapine patients had many more treatment days than their haloperidol counterparts. And you'd have to factor in how many days on drug were they versus their counterparts to get a relative risk. And I think that has to be considered as part of the equation.
Q. Sir, if you had seen this computer printout showing that discrepant difference between the Haldol users and the olanzapine users, would you have instructed

Page 89

someone to do a test of statistical significance?
A. I would be interested in the statistical significance. I would also be interested in this in the context of the overall experience across other studies to see if it was representative or, perhaps, not representative of what was seen elsewhere.
Q. Sir, am I correct that --
MR. SUGGS: How much more time do I have left?
THE VIDEOGRAPHER: About a minute.
MR. SUGGS: Let me ask one quick question and then we'll take a break.
QUESTIONS BY MR. SUGGS:
Q. Sir, am I correct that at no time that you were involved with Zyprexa did the company ever warn physicians of the incidence of high glucose in Zyprexa users as compared to Haldol users?
MR. LEHNER: Object to the form.

letter, sir?
A. Yes, I do.
Q. If I could direct your attention to the first page. In the first paragraph, the letter states, "This concerns a number of labeling" -- well, let me back up for a second. If the date of this is November 14, 1996, that would have been just weeks after Zyprexa was launched here in the United States; isn't that correct?
A. I believe so.
Q. Okay. Directing your attention to the first paragraph, the letter states, "This concerns a number of labeling pieces for Zyprexa identified as a multi-page detail aid, OL0026, stack grams identified as OL0077, and OL7708, a letter to the California Department of Health Sciences, assumed to be an example of similar letters to other states with an attached background, and a John Q Public letter, all submitted as required with the form FDA 2253 and also found during normal surveillance activities. This also concerns other

promotional activities such as an interactive telephone conference held on or about October 2, 1996. The Division of Drug Marketing, Advertising, and Communications, DDMAC, considers these promotional labeling pieces and promotional activities to be false and misleading and in violation of the Federal Food, Drug, and Cosmetic Act." Do you see that language, sir?
A. I do.
Q. And did Mr. Perry advise you that the FDA had written to him in early November stating that the promotional labeling pieces and promotional activities relating to Zyprexa were false and misleading?
MR. LEHNER: Object to the form.
A. To my recall, Mr. Perry had mentioned to me the specific comment that was made by DDMAC on Page 4 regarding an interactive teleconference I had with stock analysts on October 2nd, 1996. I don't recall mentioning the other pieces since that

would be probably a U.S. affiliate-related activity.
Q. Okay. Directing your attention to the following paragraph on Page 1, the first part of it states, "The promotional campaign, including the above identified labeling pieces and others submitted with the form 2253 is lacking an appropriate balance, thereby creating a misleading message about Zyprexa. The promotional materials emphasize efficacy data but do not provide sufficient balance relating to adverse events and cautionary information." Do you see that language?
A. I do.
Q. And were you advised of that by Mr. Perry?
A. I don't recall that. Again, it would not have been my area of responsibility. So it would not have been necessarily expected that he would have said that to me.
Q. Okay. When the FDA said that the promotional materials emphasize efficacy

data, that refers to data tending to show that the drug is effective in treating the medical condition it's to be used for, correct?
A. In this case treating the condition we call schizophrenia.
Q. Okay. And when they said that the materials, while emphasizing efficacy data, do not provide, quote, "sufficient balance relating to adverse events and cautionary information," that's referring to potentially bad experiences with the drug, correct?
MR. LEHNER: Object to the form.
A. Not necessarily bad. I think it is what it is. That is, it would be, when you evaluate the drug, you look at the risk and the benefit. Risks could be, I guess, equated to potential side effects. I'm not sure I'd use the term "bad", though.
Q. Well, is an adverse event good or bad?
MR. LEHNER: Object to the

form.
A. I think, again, you're taking it out of context. Any time any clinician would answer that question, they would say it is a risk/benefit equation.
So you're asking me if somebody has a profound response with their schizophrenia and is no longer institutionalized and is reintegrated into the community and relating to their family and loved ones again and, oh, by the way they had a headache, I'd put that into perspective.
Q. Sir, my question is, is an adverse event good or bad?
MR. LEHNER: Asked and answered.
A. I would repeat the same.
Q. Sir, you mention a risk/benefit equation. It is true, is it not, that every physician before they prescribe a drug needs to do a calculus in their head where they analyze that, okay, if I give the patient this drug, there's a potential benefit

that may result and there's also a potential risk. And the doctor needs to take into account both the positive benefit and the negative potentially bad risk, correct?
A. Correct.
Q. And what the FDA was saying here was that the promotional materials that Lilly was distributing with respect to Zyprexa emphasized the benefits and were minimizing the risks, correct?
MR. LEHNER: Object to form. That's not what the letter says. The letter talks about specific promotional activities.
MR. SUGGS: Counsel, don't be coaching the witness. Say objection.
MR. LEHNER: Then don't mischaracterize the document.
MR. SUGGS: Counsel, Counsel. Do we need to pull out CMO No. 15?
MR. LEHNER: No, but you need to be very careful.

MR. SUGGS: Then you need to say objection to form.
MR. LEHNER: Which I have done, but I'm not going to let you mischaracterize the document.
MR. SUGGS: Counsel.
Q. Do you recall the question, sir?
MR. LEHNER: Do you understand my objection?
MR. SUGGS: I understand the objection, and I also understand you're in violation of CMO15, and henceforth, I would appreciate it if you'd just say objection to form, rather than trying to coach the witness.
MR. LEHNER: I'm not going to let you mischaracterize the document.
MR. SUGGS: Do you recall the question? I'm sure you don't at this point.
THE WITNESS: I'm sorry, I

did lose it.
MR. SUGGS: Let me restate. Okay. That's what colloquy does. That's why people do it.
THE WITNESS: That's right.
MR. SUGGS: I agree with you.
QUESTIONS BY MR. SUGGS:
Q. A physician needs to consider both the benefits and the risks of a drug before he makes the decision as to whether or not he's going to use it in his patient, correct?
A. Correct.
Q. And here in this letter to the FDA, the FDA was saying the promotional materials emphasize efficacy data but do not provide sufficient balance relating to adverse events and cautionary information, correct?
MR. LEHNER: Object to the form.
A. That is what the sentence says.
Q. And when someone does a

Page 126

world's No. 1 neuroscience pharmaceutical in history," correct?
A. Yes.
Q. Was that a strategic intent that had been developed by you or was it the consensus that that should be the strategic intent?
A. That was the strategic intent of the Marketing group.
Q. When you say "the Marketing group" what do you mean?
A. Within the Zyprexa team, I think we discussed earlier that one of the functions that resided within the overall cross-functional product team was a global marketing or commercialization group. This was one of their intents.
Q. And was it part of the purpose of this meeting to, for higher management to approve such intents?
A. The intent of the strategic plan was to, ultimately, approve a research budget that would enable the team to conduct clinical studies to further inform clinicians

Page 127

about the use of Zyprexa in different indications. And so the hope was to expand the budget such that more work could be done to do a broader number of studies that would lead to, if the studies were successful and did -- addressed unmet medical needs, in turn, commercial success. And if that could be the best performing neuroscience product in history, that would be great. It's something we go to work for and would be nice to achieve.
Q. Is the strategic intent something that's stated there, that "Zyprexa would be the No. 1 neuroscience pharmaceutical in history", is that something the top level of the corporation had come down and said, "This is what you will accomplish," or was this more along the lines of the people who were working on the Zyprexa product, the Zyprexa Product Team going to management and saying, "This is what we -- this is our intent. It's our intent that Zyprexa will be the world's No. 1 neuroscience pharmaceutical in history"?

Page 128

MR. LEHNER: Object to the form.
Q. You see what -- I'm trying to draw a distinction.
A. I do. No, it was a bottom-up initiative. And No. 1 is certainly not to the exclusion or not inclusive of economics. When it says, "the world's No. 1 neuroscience pharmaceutical" it means in delivering benefit to patients.
Q. Well, when it's to be the world's No. 1 neuroscience pharmaceutical, did you mean in both number of prescriptions or dollar sales?
A. The intent --
Q. Or -- both?
A. Well, the intent was in delivering value to patients, that would be the most valuable and improving clinical conditions.
Q. Well, you did also make projections about sales, did you not, in this document?
A. It's quite possible. I'd

Page 129

have to look but --
Q. Let me direct your attention to Page 39, for example.
A. With clinical success often goes the commercial success, so, yeah, that would be part of the standard strategic document.
Q. Well, if this document was prepared in -- by the way, on Page 39 the title of the page is "Zyprexa Sales Long Range Forecast Annual Sales," correct?
A. Correct.
Q. Okay. And it shows that back in 1997, which is at the bottom left part of this graph.
A. Um-hum.
Q. Your sales were what? On the order of about $500 million at that point in time?
A. It appears at the beginning of that year.
Q. Okay. And what you projected out to 2004 was that the sales would go from 500 million to about 3.5 billion, with a B,

Page 142

Q. And did you have any discussion with the people who were advocating marketing to PCPs regarding those challenges?

MR. LEHNER: Objection to the form.

A. I didn't have any discussions. I mean, the page you've given me here suggests that there are a small subgroup of individuals referred to as top deciles, PCPs, who currently were writing a large number of these prescriptions and they would appear to be the target that they're talking about.

Q. As the Group Product President in the 2000 time period, did you have responsibilities for marketing?

A. I had responsibilities indicated earlier for a global marketing strategy. How that was implemented or if it was implemented or if it was altered in some way was at the geographic head's responsibility.

What we did is we provided

Page 143

what we thought was a global marketing template to be used, particularly by the affiliates that were smaller and didn't have a large marketing organization of their own. If larger affiliates chose to use it, it was at their discretion. Some of them did. Some of them chose to, you know, use their own local expertise to modify or adjust that strategy.

Q. Was Michael Bandick one of the marketing people under your direction?

A. No. He was in the U.S. affiliate to the best of my knowledge.

Q. Who were the marketing people under your direction?

A. Mr. James Lancaster was the Global Marketing Executive Director and I think reporting to him was a director named Robert Schmidt, and I'm not sure who was further down the line.

Q. Okay. Did you have any dealings with Jack Jordan?

A. I would see Jack on occasion. He represented the U.S. affiliate

Page 144

organization as a brand manager. Would see him on occasion in meetings, but not necessarily any kind of regular or recurring basis.

Q. Okay.

Sir, do you recall that by at least late 1999, Lilly recognized that olanzapine-associated weight gain and hyperglycemia were a major threat to the long-term success of Zyprexa?

A. I would say that I was aware that there was a perception by -- being spun by a lot of our competitors in the absence of an efficacy story that was concerning to people at Lilly.

(Whereupon, Deposition Exhibit(s) 8262, previously marked, was presented to the witness.)

MR. SUGGS: Let me show you what has been previously marked as Plaintiff's Exhibit 8262.

For the record, this is an e-mail chain. The very top one on

Page 145

the first page is dated November 10, 1999, from Charles Beasley to Norma Kim Ascroft and Anna Thornton with a copy to John Krueger but there are preceding e-mails in time.

QUESTIONS BY MR. SUGGS:

Q. And do you recognize this e-mail, sir?

A. Take a moment to look at it.

Q. Sure.

A. I do recognize it.

Q. I'm sorry, you said you do?

A. I do.

Q. Okay. And how is it -- when is the last time you saw this document?

A. I probably -- I recall seeing this during discussions with counsel that we talked about earlier. And then, of course, when it originally came out, I was one of the recipients of part of this string that, from Dr. Breier on November 9, 1999, has me as a recipient.

Q. Okay. You're referring to the e-mail that begins at the bottom of

Page 150

the record.
QUESTIONS BY MR. SUGGS:
Q. Dr. Breier went on to say, "In addition, it could be argued that Eli Lilly, with its strengths in neuroscience, metabolism, endocrinology, and diabetology, is better positioned than any other institution to elucidate the mechanisms and develop treatments for this side effect." Did I read that correctly?
A. Yes.
Q. And that's referring to the fact that Eli Lilly had a long history of involvement with diabetes drugs, correct?
A. That is correct.
Q. Okay. And the side effect that's being referred to there is the drug-associated weight gain and possible hyperglycemia; is that correct?
A. I read this to mean that the side effect was the weight gain.
Q. Okay. Well, he also --
A. I'm saying you could interpret it, I suppose, either way. I read

Page 151

it to mean he says singular side effect, I assume that to be the weight gain. Then he refers to a second side effect, possible hyperglycemia.
Q. Okay. Diabetologists are -- deal with the treatment of diabetes, correct?
A. That's correct.
Q. And he does list Lilly as having expertise -- strength, rather, in diabetology, correct?
A. That's correct.
Q. And, in fact, Lilly had been a marketer of diabetic drugs for decades at that point, correct?
A. It was one of the leading companies in providing insulin and related products for people suffering from diabetes, you are correct.
Q. Okay. And Dr. Breier goes on to say, "Thus, we have formed a cross-functional action team to meet these challenges. Success of this effort will contribute to securing the future of olanzapine and the financial health of our

Page 152

company and likely spur the development of next generation antipsychotic drugs, i.e., olanzapine without the weight gain and drugs for obesity." Did I read that correctly?
A. Yes.
Q. Now, when you say that "we have formed a cross-functional team" was that something that was initiated by Dr. Breier or did you have involvement in that as well?
A. I don't think I can take specific claim to it. I assume he means by "we" the corporate sense of we, the company.
Q. Do you recall where the impetus from that came from?
A. I remember there were a variety of discussions wanting to address the issue with the most rigorous science we could. And I could certainly, you know, it was my background and I would advocate that we include the best people that we had in the company from the relevant functions so that we could, in fact, rigorously look at the science and determine what we knew at that point.

Page 153

Also, what else we needed to know, what kind of future studies needed to be conducted to further, as he indicates here, elucidate a possible mechanism of action for the weight gain.
Q. Okay. In the following paragraph, in about the -- he refers to a meeting that's going to be occurring on November 23, 1999. Do you see that?
A. I do.
Q. And then he says, "The purpose of this meeting is for the executive steering committee comprised of Alan Breier, Jose Caro, Richard Demarchi, Chris Fibeger, Steve Paul, Greg Probst and Gary Tollefson to review the ongoing work and provide guidance for the scope and direction for future activities." Did I read that correctly?
A. Yes.
Q. We previously discussed Alan Breier, but I don't believe we've discussed any of the other folks. Who is Jose Caro and who did he report to?
A. He reported to Dr. Watanabe

and he was and is a recognized expert in obesity and metabolism.
Q. And was he part of the Neuroscience Group or was he on the diabetes side of the company?
A. He was on the metabolism side of the company.
Q. And then who is Richard DiMarchi?
A. Richard DiMarchi was a coworker with Dr. Caro. He was also in the metabolic arena and was, I believe, a vice president on the research side.
Q. When you said that Dr. Caro was on the metabolism side of the company, what did you mean by that?
A. That was one of the therapeutic areas the company had and he was a leader, international leader in endocrinology and metabolism. It's my understanding his background was in endocrinology.
Q. And what products did that metabolism side of the company deal with?

A. His particular area of interest is investigating weight loss agents, obesity therapeutics, not surprisingly because of its being a metabolic disorder. Diabetes, osteoporosis, a variety of other kinds of metabolic conditions also were resident under that particular therapeutic area.
Q. And who is Chris Fibiger?
A. He was the head of Preclinical Neuroscience and is somebody well-established in having researched dopamine and dopamine-related mechanisms of both psychosis and antipsychotic drugs.
Q. And who is Steve Paul?
A. Steve Paul became the successor to Dr. Watanabe as head of Lilly Research Laboratories. At that time he was in charge of all of the preclinical science going on at Eli Lilly regardless of therapeutic area. He was overseeing all of the areas. So, for example, Dr. Fibiger, Dr. DiMarchi, Dr. Caro reported to Dr. Paul.
Q. And what was your reporting

relationship, if any, with Dr. Paul, or were you parallel?
MR. LEHNER: At this time?
MR. SUGGS: At this time.
A. I did not have reporting relationship to him.
Q. Okay. And who is Greg Probst?
A. He was the head of Lilly's Toxicology Group.
Q. And who did he report to?
A. I believe, to Dr. Paul as well.
Q. Amongst the people that were listed there, Breier, Caro, DiMarchi, Fibiger, Paul, Probst, and yourself, who was the most senior in the corporation?
A. Probably Dr. Paul, most people would say. I would say that I was in a similar rating but probably would be No. 2.
Q. Okay. And was Dr. Paul the chairman of that steering committee?
A. I do not recall if there was

a chairperson, per se. I think Alan was the host. I don't know that there was a chair.
Q. Okay. If there was disagreement amongst that executive steering committee, who would have had the power to make an ultimate decision?
MR. LEHNER: Object to the form.
A. Well, I think this is an advisory committee. And Lilly's culture is to try to strive for consensus. So the group would have tried to work out any differences and if those differences, if there were any, which there weren't, but if there were differences that couldn't have been worked out, it typically would default to, in this case given these individuals, probably Dr. Watanabe for LRL and Dr. Lechleiter for product groups to make a decision.
Q. Okay. And how long did this executive steering committee -- let me back up a second.
How long did this cross-functional action team remain in

that something must have gone goofy there because it should, in the first instance, state greater than or equal to, and the second time it occurs it should state less than or equal to.

A. Okay.

Q. So the sentence would state, "Random glucose greater than or equal to 160 milligrams per deciliter in patients with baseline random glucose less than or equal to 140 milligrams per deciliter has been occasionally seen in clinical trials." And is that your understanding of what was proposed?

A. I don't recall a specific proposal. It seems consistent with the fact that the trials didn't exclude diabetics, so it's certainly conceivable.

Q. Okay. When you said that there was some concern expressed about the analysis, who was it that had done the analysis?

A. I don't know if it was Doctor -- I assumed it was Dr. Kwong and

someone, perhaps colleagues within his area of pharmacovigilance, his particular unit, but I don't know, specifically, who conducted it.

Q. I'll represent to you that we had some testimony just on Friday, this is Monday, by Dr. Sharp that that analysis was conducted by Dr. Beasley. Does that square with your recollection?

A. Well, Dr. Beasley's not a trained biostatistician, so it would surprise me if he conducted the statistics.

Q. Okay. Do you know what -- how long Lilly had had the data which was analyzed?

MR. LEHNER: Object to the form.

A. Yeah. The data is iterative where the database is constantly being updated as new patients and new studies complete. So there isn't a formal stop/start, there's an ongoing process. So if you were to look year-on-year, the database would continue to grow year-on-year as more

clinical trial patient data went into the database. So it's more of a continuous phenomenon.

Q. Okay. In the middle of the page there's a little box that says "how has this proposal arisen?" And the text in that box states, "Recent review of random glucose levels of patients in olanzapine clinical trials revealed that the incidence of treatment-emergent hyperglycemia in olanzapine group, 3.6 percent, was higher than that in the placebo group, 1.05 percent. For common events, incidences from clinical trials provide more meaningful information." Did I read that correctly?

A. Yes.

Q. And if you do the math, that would indicate that the -- by the way, treatment-emergent hyperglycemia refers to hyperglycemia occurring after someone has been exposed to the treatment of Zyprexa, correct?

A. I think in this case they're referring to clinical trials. So it would

have been after the point of randomization and during the conduct of the trial there was an associated event.

Q. Okay. And the event being hyperglycemia, correct?

A. In this particular case, yes.

Q. Okay. And if you do the math and the comparison between the olanzapine group and the placebo group, we see that the incidence of treatment-emergent hyperglycemia is about three and-a-half times higher in the olanzapine group than in the placebo group, correct?

A. That's what the raw numbers look like.

Q. Okay. And given the problem that you were dealing with in the marketplace at that point in time, where competitors were saying that Zyprexa had a hyperglycemia problem, if you told doctors that the incidence of treatment-emergent hyperglycemia was three and-a-half times higher in the Zyprexa group than in the placebo group, that would have presented real problems to you,

Page 206

wouldn't it?
MR. LEHNER: Objection to the form.
A. Not necessarily. I think it depends on the context of it. But it was inconsistent with earlier data we talked about where there was no difference seen between olanzapine and placebo. Thus it was something that caught one's attention and it did beg a question of why does it appear to be inconsistent with everything from the previous four and five years and, you know, a requirement to go back and look carefully to make sure mistakes weren't made unintentionally, appropriate definitions, criteria, et cetera, were used. I thought that this led them to a submission to the FDA with that three analysis subsequently.
Q. In fact it did. It led to several reports to the FDA.
And, sir, isn't it true that also as we've seen here today, we've seen computer printouts showing statistically significant increased incidence of

Page 207

hyperglycemia in Zyprexa users as compared to Haldol users back as early as 1995?
A. Well, I think as we said earlier that's misrepresenting the total data. You picked out one study that showed that. I agree that one study did show that. Many other studies did not show that. The totality of all the studies did not show that or corroborate that.
Q. Well, sir, in fact, the totality of studies that was submitted by Lilly to the FDA in 2001, showed that there was a statistically significant elevated mean levels of glucose in Zyprexa users as compared to Haldol and placebo; isn't that right?
A. That was, again, as we said, an even larger database that had accumulated by the time of that submission in 2001. And I don't know the specific numbers. That may just have been a powering phenomenon. That is, as you get more and more and more patients, as you well know with a statistical background, you may not change an incidence

Page 208

rate but you may have more power to detect a statistical significance just based on a larger sample size. I know that sample size was in excess of 4200 individuals at that point.
But the bottom line was by 2001, there was a significant difference. It first emerged in the data set that was submitted to FDA.
Q. Well, you said -- I would agree with you. That was the first time that you ever informed FDA that there was a statistically significant difference between Zyprexa and either placebo or Haldol, correct?
A. That's not true. FDA, for example, had the HGAJ study report. And every study that's completed, a study report is finalized. It's submitted to FDA. FDA can choose to look at individual studies, collective studies. They have the discretion to look at individual patients for that matter.
Q. Okay. The one study that you

Page 209

were referring to that did show a statistically significant increased incidence of high glucose was from the HGAJ study, correct, that's the one we were looking at earlier?
A. That is one we looked at earlier.
Q. And that was the largest study that had been done back in 1995, correct?
A. I think as we agreed earlier, it represented slightly over half of the patients that had been studied.
Q. Half of the total. How many studies had been done that were included in the NDA?
A. I don't recall. There probably were 15 studies, maybe more.
Q. Fifteen studies or more and yet study HGAJ accounted for more than 55 percent of the entire total of subjects, correct?
MR. LEHNER: Object to the form.

Page 222

That might be a difference.
Q. With respect to all the other language that's in there it's saying, essentially, there's not much difference between Zyprexa users and placebo users, correct?
MR. LEHNER: Object to the form.
A. Based on the analysis of the clinical trial database that's what the data said.
Q. Okay. And if, in fact, you had included language in Paragraph 2 that a review of the random glucose levels in patients in olanzapine clinical trials revealed that the incidence of treatment-emergent hyperglycemia in the olanzapine group was three and-a-half times higher than that in the placebo group, prescribing physicians would have been concerned about that, wouldn't they?
MR. LEHNER: Object to the form.
A. Again, it points to the

Page 223

validity of the data.
Q. Sir, regardless of whether --
MR. LEHNER: Let him finish his answer, please.
MR. SUGGS: Perhaps you didn't understand my question, sir.
THE WITNESS: I did. I think. But please restate and help me clarify.
QUESTIONS BY MR. SUGGS:
Q. I'm not asking whether you think the analysis that's in Exhibit 4858 is correct or whether you think the analysis that was in Exhibit 990 was correct. I'm just talking about the effect of the words, okay.
If, in fact, you had changed the label in May of 2000 to tell doctors that the incidence of treatment-emergent hyperglycemia was three and-a-half times higher in Zyprexa users as compared to placebo users, that would have caused concern on the part of prescribing physicians, would it not?

Page 224

MR. LEHNER: Object to the form.
A. I don't think I could make that kind of generalization. Hyperglycemia was already in as an adverse event term. Now you could poll physicians, some might say, "Gee, I think that means it's 8 times higher," someone else might say, "I think that means it's only 2 times higher." So I don't think you can make that kind of generalization. You want valid data in the package insert. You don't want erroneous data.
Q. Sir, in the context of what was happening in the marketplace in the spring of 2000, with the attacks that Lilly was facing in the marketplace by competitors who were saying that, "Gee, Zyprexa has all this additional weight gain. It's going to increase the risk of diabetes. It's going to increase the risk of hyperglycemia."
And that was what was being said, wasn't it, by your competitors?
A. That is what was being said by competitors.

Page 225

Q. Okay. And if in the face of that you had come out and changed the label and said, guess what, the incidence of treatment-emergent hyperglycemia is three and-a-half times higher in Zyprexa users as compared to placebo users, that would have fed right into what your competitors were saying; isn't that right?
MR. LEHNER: Object to the form.
A. To me it's already in there as an adverse event and I don't see it as materially different.
Q. You don't think that would have had -- put you at any sort of competitive disadvantage if you'd told doctors that the incidence of treatment-emergent hyperglycemia was three and-a-half times higher in Zyprexa users as compared to placebo?
MR. LEHNER: Object to the form.
Q. You don't think that would have had any effect on your sales?
MR. LEHNER: Object to the

Page 226

form.
A. Commercial consequence is never a decision in package insert inclusion.
MR. ALLEN: Objection. Nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Sir, do you recall that this label change that Lilly did without prior FDA approval in May of 2000 got struck down by FDA in October of 2000?
MR. LEHNER: Object to the form.
A. I don't know that I would have used the term "struck down."
Q. Well, they told you you couldn't use it, didn't they?
A. My understanding was that the FDA was in the process of doing their own analysis across multiple products and multiple sponsors and they did not want to reach, were not ready to reach a conclusion, and certainly not ready to reach a conclusion that was consistent with what had been

Page 227

proposed by Lilly at that point in time. They were still a work in progress to understand this issue. And, in fact, it took them several years to finally come up with a recommendation to the field.
MR. SUGGS: Move to strike as nonresponsive.
(Whereupon, Deposition Exhibit(s) 195, previously marked, was presented to the witness.)
MR. SUGGS: Sir, I'm going to show you what has been previously marked as Plaintiff's 195. For the record, this is a letter from Russell Katz at FDA to Gregory Brophy at Eli Lilly. It's dated in the upper right-hand corner as October 11, 2000.
QUESTIONS BY MR. SUGGS:
Q. Did you ever see this before, sir?
A. I believe so.
Q. And when did you see it?

Page 228

A. When it came out. Dr. Brophy shared it with me.
Q. Okay. And if I could direct your attention to Item No. 3 in the letter, the FDA said that they have completed the review of the application. That's referring back to the May 9, 2000, submission, correct?
A. I presume.
Q. And they determined that the changes proposed in Items 1 and 3 were approvable, correct?
A. I'm sorry, I'm not finding that spot. May I ask where you are?
Q. It's in Item No. 3, the very first paragraph right below that numbered?
A. Ah, yes, I've got it.
Q. Okay. The FDA said they had completed review of the May 2000 application and had determined that the changes proposed in Items 1 and 3 were approvable, correct?
A. Correct.
Q. It was Item No. 2 that had the hyperglycemia language, correct?
A. Correct.

Page 229

Q. Okay. And they go on to say, "Before this application may be approved, it will be necessary for you to submit final printed labeling revised with the deletion of the following paragraph, paren, changes effected Item 2 above." And then they quote the language of the label change that you guys had made, correct?
A. This is the label change the company submitted.
Q. Correct.
A. Yes.
Q. Okay. And then after quoting that language the FDA then said in the following paragraph, this descriptive data -- pardon me -- "The descriptive data that is provided expresses a certain level of implied safety with respect to treatment-emergent hyperglycemia. This reassuring language is not appropriate for submission under 21CFR314.70, paren, C as a special supplement changes being effected." Do you see that language, sir?
A. I do.

Q. Okay. When did you see it?
A. The first time I saw it, I believe, was during review with counsel.
Q. Okay. If I could direct your attention to the first paragraph.
By the way, Robert Baker, did he -- was he part of your product team?
A. No. He was a physician in the U.S. Affiliate organization.
Q. Okay. We have Charles Beasley, though, at this time reported to you, correct, he's one of the recipients?
A. We talked about this earlier. I'm not sure if Charles was reporting to me at this point in time or not. He has before or after this time may have been.
Q. Alan Breier, though, certainly reported to you, correct?
A. Yes, for another couple weeks.
Q. Okay. And in the first paragraph Dr. Baker writes, "FYI, the Lilly diabetes/endocrine group held an academic advisory board meeting this weekend in

Atlanta. They kindly allotted two hours for discussion of olanzapine's potential hyperglycemia risks, and Charles Beasley, Chris Bomba, Patrizia Cavazzoni, Suni Keeling and I attended. Unfortunately, this consultation reinforced my impression that hyperglycemia remains quite a threat for olanzapine and may merit increasing even further medical attention and marketing focus on the topic."
Do you see that language, sir?
A. I do.
Q. Were you aware of, that there was such a meeting back in October of 2000?
A. I don't believe so.
Q. Okay. Dr. Baker goes on to say, "On the positive side like other endocrinologists they were not impressed with the Newcomer findings." Do you see that?
A. Yes.
Q. Do you take that to mean a reference to Dr. John Newcomer at Washington University?

A. Yes.
Q. The same one that you said we ought to send cousin Guido to go talk to him?
A. Actually, Mr. Dennis West, but, yes, the same John Newcomer.
Q. Okay. They go on to say, "They were, however, concerned by our spontaneous AE reports and quite impressed by the magnitude of weight gain on olanzapine and the implications for glucose."
Do you see that language?
A. I do.
Q. And is it your testimony that you were not apprised of the results of that meeting?
A. I don't remember being informed of the meeting or, specifically, the results of this meeting.
Q. Okay.
A. There's nothing here that's inconsistent with, I think, some of the feedback that the company had been receiving and taking into consideration.
Q. I'm sorry, you said there's

nothing here that's inconsistent with, I think, some of the feedback that the company had been receiving?
A. Yeah, from different opinion leaders, prescribers.
Q. And for how long had you been getting that type of feedback? Well, what you're talking about that you're saying is not inconsistent is the concern as reported here about the spontaneous adverse event reports and the magnitude of weight gain on olanzapine and the implications for glucose, correct?
A. No. I was saying, No. 1, not impressed with the Newcomer findings and, 2, the magnitude of the weight gain. I think those are issues that, you know, I had certainly heard about on more than one occasion when it came to prescriber issues.
Q. For how long had you been hearing that concern expressed?
A. At least two years, I would imagine.
Q. So at least 1998?

that happened with Zyprexa between 2000 -- strike that.

Between 2000 and 2004, the only label changes that occurred in the Zyprexa label with respect to hyperglycemia were, 1, the label change that you folks did in May of 2000 that we've already discussed that the FDA made you take out later that same year, and the label change that was imposed, mandated, by the FDA in September 2003, correct?

MR. LEHNER: Object to the form.

A. I believe that's correct.

Q. And in that label change there was discussion about hyperglycemia and diabetes in the warning section, correct?

A. There was a class labeling that was issued. But I think the FDA was very clear that they did not rank one drug as greater risk than any other drug, did not see that it was related to weight gain, that relationship had not been established, and wasn't even sure if this was causally related

to these drugs. But we're suggesting appropriate medical monitoring per ADA kinds of criteria for patients. That's how I understood it.

MR. SUGGS: Move to strike the nonresponsive portion.

QUESTIONS BY MR. SUGGS:

Q. Sir, in your continued involvement with Zyprexa after 2000, were you ever consulted with respect to whether Lilly should make a label change to warn about hyperglycemia after the Japanese government required such a warning in April of 2002?

A. Not that I know of.

Q. I have one last document I want to show you, sir, if I can find my copy.

MR. ALLEN: What is it?

MR. SUGGS: I'm going to hand you what's been previously marked, -- oops, that isn't it.

MR. ALLEN: Let's go off the record while we're looking for a document.

THE VIDEOGRAPHER: Off the

record.

(At this time, the parties went off the record, after which the following proceedings were had:)

THE VIDEOGRAPHER: We're back on the record.

(Whereupon, Deposition Exhibit(s) 8666, previously marked, was presented to the witness.)

MR. SUGGS: I'm handing you Plaintiff's Exhibit 8666. For the record, this is a June 27, 2002, e-mail from Simeon Israel Taylor to Willard Dere, with copies to a number of individuals including Dr. Tollefson.

QUESTIONS BY MR. SUGGS:

Q. Dr. Tollefson, you seem to be chuckling when you saw this e-mail, why is that?

A. No. I was just enjoying your inflection of my name.

Q. Did I mispronounce it?

A. No. Dr. Dere you did mispronounce. It's Dr. Dere, Will Dere.

Q. Okay. How did I pronounce it -- Dare?

A. Yeah, I think so.

Q. I guess I'm still missing what was so humorous about my pronunciation of your name. Did I mangle it somehow?

A. No. It's fine.

Q. Okay. Do you recall receiving this e-mail on or about June 27, 2002?

A. I'd have to look at it for a moment.

I don't remember this one, no.

Q. Okay. Would you agree with me that this appears to be some discussion in this e-mail about appointing a panel to look at the issue of hyperglycemia?

A. I'm having a hard time determining what the topic for the panel is.

Q. Well, if I could direct your

attention to the third page there's an e-mail from Meng Tan to Willard Dere with copies to other folks including yourself.

A. Um-hum.

Q. And he says, "Will, Thank you for inviting me to the June 25-26 meetings on Zyprexa and hyperglycemia meetings." Do you see that?

A. I do.

Q. And then there's some discussion about five potential candidates to consider for that meeting, correct? All of whom appear to be involved with diabetes issues, correct?

A. Yes.

Q. Okay. And then in the succeeding e-mails, there's discussion about various people who might be appropriate to serve on this outside consultant panel, correct?

A. Yes.

Q. And then finally, the last e-mail in this chain is from Dr. Simeon Israel Taylor, correct, on the first page?

A. Yes.

Q. And who's Dr. Taylor?

A. He was a, I believe, sort of a guest researcher at Lilly on sabbatical, who had an interest in a variety of areas of internal medicine but I think inclusive of metabolic concerns.

Q. And do you recall where he was on sabbatical from?

A. I do not. I did not know him well.

Q. Okay. Looking at his e-mail, the last part of his first paragraph -- well, actually starting at three lines or four lines up from the bottom in the middle of the line there he says, "Perhaps we should retain the right to veto panel members, but probably not to choose the members. Clearly, this approach entails some risk that we will be unhappy with the panel's findings. However, I feel that we need to deal with the scientific facts, whatever they are. Ultimately, I am expect that a fair-minded, scholarly evaluation of the available data is

likely to support several conclusions." And then he lists what those conclusions are, correct?

A. Yes.

Q. And the first conclusion is "Zyprexa, like other members of the class, causes weight gain."

A. Correct.

Q. And would you agree with Dr. Taylor that Zyprexa causes weight gain?

A. Yes.

Q. Okay. And then he goes on to say in point two, "Like other causes of weight gain, Zyprexa-induced weight gain probably increases the risk of diabetes." Do you see that language?

A. That's what he says.

Q. And did you respond back to Dr. Taylor?

A. I don't recall.

Q. I take it you would disagree that Zyprexa-induced weight gain probably increases the risk of diabetes; is that correct?

A. I can only echo the position of the Food and Drug Administration that they didn't see the anticipated connection between the two when they reviewed multiple drugs in this class.

MR. SUGGS: Move to strike as nonresponsive.

QUESTIONS BY MR. SUGGS:

Q. Sir, you take the position today that Zyprexa does not increase the risk of diabetes, correct?

A. Whether it does or doesn't I think is unknown.

MR. SUGGS: Okay. I have no further questions at this time.

MR. ALLEN: Dr. Tollefson, Scott Allen from Houston, Texas. How are you doing?

THE WITNESS: Good, Mr. Allen.

MR. ALLEN: I'm going to have some questions that follow up to Mr. Suggs. Just mainly, it's going to be clarification for the record

it could also imply the risks associated with not treating or inadequately treating the disease. So risks can come from the disease itself, risk can be related to the drug in question a person's taking, or the risk, in theory, could be coincidental as part of a predisposition the person might have. So risks can be multifaceted. They are multifaceted.

Q. Thank you, sir. Let's talk about -- the facet I'd like to focus on is are risks or adverse events associated with treatment. That's one of the facets you just identified, wasn't it?

A. Yes.

Q. Should a corporation who manufactures and markets a pharmaceutical ever try to minimize those adverse events associated with the drug treatment?

A. I think the company should always say the data as the data is.

Q. My question to you is -- let me just get right to Zyprexa. In identifying, I asked you to give this jury

your definition of risk. You gave us some facets and one of the facets was adverse events associated with treatment, correct?

A. Um-hum. Correct.

Q. Would it be appropriate for Eli Lilly to try to minimize adverse events associated with Zyprexa, yes or no?

MR. LEHNER: Object to the form.

A. I'm not sure what you mean by "minimize."

Q. Is that your best answer to that question?

A. I was just asking if you would like to elaborate what you meant by minimize because I'm not sure what you meant.

Q. Is that your best answer to my question?

A. Again, I think the data is the data. And you share the data, once it's been validated, and you don't maximize or minimize. The data is the data. The data tells the story. That's my view. But I'm not sure what you meant by "minimize."

Q. You just used the term "minimize," how do you use the term "minimize?"

A. If I were using it --

Q. I'm sure you've used it your entire life.

A. Probably something different than maximize. Something less than maximize.

Q. You know what maximize means. I've seen documents with your name on it talking about maximization of profit, right? You know what that means, don't you?

MR. LEHNER: Objection to form.

A. I do.

Q. To maximize something means to make it -- to highlight it, to get it as great as possible. Is that a fair definition of maximize?

A. That is a definition, yes.

Q. Okay. Minimize. What do you mean when you talk about minimizing something, you, Dr. Tollefson?

A. Not overstating it.

Q. So to minimize doesn't mean to downplay it to you? To downplay it, make it less significant?

A. That could be an extreme of it.

Q. Yes. Would it be appropriate for Eli Lilly to minimize, downplay, make less significant, an adverse event associated with Zyprexa?

MR. LEHNER: Objection to the form.

A. I think if someone is unsure whether there is a causal relationship, there is a detriment to either over or maximizing or minimizing in the absence of knowing whether there's causality.

Q. And my question to you --

MR. SUGGS: Objection. Nonresponsive.

Q. My only question to you was should Eli Lilly try to minimize the adverse events associated with Zyprexa?

MR. LEHNER: Objection to the form.

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
-v-	)	CAUSE NO.
	)	3AN-06-5630 CIV
ELI LILLY & COMPANY,	)	
	)	
Defendant.	)	

The videotaped deposition upon oral examination of ROBIN PITTS WOJCIESZEK, a witness produced and sworn before me, Nancy M. Kottenstette, Notary Public in and for the County of Marion, State of Indiana, taken on behalf of the Plaintiff at the offices of Ice Miller, One American Square, Suite 3100, Indianapolis, Indiana, on December 11, 2007, at 9:37 a.m., pursuant to all applicable rules.

C O N F I D E N T I A L

EXHIBIT I
Page 1 of 4

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I 4

that this important finding was not included in your proposed label." Do you see that?
A Yes.
Q Okay. And do you know who it was that made the decision not to include that information in the proposed label?
A That's a decision that's made -- it's actually a very cross-functional group of individuals within medical, regulatory, and global patient safety.
Q Was there a particular individual who would have been -- I'll use a football term -- the quarterback in terms of making that decision?
A No. A lot of our decisions are made -- we have a various -- a sign-off form. So it's definitely made within the consensus of the group.
Q Okay. Am I correct, though, that the proposed labeling that you had submitted did make reference to the first analysis that we talked about --
A That's correct.
Q -- showing 2.9 percent of the patients having blood glucose below 140 going over 200. That was, in fact, in the -- in the proposal that you guys had; correct?
A That's correct.
Q And I see you pawing through the document there.

Are you going to --
MR. KANTRA: Object to the characterization of pawing.
MR. SUGGS: Well, I didn't -- I didn't mean it in a bad way. Let me restate the question.
THE WITNESS: Pawing.
Q Let me withdraw that. I see you paging through the document. Are you able to point to the section in the proposed labeling that does indicate where that was included?
A Yes.
Q And can you point that out to me, please?
A Sure. It is on page -- oh, my, with various page numbers on this fax, isn't it -- 20 of 38, top right-hand corner under laboratory changes.
Q Okay. In about the middle of the page. Actually, a little lower than that.
A Yes, uh-huh.
Q Okay. Okay. And this would have been the proposed labeling that Lilly had submitted to FDA; correct?
A That's correct.
Q Okay.
A My pawing's over.
Q I'm sorry. I don't know why -- I don't know why

that word came to mind. Let's see here. Do you know when it would have been -- that particular data that we've been talking about on which those analyses were made, do you know when they would have been -- when that data would have been generated?
A That data would have been generated, you know, prior to our submissions, so the summer of 2006.
Q Okay. I thought you said that the -- that the data ranged from between 2002 and 2005?
A Correct. But this particular analysis is a pooling of studies.
Q Ah, okay. Okay. So this analysis was done, you believe, probably in the summer of 2006?
A Yes.
Q But it was done on data that was a pooling of data that was in that 2002 to -- strike that. The analysis that was done in the summer of 2006, as referred to in this first full paragraph on page 2, was an analysis of data that had been actually generated sometime between 2002 and 2005. Fair statement?
A That's correct.
Q Okay. I'd like to direct your attention to the third full paragraph on the second page of the

FDA's letter, the one that starts off "Our overall goal..." Do you see that?
A Yes, I do.
Q It states "Our overall goal is to improve labeling with regard to these findings so that clinicians will be better informed on what the risks are for their patients. They cannot make reasonable treatment decisions until they have such information.
We do not feel that current labeling for either Symbyax or Zyprexa provides sufficient information on these risks, and we fully intend to insure that these labels are enhanced with the best available information to characterize these risks."
Do you see that language?
A Yes, I do.
Q Now, are you aware that in the Zyprexa litigation, not only in this case in Alaska, but in thousands of other cases around the country, Lilly has been asserting that its Zyprexa label was already sufficient and adequate?
A Yes.
Q But at least the -- and Lilly has never, to your knowledge, admitted that its labeling was inadequate, has it?

MR. SUGGS: Can you read it back, please.
(The requested material was read back by the reporter.)
A Our -- our proposal to FDA was to include the very specific clinical trial data within the laboratory section, which was kind of, in our experience and interpretation of FDA's labeling guidance, was to put that particular information in the adverse reactions section.
Q And not in the warning section?
A Not in the warning, but keep the warning to very specific of recommendations of -- around monitoring, etc., so...
Q So I was correct that you wanted to take the analyses of the data that was in the warning section proposed by FDA, you wanted to take that out and put it into the adverse reactions section; correct?
A Right. With the statement of -- that the -- within the warning section that additional information that was seen in clinical trials is referenced in that adverse reactions section.
Q Okay. If I could direct your attention to the second page of Exhibit 9, the title there under Section A is "Hyperglycemia Warning Class

Labeling," and then in the second paragraph you state "The language proposed below would be appropriate across the class of atypical antipsychotics for the hyperglycemia warning and not specific only for inclusion in the Zyprexa and Symbyax USPIs." Did I read that correctly?
A Yes, you did.
Q And USPI is the abbreviation for U.S. package insert; correct?
A Correct.
Q And, basically, Lilly was saying that you wanted to have the language proposed below, which we'll get to, in all of the package inserts for other atypical antipsychotics; correct?
A What -- what it says is that we feel it's appropriate that that language be reflected.
Q And as far as you know, the FDA has not agreed with that because you're not aware of any other manufacturer being requested to put that information in their labeling; correct?
A And I don't know if they have agreed to it, but it's not currently reflected across the class.
Q Okay. And if I could direct your attention to the warning section at the bottom of the page on page 2 there, that is the warning language that Lilly had

come back with as a response or counter proposal to FDA; is that correct?
A That's correct.
Q Okay. And who was it that -- at Lilly that actually drafted or crafted that language?
A It was -- as our process indicates and what we typically do for our labeling is to have a cross-functional group of representation from regulatory and -- and medical primarily.
Q Okay. And who was it that was ultimately in charge of that effort?
A Numerous individuals had to approve it.
Q In -- in the context of this particular project, if there was a difference of opinion as to whether particular language should or should not be used, was there -- who was the person that had the capability or the authority to say, no, we're going with Version B, not Version A?
A You know, in this particular situation, we didn't have to escalate. We were all in consensus around it.
Q Well, was it made clear at the beginning of the process or during the process that there was indeed an individual in the group that had that authority if the issue arose?

MR. KANTRA: Objection, asked and answered.
A We would go through a various escalation process if we felt that was necessary.
Q Well, and who would it get escalated to?
A Typically, it would get escalated to individuals that head the GRA or regulatory affairs in medical.
Q And who would those individuals be?
A I would say in this particular situation it would be an individual such as Tim Fransin in regulatory affairs, and within medical probably through the GBD organization. Someone --
Q Through the GBD?
A Yeah. The global brand development, so similar to the team that you brought up before.
Q Zyprexa product team?
A Yeah. Zyprexa product team, someone such as John Hayes.
Q Okay. Did, in fact, Mr. Fransin and Mr. Hayes pass on or approve the labeling that was proposed here in this briefing document?
A They did not sign off on this -- this labeling because it was done, again, through the team as our proposal.
Q Okay. Who was the leader of that team?
MR. KANTRA: Objection, asked and answered.

this issue of impaired glucose tolerance/diabetes, the message was clear. Don't get too aggressive about denial, blaming it on schizophrenia, or claiming no worse than other agents until we are sure of the facts and sure we can convince regulators and academicians." Do you see that language?

A Yes.

Q And when you saw this e-mail for -- in connection with responding to the New York Times articles, was that the first time that you were aware that outside consultants had warned about not claiming that Zyprexa was any worse than other agents?

MR. KANTRA: Objection to the form.

Q In 2000?

A As part of my involvement in the New York Times, I was aware of this particular e-mail. I was not briefed or discussed on the overall context of what it was referring to, other than the fact that this was one of the documents that was part of the allegations so...

Q And I take it you were not aware of the facts reflected in this e-mail before 2000?

MR. KANTRA: Objection. Objection to the form.

Q I take it you were not aware of the facts related in this e-mail before your involvement in the response to the New York Times article; is that a fair statement?

A Could you repeat the question?

Q Sure. Were you aware of this e-mail or the contents of the e-mail before becoming involved in the response to the New York Times query from the FDA?

A No, I was not.

Q Okay. Were you aware that between 2000 and thereafter -- strike that. Were you aware that after 2000 and for years thereafter Lilly trained its sales force to assert that the rates of hyperglycemia and diabetes were comparable between the various atypical antipsychotics?

MR. KANTRA: Objection to the form, beyond the scope.

A I'm aware that it was included in -- in materials, but the specifics I was not involved in.

Q Okay. And when you say "It was included in materials," you're referring to the "it" being an assertion of comparable rates; correct?

A That particular statement that you had mentioned before, yes.

Q Okay. And when you referred to materials, you're referring to materials that were used by sales representatives?

A That's correct.

Q And distributing to physicians to influence their prescribing practices; correct?

MR. KANTRA: Objection to the form.

A It was included in various materials. I don't know the specifics of how they were distributed.

Q And to this day, has Lilly instructed its sales force to stop saying that rates of hyperglycemia or diabetes are comparable amongst various atypical antipsychotics?

MR. KANTRA: Objection to the form, also beyond the scope.

A I'm not aware of a specific communication related to that.

Q So as you sit here today, you're not aware of any communication to the sales force telling them not to assert that there are comparable rates of diabetes and hyperglycemia between the various atypical antipsychotics?

MR. KANTRA: Objection to the form, beyond the scope.

Q Fair statement?

MR. KANTRA: I'm sorry.

Q Fair statement?

MR. KANTRA: Objection to the form, beyond the scope.

A Could you repeat that again? I'm sorry. I just --

Q I know it's hard to keep track of the question and come up with an answer when there's an objection there.

A Yeah. Sorry.

Q As you sit here today in December of 2007 --

A Correct.

Q -- you are not aware of any communications to the sales force to stop claiming that there are comparable rates; correct?

MR. KANTRA: Beyond the scope.

A That's -- that's correct. What we involve is that the sales force should use the consistency of the label, which the labeling changes that occurred this year should be part of that -- that sales material.

Q Okay. Now, we've talked about the -- the consensus statement before, which was Exhibit 2368, I believe, and I believe we established that, at least in the language of the consensus statement, there was the assertion by that statement that

06-5630 CA

Case # 06-5630 CR/CI

Case Title: SDA v. Lufkin & Co

Type of Document Enclosed: Amended Trial Dep Desig

Date Filed: 2/4/08 Judge: Rendner

~~SEALED~~ *

No one, including court personnel, may view the contents of this envelope without a written order of the court.

Comments: filed 2/4/08

Amended Trial Dep Desig under Seal

TF-330 (8/89) (TCB Fl. Pink 4"x5½")

* See Judge Rindner's 6/13/08 order page 21, #17

Documents unsealed Lwade 8/11/08

Pages 6604-6928

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Case No. 3AN-06-05630 CI
	)	
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	
	)	

PLAINTIFF'S AMENDED TRIAL DEPOSITION DESIGNATIONS

Pursuant to the Court's request and Alaska Rule of Civil Procedure 26(A)3(B), Plaintiff, the State of Alaska, hereby amends its Trial Deposition Designations as indicated below and on the attached Exhibits.

Exhibit 1	Michael Bandick ; *see* Amended Designations attached hereto;
Exhibit 2	Charles Beasley, Jr., M.D.; *see* previously produced Designations;
Exhibit 3	Charles Beasley, Jr., M.D.; *see* previously produced Designations;
Exhibit 4	Alan Breier, M.D.; *see* previously produced Designations;
Exhibit 5	Alan Breier, M.D.; *see* previously produced Designations;
Exhibit 6	Jerry Clewell, Pharm.D., MBA.,BCPS; withdrawn. However, plaintiff reserves the right to offer previously produced designations if necessary;

FELDMAN ORLANSKY & SANDERS
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TEL: 907.272.3538
FAX: 907.274.0819

006604

Exhibit 1
Michael Bandick

Exhibit 7	Jack E. Jordan; *see* Amended Designations attached hereto;
Exhibit 8	Bruce Kinon, M.D.; *see* Amended Designations attached hereto;
Exhibit 9	Kenneth Kwong, M.D.; withdrawn. However, plaintiff reserves the right to offer previously produced designations if necessary;
Exhibit 10	John C. Lechleiter, Ph.D.; *see* previously produced Designations;
Exhibit 11	David Noesges; *see* previously produced Designations;
Exhibit 12	Susan Kay Schuler; withdrawn. However, plaintiff reserves the right to offer previously produced designations if necessary;
Exhibit 13	Michele Sharp, Pharm.D.; withdrawn. However, plaintiff reserves the right to offer previously produced designations if necessary;.
Exhibit 14	Sidney Taurel; *see* previously produced Designations;
Exhibit 15	Gary Tollefson, M.D.; s*ee* previously produced Designations;
Exhibit 16	Denice M. Torres; s*ee* Amended Designations attached hereto; and
Exhibit 17	Robin Pitts Wojcieszek; s*ee* previously produced Designations.

DATED this 1 day of February, 2008.

FELDMAN, ORLANSKY & SANDERS
Counsel for Plaintiff

By_____
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Exhibit 1
Michael Bandick

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H. Blair Hahn
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I hereby certify that a true and correct copy of the foregoing **Plaintiff's Amended Trial Deposition Designations** was served by messenger on:

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Exhibit 1
Michael Bandick

Bandick, Michael (June 9, 2006)
49:12-51:14
Issues: 01 Plaintiff's Trial Designation

49:12 Q. State your name for the Court
13 and Jury, please, sir.
14 A. My name is Michael Edwin
15 Bandick.
16 Q. Mr. Bandick, my name is Scott
17 Allen, I'm from Houston, Texas. I'm here to
18 take your deposition today, do you understand
19 that?
20 A. I do.
21 Q. You understand the court
22 reporter has sworn you in and you're under
23 oath?
24 A. I do.
50: 1 Q. And your testimony is being
2 taken down by the court reporter and in all
3 likelihood will be played back to a jury in a
4 court at the time of trial?
5 A. I understand.
6 Q. You understand the oath?
7 A. I do.
8 Q. You're required to tell the
9 truth, right?
10 A. That's correct.
11 Q. The whole truth?
12 A. That's correct.
13 Q. And nothing but the truth?
14 A. Yes.
15 Q. You understand your answers
16 matter?
17 A. Yes.
18 Q. You understand the meaning of
19 "answers matter," do you not?
20 A. I believe so.
21 Q. And when your answers matter
22 that means you're always supposed to tell the
23 truth, the whole truth and nothing but the
24 truth, do you agree?
51: 1 A. I will do those.
2 Q. Yes.
3 Did you do those when you
4 were working at Lilly?
5 A. Yes, I did.
6 Q. What's your age, sir?
7 A. I'm 44.
8 Q. And where do you live?
9 A. I live in Carmel, Indiana.
10 Q. And I've only been to Indiana
11 once in my life, and I don't know where
12 Carmel is; is it somewhere near Indianapolis?
13 A. It's a suburb north of
14 Indianapolis.

Bandick, Michael (June 9, 2006)
54:5-6
Issues: 01 Plaintiff's Trial Designation

54: 5 Q. When did you become employed
6 by Eli Lilly?

Bandick, Michael (June 9, 2006)
54:7-10
Issues: 01 Plaintiff's Trial Designation

54: 7 A. May of 1991.
8 Q. Directly after your education
9 and MBA at Duke?
10 A. That's correct.

Bandick, Michael (June 9, 2006)
55:6-57:7
Issues: 01 Plaintiff's Trial Designation

55: 6 Mr. Bandick, I have a
7 document in front of me which has been
8 identified as Bandick Exhibit No. 1 for
9 today's deposition, and it's a marketing --
10 for lack of a better word, what do you call
11 this document?
12 A. I would call this document an
13 organization chart.
14 Q. That's exactly right. And
15 it's an organization chart ZBT Marketing
16 dated August of 2002. ZBT stands for what,
17 sir?
18 A. Zyprexa Product Team.
19 Q. And your name is on this
20 document?
21 A. Yes, it is.
22 Q. And you're at, your title's
23 described here under Denice Torres, who was
24 director of global marketing, there are four
56: 1 people who reported directly to her; is that
2 correct?
3 A. Yes, it is.
4 Q. And you were one of those
5 four individuals?
6 A. Yes.
7 Q. And your title is listed Mike
8 Bandick, Director Marketplace Management; is
9 that correct?
10 A. Yes, it is.

Q. Can you tell the jury, please, what location you worked in when you were Director Marketplace Management for Zyprexa Marketing Team in August of 2002?
A. That was based in Indianapolis.
Q. Okay. And the address was?
A. It was Lilly Corporate Center. I don't recall the zip code.
Q. Here in Indianapolis; is that correct?
A. That's correct.
Q. I've also seen documents, Mr. Bandick, that indicated you were Brand Manager for Zyprexa for Lilly?
A. I did have that role previously.
Q. Okay. And when you left -- what year did you leave Lilly?
A. 2004.
Q. What was your title when you

Bandick, Michael (June 9, 2006)
57:14-17
Issues: 01 Plaintiff's Trial Designation

Q. All right. Can you describe for the jury, please, what you did in your role as Director of Marketplace Management and/or Brand Manager in Zyprexa for Lilly?

Bandick, Michael (June 9, 2006)
57:21-59:15
Issues: 01 Plaintiff's Trial Designation

A. It's two different roles so I can describe them separately for you.
Q. Why don't we do that? What did you do as Brand Manager?
A. In that particular role I was responsible for the marketing of Zyprexa in one segment of its U.S. operations.
Q. What year were you Brand Manager, years?
A. Part of 2000, part of 2001.
Q. Okay, when were you Director of Marketplace Management for Zyprexa?
A. From the latter part of 2001 to the early part of 2004.
Q. Okay. We're going to go back into this in some detail but I just want the jury, initially, to have some idea who you

were.
You said as Brand Manager for 2000/2001, your answer was something like: I handled one segment of Zyprexa's market. Right?
A. That's correct.
Q. What segment did you handle?
A. The primary care segment.
Q. That's the PCP segment?
A. It was also called PCP.
Q. I've seen documents with that name on it. Okay.
And then you took that role as Brand Manager for the PCP segment of the Zyprexa market in 2000; is that correct?
A. Yes, it is.
Q. What month of 2000 did you assume that role?
A. I believe it was July.
Q. Who had that role before you?
A. It was a new role.
Q. Right. So you were the initial brand manager for PCP, primary care physician marketing, for Zyprexa, and you took that role in July of 2000, correct?
A. Yes.

Bandick, Michael (June 9, 2006)
61:10-63:7
Issues: 01 Plaintiff's Trial Designation

Q. Okay. In regard to the marketing role for the PCP marketing of Zyprexa in July of 2000 as Brand Manager was there anybody higher than you in marketing?
A. Yes.
Q. Who would that be?
A. My supervisor in that role was Jack Jordan, and he reported into a broader marketing organization. I believe his supervisor at the time, at the time was Glyn Parkin, G-L-Y-N, P-A-R-K-I-N, and Glen reported into the head of what would be our US affiliate commercial operations and I believe that was Bill Robinson.
Q. As Brand Manager for PCP marketing of Zyprexa, the role you held from July of 2000 until late 2001; is that correct?
A. September of 2001.
Q. From July of 2000 till September of 2001, you reported to Jack Jordan. And what was Mr. Jordan's title?
A. I believe his title was Brand

Team Leader or Brand Leader.
Q. And in September of 2001, were you promoted?
A. Yes, I was.
Q. So for your activities, whatever they were, we're going to talk about them, but whatever you did from July of 2000 until September of 2001 impressed your superiors so much that you got a promotion; is that fair?
A. At the time I had been with Lilly for ten years and had been in four different manager level roles and I assume that the promotion was based on my performance in all those roles.
Q. Okay. That's good.
So including all of your work that you had done at Eli Lilly, including the work you had done as Brand Manager for PCP marketing in Zyprexa from July of 2000 until September of 2001, you received a promotion?
A. Yes, that's correct.
Q. Okay. Tell the jury the

Bandick, Michael (June 9, 2006)
65:12-66:2
Issues: 01 Plaintiff's Trial Designation

Q. And in November of 2001 you got a new title; is that right?
A. That's correct.
Q. Tell the jury, please, what that title was?
A. Director of Marketplace Management for the Zyprexa Product Team.
Q. Exhibit No. 1?
A. That was the organization I joined, yes.
Q. Yes. And that's the title you held, which is reflected in Exhibit No. 1?
A. That's correct.
Q. Was that a promotion?

Bandick, Michael (June 9, 2006)
66:5-20
Issues: 01 Plaintiff's Trial Designation

Q. Okay. How long did you hold the title Director Marketplace Management Zyprexa Product Team?
A. From late 2001 to early 2005.

Q. When you say "late," I think you agreed with me that was November of 2001 when you became Director Marketplace Management for the Zyprexa Product Team; isn't that right?
A. It was either November or December, I don't recall the exact date.
Q. And you held that role until January of 2004?
A. I believe that's correct, January or February of 2004.
Q. And what happened then?

Bandick, Michael (June 9, 2006)
69:3-70:4
Issues: 01 Plaintiff's Trial Designation

Q. And where is the Global Marketing Department for Eli Lilly located?
A. Indianapolis.
Q. So the Global Marketing Department for Lilly and all of its drug products is located right here in Indianapolis, Indiana, of the United States of America; is that right?
A. That's correct.
Q. How many countries around the world does Lilly market its drug products in?
A. I don't know the exact number.
Q. Well, can you give the jury, please, for the jury, an estimation?
A. I would estimate that it's more than 50 and less than a hundred.
Q. Okay. Somewhere between 50 and a hundred; is that right?
A. Yes.
Q. That's your best estimate as somebody that was employed at Eli Lilly from 1991 to 2004 in the marketing department, your best estimate is somewhere between 50 and a hundred countries is where they market drugs; is that correct?

Bandick, Michael (June 9, 2006)
70:5-5
Issues: 01 Plaintiff's Trial Designation

A. That's correct.

Bandick, Michael (June 9, 2006)
70:21-71:5
Issues: 01 Plaintiff's Trial Designation

70:21 Q. So Eli Lilly is a worldwide
22 pharmaceutical manufacturer and distributor
23 of medicines and drugs; is that true?
24 A. Yes, it is.
71: 1 Q. And the marketing department
2 for Eli Lilly's worldwide operations is
3 located here, is located here in
4 Indianapolis, Indiana?
5 A. Yes, it is.

Bandick, Michael (June 9, 2006)
79:6-80:21
Issues: 01 Plaintiff's Trial Designation

79: 6 During the time that you were involved in any
7 way, in whatever role, in Zyprexa marketing
8 what are the names of the teams, groups, or
9 committees that you were a member of?
10 A. There are a lot of different
11 groups that would come together for different
12 reasons and even the ones that you just named
13 were for very different purposes, so I may
14 not be able to give you every last one that I
15 may have had some involvement in.
16
17 Primarily, I was part of the
18 Zyprexa Product Team. I was also part of the
19 Lilly U.S. Brand Team. I also had a role
20 within U.S. Market Research. Those were the
21 primary ones.
22 Q. Give me the secondary ones.
23 A. I, probably, was a member of
24 the Limitless Team. That was more for a,
80: 1 that wasn't a specific project or
2 designation, that was part of the U.S. Brand
3 Team.
4 I was also with a part of a
5 cross-functional group called the Zyprexa
6 Issues Management Team.
7 Q. Any more?
8 A. Not that I can think of.
9 Q. How about the Medical
10 Marketing Team? When I looked at a document
11 it looked like a cross-functional team of
12 medical and marketing. Do you remember that
13 one?
14 A. When I was in the market
15 research role I believe there was a group
16 called that. That wasn't something that had
an official designation, that was more just a

description of some of the different people who might be invited to a discussion, but, yes, that does ring a bell.

Q. That rings a bell?

A. It does.

Bandick, Michael (June 9, 2006)

82:7-17

Issues: 01 Plaintiff's Trial Designation

Q. Next question: Did you assist in writing documents that were prepared for the sales force to give to physicians about Zyprexa?

A. Sometimes.

Q. Okay. Do you remember any document in particular, or are there too many to remember, that you wrote in marketing that would be provided to the sales force that you knew would end up in doctors' hands?

MR. FAHEY: Objection to

Bandick, Michael (June 9, 2006)

82:19-83:2

Issues: 01 Plaintiff's Trial Designation

A. As I mentioned, I was involved in that activity. There are too many for me to recall any single one for you.

Q. Right. And that's a fair answer. You wrote a lot and lot of documents that you knew would be used by the Zyprexa marketing department and/or sales force that would be given to doctors concerning Zyprexa.

Bandick, Michael (June 9, 2006)

104:22-106:8

Issues: 01 Plaintiff's Trial Designation

I'm looking down, I made myself notes, I have my next question I wrote down is "why is there a marketing department?" So I'll ask it to you, why is there a marketing department?

THE WITNESS: Can I ask you to be a little more specific?

MR. ALLEN: Well I could, and I appreciate that. But let me tell you my train of thought and maybe this will help.

QUESTIONS BY MR. ALLEN:
Q. You talked about products in the pipeline, we talked about that earlier, right?
A. We have.
Q. Okay. We're going to talk about that some here later. You have research and development, you have products in the pipeline, you have a regulatory affairs department, clinical studies are done and the data and information is submitted to the FDA and the product receives FDA approval for its indicated purpose. You with me so far?
A. Yes, I am.
Q. Okay. You have FDA approval for its indicated purpose of a pharmaceuticals product. Are you with me now?
A. Yes.
Q. Why not just put the product on the market, ship it to the pharmacies and be done with it? You understand what I'm saying?

Bandick, Michael (June 9, 2006)
106:11-22
Issues: 01 Plaintiff's Trial Designation

A. I do.
Q. Okay. That's not what happens, is it?
A. In most cases that's correct.
Q. Okay. I mean, if you've researched the product, you developed the product, it's approved by the FDA, the package insert's included within the PDR, it's known that the product's available, and doctors can prescribe it or not prescribe it as they see fit, why not just leave it at that?

Bandick, Michael (June 9, 2006)
107:2-10
Issues: 01 Plaintiff's Trial Designation

A. The reason to not leave it at that is that it would likely not be as aware to physicians what the product's strengths and weaknesses are.
Q. Fair. I'll go back to where I started, and maybe that's the question you

8 answered. Why is there a marketing
9 department for drugs that are approved and on
10 the market?

Bandick, Michael (June 9, 2006)
107:13-108:8
Issues: 01 Plaintiff's Trial Designation

107:13 A. The role of the marketing
14 department is to provide some of that
15 awareness and detail around the product and
16 its strength and weaknesses. There are also
17 strategic elements of where the product might
18 be promoted in the future, and other
19 products, products in the pipeline, what
20 their position might be in the market.
21 Q. I'm going to see if I can
22 break that down or see if we have a clear
23 understanding -- I tell you, we're going to
24 have to get some quiet Coke openers -- let me
108: 1 see here.
2 In answer to my question
3 about why there's a marketing department, you
4 said it helps create an awareness about a
5 product's strength and weaknesses. In
6 addition, it also helps create such awareness
7 involving products in the pipeline. Did I
8 paraphrase that accurately?

Bandick, Michael (June 9, 2006)
108:11-109:3
Issues: 01 Plaintiff's Trial Designation

108:11 A. No.
12 Q. Tell me where I'm wrong,
13 please.
14 A. It does create awareness for
15 products that are approved. The strategic
16 piece for products in the pipeline or future
17 indications would not be for the purposes of
18 creating awareness but rather to understand
19 potential positioning, understand unmet
20 medical need, things like that.
21 Q. Okay. So the marketing
22 department creates awareness of strength and
23 weaknesses of a product, but also, it helps
24 understand, strategically, the views of the
109: 1 marketplace concerning potential future
2 products and/or extended indications of
3 existing products; is that right?

Bandick, Michael (June 9, 2006)
109:6-111:13
Issues: 01 Plaintiff's Trial Designation

109: 6 A. That's a little different
7 from what I think I said.
8 Q. All right. Where did I mess
9 up?
10 A. Without the benefit of
11 playing back exactly what I said and
12 remembering exactly what you said, the piece
13 that I was alluding to with the strategic
14 piece is for both existing products and not
15 only future indications and disease states
16 but understanding unmet medical need, in
17 forming future clinical trials, understanding
18 disease states that are unsatisfied so there
19 can be a piece that's specific to a single
20 product, it can be more broad to a disease
21 state, it can even be more broader than that.
22 Q. Okay. Now, in your original
23 answer you indicated that, at least one of
24 the reasons for a marketing department was to
110: 1 create awareness of in doctors of the
2 strengths and weaknesses of a product. Do
3 you recall that?
4 A. Yes, I do.
5 Q. But doctors are not your only
6 customer, are they?
7 A. There can be other audiences,
8 yes.
9 Q. I use "customer" you use
10 "audiences". Are we using those words
11 interchangeably or is a term of art
12 "audience" in marketing?
13 A. I was not using it
14 interchangeably with customer.
15 Q. So when I asked you there are
16 other customers and you answered, yes, there
17 can be other audiences, you were not using it
18 in the nature of my question as the word
19 customers; is that right?
20 A. If what you mean by customer
21 is a physician who has the ability to
22 prescribe then I'm comfortable with that as
23 customer.
24 Q. Okay. What do you mean by
111: 1 audience?
2 A. An audience could be a group
3 that isn't a prescriber or a customer but
4 could be, either an internal or an external
5 audience; for example, an internal audience
6 could be a sales organization.
7 Q. Give me some more example of
8 some external audiences?
9 A. External audiences could

include payors, they could include patients.
Q. Regulatory affairs at the FDA, would that be an audience?
A. Yes, it could be.

Bandick, Michael (June 9, 2006)

112:9-113:20
Issues: 01 Plaintiff's Trial Designation

Q. I have seen a company document describing Lilly's customers as patients, doctors, payors, and regulatory agencies. Do you agree that those are Lilly's customers for its drug products?
A. That's not how I use the concept of customers and that's why I broadened it to include audiences.
Q. Okay. And that's what I thought you were going to say. So let's see if you and I can agree on this. Do you agree that Lilly's audiences for its drug products and the marketing surrounding its drug products are patients, doctors, payors, and regulatory agencies, among others?
A. Yes, among others.
Q. Okay. But we at least agree on those four, right?
A. As audiences, yes.
Q. And where I come from -- it doesn't matter where I come from.
Let me ask you what do you mean by audience in the marketing realm?
A. A group for whom a message could be developed.
Q. So an audience is a group for whom a message can be developed; is that correct?
A. Yes.
Q. What's a message?
THE WITNESS: It's a very broad question, can you be more specific?
MR. ALLEN: No, sir.
QUESTIONS BY MR. ALLEN:
Q. What's a message?

Bandick, Michael (June 9, 2006)

113:23-114:23
Issues: 01 Plaintiff's Trial Designation

A. The best I can define that as is a concept that is conveyed to that

audience in some form.
Q. Yeah. You use the word "message" before I did. So I -- so a message is a concept conveyed to an audience; is that right?
A. Yes.
Q. Okay. As a matter of fact, let me just look, you use the word "message" all the time in your business in marketing, don't you, every day?
A. It's a frequently used word.
Q. Okay. So when I ask you what a message was and you said that's an awful broad question, the fact of the matter is in marketing you use the terminology and the word message almost every single day, don't you?
A. Yes.
Q. Okay. And you said an audience, which includes patients, doctors, payors, and regulatory agencies, an audience is someone to whom you can give messages; is that correct?

Bandick, Michael (June 9, 2006)
115:2-6
Issues: 01 Plaintiff's Trial Designation

A. An audience could be construed as a group who would receive a message. That's not the only way I would define an audience but for purposes of answering your question, yes.

Bandick, Michael (June 9, 2006)
115:23-117:10
Issues: 01 Plaintiff's Trial Designation

Q. In your role and roles in the marketing of Zyprexa, why would you want to send audiences messages about Zyprexa?
A. As I indicated earlier, conveying a concept can be a very valuable piece of what we think those audiences would need to know. And I guess the difficulty I'm having in answering your question is the work that we did was always in the context of a particular situation. So without that context it's hard for me to give you a very satisfactory answer.
Q. I think your answer's quite satisfactory. You said the reason you want

to send messages to audiences is in order to convey valuable information that they may need to know; is that correct?
A. Yes.
Q. When you send these messages concerning Zyprexa to your audiences and you convey this information that the audiences may need to know, do you have a responsibility to be truthful?
A. Yes. Excuse me, yes.
Q. Accurate?
A. Accurate, yes.
Q. Do you have a responsibility to tell not only the truth but the whole truth?
A. We have the responsibility to be truthful and accurate.
Q. And that wasn't my question. When you convey this information to the audiences in these messages, do you have the responsibility to tell not only the truth but the whole truth?

Bandick, Michael (June 9, 2006)
117:13-23
Issues: 01 Plaintiff's Trial Designation

A. I'm not sure how to answer your question in the context of the way that we would deliver those messages. They were truthful and accurate.
Q. Sir, that's when we started this whole deposition. Remember you raised your right hand, do you remember that?
A. I do.
Q. You took an oath, do you recall that?
A. I do.

Bandick, Michael (June 9, 2006)
118:8-19
Issues: 01 Plaintiff's Trial Designation

Q. Your oath was to tell the truth, the whole truth and nothing but the truth. Did you understand that oath?
A. I did.
Q. Back to my question concerning messages concerning Zyprexa to the audiences. Do you have the responsibility when you send messages and this valuable information which the audiences may need to

know, do you have the responsibility to tell those audiences the truth and the whole truth?

Bandick, Michael (June 9, 2006)
119:1-10
Issues: 01 Plaintiff's Trial Designation

Q. Do you have that responsibility?
A. We have the responsibility to be truthful and accurate. And I'm not sure how to understand your question about the whole truth. That to me, I don't make that distinction. That's something that I would defer to, to a legal expert, which I'm not, but we do have the responsibility to be truthful and accurate.

Bandick, Michael (June 9, 2006)
123:4-12
Issues: 01 Plaintiff's Trial Designation

Q. Do you have the responsibility to tell the whole truth?
A. I'd have to understand the context of your question because --
Q. In the context of your job as the Director of Marketplace Management when you provide information concerning Zyprexa do you have the responsibility to tell the whole truth?

Bandick, Michael (June 9, 2006)
123:15-126:9
Issues: 01 Plaintiff's Trial Designation

A. The best way I can answer your question is to say that in the context of being accurate and truthful we had also the responsibility not to provide false or misleading information.

But I don't know how to answer your question. I, honestly -- I did not make that distinction. It was something that, truthful was something that we abided by.
Q. I understand. You've given me that answer. Let me see if I can help you about the whole truth. If I told you I have

a car, you understand what I'm saying? I have a car.

A. Yes, I understand.

Q. That's true, all right? But if I knew -- and I said I'm going to loan you my car because you needed to borrow a car. Are you with me so far?

A. Yes, I am.

Q. Okay. And you said to me, can I drive it from Indianapolis to Louisville, Kentucky, I'd like to do that? All right? Are you with me so far?

A. Yes, I am.

Q. And I throw you the keys. Are you with me?

A. I am.

Q. So I told you I have a car. I told you you can borrow my car. And you're getting in the car and you're going to drive it from Indianapolis to Louisville in Kentucky. Are you with me so far?

125: A. Yes, I am.

Q. You look at the gas gauge before you leave and it says it's full. Are you with me?

A. Yes.

Q. You're 20 miles down the road and you run out of gas. Are you with me?

A. Yes.

Q. But the gauge never moved and it said it was full when you left, right?

A. That's what you said.

Q. Right. Well, had I lied to you at any point during the process?

A. I don't know.

Q. Well, it didn't sound like it. I told you I had a car. You could drive it from Indianapolis down to Louisville, Kentucky. I threw you the keys and you drove off and you saw the gas gauge on full, right?

A. That was your hypothesis.

Q. Right. I told you the truth, I just didn't tell you all the truth. I forgot to tell you and I didn't tell you that when my gas gauge says it's full there may be

126: only one gallon left. Are you with me so far?

A. Yes, I am.

Q. Now, back to my question. Do you have the responsibility to tell the truth about the drug product, right?

A. Yes.

Q. Do you have the responsibility to tell the whole truth?

Bandick, Michael (June 9, 2006)
126:12-17
Issues: 01 Plaintiff's Trial Designation

126:12 A. As I said before, without
13 specific context that's going to be
14 difficult. You could have told me -- you
15 didn't tell me that the car was blue, either.
16 Q. That's your best answer?
17 A. That's my best answer.

Bandick, Michael (June 9, 2006)
126:20-127:7
Issues: 01 Plaintiff's Trial Designation

126:20 Q. Okay. Are there segments
21 within markets?
22 A. There can be.
23 Q. What's a market?
24 A. Broadly defined, it would be
127: 1 a group of customers or potential customers
2 for whom a product would be appropriate.
3 Q. A market is customers or
4 potential customers for whom a product would
5 be appropriate. And within markets there can
6 be segments; is that correct?
7 A. Yes.

Bandick, Michael (June 9, 2006)
127:9-21
Issues: 01 Plaintiff's Trial Designation

127: 9 let me rephrase the question. Can you
10 describe to the jury, please, sir, what
11 markets did Eli Lilly market Zyprexa to?
12 A. Primarily, physicians who
13 could be either in psychiatry or other
14 specialties. Would you like me to --
15 Is that a satisfactory answer
16 to you?
17 Q. Well, my question was what
18 markets did Lilly market Zyprexa to and your
19 answer was, primarily, psychiatrists or other
20 physicians. And so, no, it's not a
21 satisfactory answer.

Bandick, Michael (June 9, 2006)
127:24-129:20
Issues: 01 Plaintiff's Trial Designation

127:24
128: 1 THE WITNESS: Could you rephrase it, please?
2 QUESTIONS BY MR. ALLEN:
3 Q. I didn't ask "primarily", I
4 asked this question, "to what markets did
5 Lilly market Zyprexa to?
6 A. Psychiatrists, primary care
7 physicians. I can't think of any others.
8 Q. What about patients?
9 A. As I mentioned, I would
10 consider them as a separate audience and I
11 understood your question to be something more
12 specific to a customer group.
13 Q. Well, let me ask this, aren't
14 patients your ultimate market for all of your
15 drug products?
16 A. No.
17 Q. They're not. Is that right?
18 A. No. That's correct.
19 Q. Okay. Aren't patients your
20 most important customers for your drug
21 products?
22 A. Patients are very important.
23 I don't know how to say they're more
24 important than another.
129: 1 Q. Okay. Can you think of
2 anybody that's more important -- let me
3 rephrase that. Can you think of anybody
4 that's more of an important customer for your
5 drug products than patients?
6 A. I can't think of anything
7 that's more important than patient safety but
8 I would say that physicians having the
9 responsibility to prescribe the medications
10 also represent an extremely important market
11 and I wouldn't distinguish between those two.
12 Q. Okay. The two most important
13 markets for your products are patients and
14 customers, excuse me, patients and doctors;
15 is that correct?
16 A. Yes.
17 Q. Okay. So you better be
18 truthful, accurate, fair, balanced, not
19 withhold information, and don't make
20 misrepresentations to them, correct?

Bandick, Michael (June 9, 2006)
129:23-130:12
Issues: 01 Plaintiff's Trial Designation

129:23 A. I would say that we need to
24 be truthful and accurate in all of our
130: 1 characterizations.
2 Q. What about fair and balanced?

A. Fair and balanced [illegible]o an obligation.
Q. How about not lying to them?
A. That's part of truthful.
Q. How about not withholding important information?
A. It depends on how you would define "important information."
Q. Which word do you not understand about important information?

Bandick, Michael (June 9, 2006)
130:15-133:14
Issues: 01 Plaintiff's Trial Designation

130:15 A. I understand all the words.
Q. You understand all the words?
A. I do.
Q. You agree you shouldn't withhold important information from doctors and patients about a drug product and in this case in particular Zyprexa?
A. That's not what I said.
Q. Okay. Well, then I'll ask you another question. Do you agree you
131: 1 shouldn't withhold important information from doctors and patients about Zyprexa?
A. Without a specific reference to what you might mean by important information I'm not sure how to answer your question.
Q. Thank you.
Now you said the doctors to whom you market the products are psychiatrists and primary care physicians; is that correct?
A. Yes.
Q. Tell the jury what primary care physicians are?
A. Primary care physicians are comprised of family practice, general practice, and internal medicine. And they see patients of all ages on a wide variety of health issues.
Q. There are other primary care physicians, are there not?
A. Not that I'm aware of.
Q. Okay. So when you use the term "primary care physicians" in reference
132: 1 to the marketing of Zyprexa, to you, at least today under oath, it means family practitioners, general practitioners and doctors of internal medicine, correct?
A. Yes.

Q. How about pediatr[illegible]ans?
A. I would consider pediatrician a specialty, that's why I didn't mention it.
Q. How about obstetrician and gynecologist?
A. Also a specialty.
Q. Did Lilly, at any time, to your knowledge, market Zyprexa to pediatricians?
A. Not to my knowledge.
Q. Did Lilly, at any time, to your knowledge, market Zyprexa to obstetricians and gynecologists?
A. Not to my knowledge.
Q. Did pediatricians, excuse me, did Lilly at any time market Zyprexa to gerontologists?
A. To gerontologists?
Q. Yes, sir?
133: 1 A. Within my role in Zyprexa primary care we did not, I don't know, I can't say with certainty whether we would have marketed to a gerontologist for any reason.
Q. Okay. That's fair. That's all I asked.
Now we've talked about markets and market segments. We talked about doctors and you said they're psychiatrists and primary care physicians and you've defined primary case physicians, correct, thus far?
A. Yes.

Bandick, Michael (June 9, 2006)
135:5-17
Issues: 01 Plaintiff's Trial Designation

135: 5 Are there segments within the patient market?
THE WITNESS: Are we talking specific to Zyprexa or are we talking broadly?
MR. ALLEN: Let's talk broadly first.
A. Yes, there are.
Q. We've got that established. We've got segments within the patient market.
With regard to Zyprexa are there segments within the patient market?
A. Yes.

Bandick, Michael (June 9, 2006)

142:13-143:3
Issues: 01 Plaintiff's Trial Designation

142:13 Q. Okay. Well, who did, who
14 did -- let me ask this: Who did you market
15 to such that Zyprexa would hopefully make its
16 way for a schizophrenic patient?
17 A. Psychiatrists and primary
18 care physician.
19 Q. Okay. Now other than
20 marketing to psychiatrists and primary care
21 physicians for the treatment of
22 schizophrenia, and to, I guess, psychiatrists
23 and primary care physicians for the treatment
24 of bipolar disease and/or marketing Zyprexa
143: 1 to patients with bipolar disease, did you
2 have any other markets in the doctor and/or
3 patient community for Zyprexa?

Bandick, Michael (June 9, 2006)

143:6-13
Issues: 01 Plaintiff's Trial Designation

143: 6 A. If your question is outside
7 of patients with bipolar disorder,
8 psychiatrists, and primary care physicians
9 who would treat patients with schizophrenia
10 and bipolar disorder, did we have any other
11 markets among patients and physicians to whom
12 we marketed Zyprexa, I would say not that I'm
13 aware of.

Bandick, Michael (June 9, 2006)

148:7-149:18
Issues: 01 Plaintiff's Trial Designation

148: 7 Q. You told us the doctors and
8 the patients to whom Zyprexa is marketed.
9 You've told us that, right?
10 A. Yes.
11 Q. And you've given us your best
12 testimony under oath, correct?
13 A. Yes.
14 Q. Okay. So I guess it's your
15 testimony here today that Lilly did not try
16 to market Zyprexa to Donnas; is that true?
17 A. What do you mean by "Donnas"?
18 Q. Do you not know that?
19 A. I'm not sure what you mean by
20 it.
21 Q. Thank you.

I guess it's your best testimony under oath today that Lilly did not try to market Zyprexa to Marks?
A. I don't know what you mean by that.
Q. Okay. I guess it's your best testimony under oath here today that Lilly did not try to market Zyprexa to Marthas?
A. I don't know what you mean by that.
Q. I guess it's your best testimony under oath here today that Lilly did not try to market Zyprexa to Christines; is that correct?
A. I don't know what you mean by your question.
Q. Okay. My questions are totally foreign to you about Donna, Martha, Mark, Christine, you just don't understand?
A. I don't understand what you want me to answer.

Bandick, Michael (June 9, 2006)
151:17-22
Issues: 01 Plaintiff's Trial Designation

here it is. Did Lilly market Zyprexa as a mood stabilizer?
A. Upon receiving approval for bipolar disorder, and mood stabilizers being a general label for products that would treat bipolar, yes, it did.

Bandick, Michael (June 9, 2006)
152:4-7
Issues: 01 Plaintiff's Trial Designation

Q. So the answer to my question is, yes, Lilly marketed Zyprexa as a mood stabilizer, is that right?
MR. HAMMERLE: I'd object as

Bandick, Michael (June 9, 2006)
152:11-154:11
Issues: 01 Plaintiff's Trial Designation

A. If your question is did Lilly at some point market Zyprexa as a mood stabilizer, I would say yes.
Q. Thank you. Did Lilly market

Zyprexa for use in treating symptoms of mood?
A. No.
Q. Did Lilly market and/or promote Zyprexa for treatment of symptoms of anxiety?
A. No.
Q. Did Lilly market and/or promote Zyprexa for the treatment of symptoms of depression?
A. No.
Q. Did Lilly market Zyprexa or promote Zyprexa for the treatment of Alzheimer's?
A. No.
Q. Did Lilly market and/or promote Zyprexa for the treatment of behavioral disorders?
A. No.
Q. Did Lilly market or promote Zyprexa for the treatment of behavioral disorders associated with Alzheimer's?
A. No.
Q. Did Lilly market or promote Zyprexa for the treatment of symptoms of dementia?
A. No.
Q. Did Lilly market or promote Zyprexa for the treatment of decline in cognitive function related to Alzheimer's?
A. No.
Q. Did Lilly market and/or promote Zyprexa for the treatment of children with attention deficit disorder?
A. No.
Q. Did Lilly market or promote Zyprexa for the treatment of nausea?
A. No.
Q. Did Lilly market or promote Zyprexa for the treatment of irritability symptoms?
A. No.
Q. Did Lilly market or promote Zyprexa for thought disorders in nonpsychotic patients?
A. No.

Bandick, Michael (June 9, 2006)
154:12-14
Issues: 01 Plaintiff's Trial Designation

Q. Did Lilly market or promote Zyprexa for the treatment of symptoms?
A. No.

Bandick, Michael (June 9, 2006)
164:9-14
Issues: 01 Plaintiff's Trial Designation

164: 9 Q. Okay. Sir, are there legal
10 and regulatory limitations on how a
11 pharmaceutical company, in this case Lilly in
12 particular, can market a particular drug
13 product?
14 A. Yes, there are.

Bandick, Michael (June 9, 2006)
164:20-165:8
Issues: 01 Plaintiff's Trial Designation

164:20 Do you agree that Lilly
21 cannot actively promote and/or market Zyprexa
22 outside of the FDA approved indications on
23 the label?
24 A. Yes. I agree that Lilly
165: 1 cannot promote Zyprexa outside of the
2 approved indication on its label. There are
3 opportunities to share data that might fall
4 outside of that.
5 So when you said promote and
6 market, I'm dividing the two, and I would say
7 it's true that Lilly would not be promoting
8 Zyprexa outside of its approved label.

Bandick, Michael (June 9, 2006)
165:17-166:5
Issues: 01 Plaintiff's Trial Designation

165:17 Q. Can Lilly market Zyprexa
18 outside the indications on the label?
19 A. Under specific circumstances
20 and guidelines Lilly can share data that is
21 outside that. And so, I wouldn't define that
22 as marketing, per se, but it can come through
23 the form of a sales organization or through a
24 marketing department, but it would be
166: 1 governed by specific guidelines as to what is
2 and isn't appropriate dissemination of that
3 clinical data.
4 Q. Where would I find those
5 guidelines?

Bandick, Michael (June 9, 2006)
166:8-11

Issues: 01 Plaintiff's Trial Designation

166: 8 Q. Where would I find those
9 guidelines?
10 A. I don't know exactly where to
11 point you at this point.

Bandick, Michael (June 9, 2006)

167:14-168:15
Issues: 01 Plaintiff's Trial Designation

167:14 Q. Now, sir, you said there's
15 some guidelines concerning marketing outside
16 the label. You said that, right?
17 A. I said there was some
18 guidelines for disseminating data outside of
19 the label.
20 Q. What do you call those
21 guidelines?
22 A. Well, in general, the
23 guidelines that the company follows are
24 called good promotional practices or GPP.
168: 1 There can be other specific guidelines for
2 that dissemination of data, and I don't, I
3 don't know where to point you to to look
4 those up.
5 Q. Well, and I appreciate that
6 answer if you just don't remember, but I
7 would assume as the Brand Manager and as the
8 Director of Marketplace Management you would
9 frequently refer to the GPPs, would you not?
10 A. Yes, I would.
11 Q. Okay. Were they kept in the
12 marketing department?
13 A. I had access to a copy of
14 them. I don't know what might have existed
15 in other areas.

Bandick, Michael (June 9, 2006)

169:1-172:3
Issues: 01 Plaintiff's Trial Designation

169: 1 Q. Okay. Can Lilly under FDA
2 regulations or the GPP direct the Zyprexa
3 sales force to actively proceed to a
4 physician's office on a routine sales call
5 and promote Zyprexa for the treatment of
6 symptoms?
7 A. No.
8 Q. Why not?
9 A. Company policy is clear on

the fact that all promotion will be within the approved label and the indications that follow from that.

Q. So the company policy is clear that all promotion of drug products, including Zyprexa, must be within the approved indications on the product's label, correct?

A. For promotional activities, that's correct.

Q. Okay. What's the difference between promotion and marketing?

A. Well, I was distinguishing between promotional activities and nonpromotional activities. I would say that the promotional activities can be part of what a marketing team assists with but I don't see them as an either/or, the difference in my mind is what's promotional and what's nonpromotional.

Q. Okay. What's the difference between promotional and nonpromotional activities?

A. Promotional activities are those that are on label and are for approved indications. Nonpromotional activities can include a wide range of interactions with clinicians. It can involve clinical data that may not be, may or may not be part of the current label. And it can involve responses to questions that are potentially outside of the label.

So that's how I would distinguish between promotional and nonpromotional.

Q. Can Lilly provide data as part of its promotional activities to a physician concerning clinical study information on Zyprexa for nonindicated uses of Zyprexa?

A. Yes, with very specific guidelines for how that discussion takes place.

Q. Tell the jury what the specific guidelines are.

A. There may be others who can describe it better than me but my recollection of how we trained sales representatives to handle situations like that was to make very clear when the discussion involved off-label information, either because it was in response to a question or at a specific time in the call there was a, an indication from the sales representative that we were now going to be in a different part of the discussion, so that would be considered a stop sign for

promotional activity and then would transition into nonpromotional.

Q. Okay. So, if at any time a Lilly sales representative would discuss off-label uses of the product they were supposed to and, in fact, were required by law and by GPP at Lilly to inform the physician "that I'm now discussing off-label uses."

Bandick, Michael (June 9, 2006)

172:6-13

Issues: 01 Plaintiff's Trial Designation

A. There were other, there are other ways that that could occur in a call. It could be in response to a question. But Lilly sales representatives were trained to be very clear as to what the approved indications were and if there was content or material outside of that to acknowledge it as such.

Bandick, Michael (June 9, 2006)

173:8-174:9

Issues: 01 Plaintiff's Trial Designation

Q. Okay. Let me ask this: Did Lilly promotional materials ever discuss off-label uses of Zyprexa?

A. A promotional material is, by definition, going to have limitations specific to its approved indications.

Q. Okay.

A. There can be other materials that I would say fall outside of promotional materials.

Q. I understand what you're saying but I think, I want to get my question answered, did Lilly promotional materials for Zyprexa ever discuss, recommend, off-label uses for Zyprexa?

A. For what I'm defining as promotional materials, no, I can't think of any examples when it did.

Q. Why not?

A. As I said, by definition promotional material would be that which is limited to the approved indications.

Q. Why?

A. That was the definition and understood guidelines around the regulations

for that type of promotional activity.

Bandick, Michael (June 9, 2006)
180:18-18
Issues: 01 Plaintiff's Trial Designation

180:18 A. As we've discussed.

Bandick, Michael (June 9, 2006)
194:20-195:5
Issues: 01 Plaintiff's Trial Designation

194:20 Q. **Back to my question. Would**
21 **you consider the Zyprexa sales force part of**
22 **the tool of the marketing department in the**
23 **marketing of Zyprexa?**
24 A. Part of the tool. I would
195: 1 consider it a channel.
2 Q. **Okay. Tell the jury what you**
3 **mean by channel.**
4 A. There are a number of
5 different ways in which --

Bandick, Michael (June 9, 2006)
195:16-198:6
Issues: 01 Plaintiff's Trial Designation

195:16 A. The sales force was a channel
17 for marketing in the U.S. Other channels
18 included things like direct-to-physician
19 advertisement as you mentioned. There may be
20 others.
21 Q. **Okay. Fine. When you said**
22 **the sales force was a channel for the**
23 **marketing of Zyprexa, what did you mean by**
24 **that, that statement alone?**
196: 1 A. As we were discussing earlier
2 about delivering messages and effectively
3 conveying a concept, the sales force would be
4 one channel, one carrier, one conveyor of
5 those messages or concepts to an audience, in
6 this case physicians.
7 Q. **Okay. So the sales force**
8 **delivered messages and concepts concerning**
9 **the proper prescription and use of Zyprexa to**
10 **physicians?**
11 A. Yes.
12 Q. **That was one of their main**
13 **roles?**
14 A. Yes.

Q. One of their roles to help in the marketing of Zyprexa was help to deliver samples, was it not?
A. That's correct.
Q. One of their roles in the marketing of Zyprexa was to determine physician attitudes and report those back to the company?
A. We sometimes got that feedback but we relied on other means to collect or solicit that information more formally.
Q. One of the marketing roles of the Zyprexa sales force was to overcome obstacles presented by the doctors when they would ask questions about Zyprexa?
A. That's a phrase that is used in sales training as a way to help direct a sales representative in the context of a call.
Q. One of the roles of the Zyprexa sales force in the area of marketing was to accurately respond to doctor's questions concerning the risk of Zyprexa?
A. That's correct.
Q. One of the roles of the Zyprexa sales force was to accurately convey to the doctors the approved indications by the FDA for Zyprexa?
A. That's correct.
Q. Another tool or channel for Zyprexa marketing was continuing medical education sponsored activities?
A. The key word being sponsored. The Zyprexa team didn't create that content but did provide funding for certain activities in accordance with regulations or in CME.
Q. Everything you did was in accordance with regulations?

Bandick, Michael (June 9, 2006)
198:9-199:1
Issues: 01 Plaintiff's Trial Designation

Q. Is that right? In regard to CME?
A. We were very careful to follow the rules and regulations of whatever the activity was.
Q. In all respects in regard to Zyprexa marketing?
A. As far as I know.
Q. Okay. Another tool or

channel for the marketing of Zyprexa was the development of publication plans?

A. In conjunction with our medical group, that's true.

Q. Another tool or channel in the marketing of Zyprexa was the development of a speaker's bureau?

A. Yes, that's true.

Bandick, Michael (June 9, 2006)
200:24-202:11
Issues: 01 Plaintiff's Trial Designation

to my question. Part of the tool or channels of marketing for Zyprexa was Lilly giving money to medical organizations?

A. There were medical associations that received that type of funding, yes.

Q. As part of the marketing activities for Zyprexa from Eli Lilly?

A. Yes.

Q. And it was part of the Eli Lilly marketing department's budget to allocate monies to medical organizations and/or associations?

A. I don't know if that was part of the marketing group's budget or not.

Q. You just know it's part of the marketing activities?

A. Typically, funds that were assigned to medical associations would be more for clinical, that types of activities. Again getting back to who holds the budget I don't recall there being dollars from marketing that went to medical associations. It's possible, I don't know.

Q. Tell the jury, please, those medical organizations or associations to whom money was given as part of the channel or tool in the marketing of Zyprexa?

A. The only two associations that come to mind are the American Psychiatric Association and the American Diabetes Association.

Q. How many millions of dollars was given to those organizations over the period of let's say 1995 to 2004 at the time you left?

Bandick, Michael (June 9, 2006)
202:14-22
Issues: 01 Plaintiff's Trial Designation

202:14 A. I don't have any idea.
15 Q. It was millions, wasn't it?
16 A. I can't confirm that.
17 Q. Do you think it was in the
18 millions?
19 A. I don't know.
20 Q. Do you have any idea?
21 A. I don't.
22 Q. Thank you.

Bandick, Michael (June 9, 2006)
203:18-24
Issues: 01 Plaintiff's Trial Designation

203:18 Q. Concerning tools and/or
19 channels involved in the marketing of
20 Zyprexa, you told us about the sales force,
21 advertising, CME sponsored event, publication
22 plans, speaker's bureaus and grants and
23 honoraria to medical organizations or
24 associations, right?

Bandick, Michael (June 9, 2006)
204:3-11
Issues: 01 Plaintiff's Trial Designation

204: 3 A. I talked about a couple of
4 associations, neither of those were in
5 conjunction with primary care, but I believe
6 elsewhere within Zyprexa that may have been
7 appropriate.
8 The only other channel or
9 tool that I would add to your list would be
10 in the area of direct-to-physician or
11 peer-to-peer programming.

Bandick, Michael (June 9, 2006)
204:15-205:16
Issues: 01 Plaintiff's Trial Designation

204:15 Q. Oh, by the way, you agree
16 that the CME courses are, it's what they
17 stand for, continuing medical education, are
18 generally directed at doctors, right?
19 A. They're directed at doctors.
20 Q. Right. And medical
21 publications are generally directed at
22 doctors, right?

A. Generally.
Q. Sales force is generally directed at doctors, correct?
A. Generally.
Q. Marketing materials are generally directed at doctors, correct?
A. Yes.
Q. Medical organizations are made up of doctors and they provide information to doctors, correct?
A. As we were talking about medical associations, yes, that's what I understand them to do.
Q. Okay. And, of course, the package insert or the label that's included, among other places, in the PDR is directed at doctors as well as patients, correct?
A. Primarily, directors.

Bandick, Michael (June 9, 2006)

206:19-208:8

Issues: 01 Plaintiff's Trial Designation

Q. Now, doctors receive information concerning Zyprexa from the package insert, correct?
A. Yes.
Q. Doctors receive information concerning the benefits and risks of Zyprexa from peers and educators?
A. Yes.
Q. Doctors receive information concerning the benefits and risks of Zyprexa from publications?
A. Yes.
Q. Doctors receive information about the benefits and risks of the product from the sales force?
A. From the Lilly sales force, yes.
Q. Doctors receive information about the benefits and risk of the product from marketing materials?
A. Yes.
Q. Doctors receive information about the benefits and risks of Zyprexa from continuing medical education courses?
A. Yes.
Q. And doctors receive information about Zyprexa from medical organizations such as the American Diabetes Association and the American Association of Clinical Oncology -- Endocrinology?
A. As two examples, yes.

Q. Okay. I'm going to show you exhibit -- oh, and by the way, doctors, you knew that doctors would then pass along or could pass along or may pass along that information they learned from those sources to the patient?
A. That's possible.

Bandick, Michael (June 9, 2006)
208:9-16
Issues: 01 Plaintiff's Trial Designation

Q. Right. And, of course, each one of those I talked about, the package insert, peers and educators, publications, sales force, marketing materials, CME and medical organizations were all used as channels and/or tools by the marketing department at Eli Lilly to market Zyprexa, correct?

Bandick, Michael (June 9, 2006)
208:19-22
Issues: 01 Plaintiff's Trial Designation

Mr. Allen?
A. I was looking at your exhibit here. Could you repeat your question, please?

Bandick, Michael (June 9, 2006)
208:23-209:18
Issues: 01 Plaintiff's Trial Designation

(Whereupon, Deposition Exhibit(s) 2 duly received, marked and made a part of the record.)
QUESTIONS BY MR. ALLEN:
Q. Yes. Exhibit No. 2, we have the doctor. Lilly's on the top, right?
A. On this document, yes.
Q. And then we have various sources, the doctor's right there in the middle and we have the sources we discussed, we have the medical organization, the package insert, the peers and educators, the publications, the sales force, the marketing materials, and the CME, are all places where the doctor gets information, right?
A. Those are all places where

Q. And they're also all tools and channels Eli Lilly used in the marketing of Zyprexa, correct?

Bandick, Michael (June 9, 2006)

209:24-210:18

Issues: 01 Plaintiff's Trial Designation

209:24 A. Each of those are channels
210: 1 through which certain types of information
2 could be provided.
3 Q. And, in fact, was provided by
4 Eli Lilly?
5 A. Different types of
6 information would appear in different
7 channels but each of these, in some form,
8 were used by Zyprexa, yes.
9 Q. Okay. And you said that the
10 doctor would take that information and could
11 or might, convey to the patient, right?
12 A. It's possible.
13 Q. Therefore, when Eli Lilly
14 used those tools and channels, such as
15 publications or CME courses, it is important
16 for Eli Lilly to be truthful, accurate, fair,
17 and balanced, and to tell the whole truth,
18 correct?

Bandick, Michael (June 9, 2006)

211:8-11

Issues: 01 Plaintiff's Trial Designation

211: 8 For purposes of publications
9 that was clinical trial data. And yes, it
10 would be important to be accurate and
11 truthful about the portrayal of those data.

Bandick, Michael (June 9, 2006)

213:9-215:10

Issues: 01 Plaintiff's Trial Designation

213: 9 I assume you have a drug
10 product, in this case, Zyprexa, would you
11 like it to have a bigger market or a smaller
12 market?
13 A. Well, in the case of Zyprexa,
14 the market got bigger as we expanded the
15 label and that was seen as a positive.
16 Q. You mentioned that several

communicating. In 1996, when the product was approved, being Zyprexa, it was indicated for schizophrenia, correct?

A. The actual language was a little different. It later was focused on schizophrenia, yes.

Q. So you and I are communicating and you agree with me?

A. I agree that it started with some language that later was narrowed to schizophrenia.

Q. Okay. And then I believe it was the fall of 2000, if I'm correct, that the indication was added bipolar mania; is that correct?

A. I believe that was March of 2000.

Q. March of 2000, thank you very much.

And tell this journey any other indications besides schizophrenia and bipolar mania that were ever added and approved by the FDA for Zyprexa?

A. I don't recall the date, but later, after March of 2000, there was a broadening of the bipolar indication to include maintenance, bipolar maintenance.

Q. So the three FDA approved indications for Zyprexa since it's been on the market are schizophrenia, bipolar mania and bipolar mania maintenance, correct?

A. Bipolar maintenance.

Q. Okay. Any other indications approved by the FDA other than those you just identified?

A. Not that I'm aware of.

Q. Okay. Now, in the case of Zyprexa, did you want a psychiatric only market or did you, you being Eli Lilly, want a larger market than the psychiatric physician market?

Bandick, Michael (June 9, 2006)
216:7-217:2
Issues: 01 Plaintiff's Trial Designation

A. We were looking for markets that treated the psychiatric illnesses for which Zyprexa was indicated. The first market we went into is psychiatry but later determined that it would be appropriate to pursue a primary care market for those same psychiatric illnesses.

218:13 A. As with your previous example
14 I don't consider those to be comparable.
15 Q. And why aren't they
16 comparable?
17 A. For the same reason that I
18 stated before.
19 Q. And that is, Zyprexa as a
20 drug for the elderly patient with symptoms of
21 dementia is not an FDA-approved indication,
22 correct?
23 A. That's correct.
24 Q. And one that it would be
219: 1 illegal and improper for Lilly to promote?

Bandick, Michael (June 9, 2006)
219:4-15
Issues: 01 Plaintiff's Trial Designation

219: 4 Q. Correct?
5 A. Consistent with company
6 policy we would not promote the product for
7 unapproved indications or things that fell
8 outside the label.
9 Q. And would promoting Zyprexa
10 for the elderly patient with symptoms of
11 dementia be illegal and outside company
12 policy?
13 A. It would be inconsistent with
14 company policy to promote for something that
15 fell outside of the approved indications.

Bandick, Michael (June 9, 2006)
219:20-23
Issues: 01 Plaintiff's Trial Designation

219:20 Q. Would it be illegal and
21 improper and outside Lilly's policies to
22 promote Zyprexa for the elderly patient with
23 symptoms of dementia?

Bandick, Michael (June 9, 2006)
220:3-12
Issues: 01 Plaintiff's Trial Designation

220: 3 A. It would be inconsistent with
4 Lilly company policy to promote Zyprexa for
5 the patient type that you just described.
6 Q. Thank you very much.
7 If you were able and chose to

promote to young mothers with symptoms of anxiety and irritability for Zyprexa that would be a much larger market than promoting to the antipsychotic drug market for the diagnosis of schizophrenia, wouldn't it?

Bandick, Michael (June 9, 2006)
220:15-22
Issues: 01 Plaintiff's Trial Designation

A. I can't speak to the size of that market.
Q. Which market?
A. Mothers with symptoms of anxiety that you just described.
Q. You all never looked into that? You all being the marketing department?

Bandick, Michael (June 9, 2006)
221:1-4
Issues: 01 Plaintiff's Trial Designation

A. I'm not aware of any analysis of the patient type that you just described.
Q. You're not?
A. No.

Bandick, Michael (June 9, 2006)
221:13-23
Issues: 01 Plaintiff's Trial Designation

Q. What about Donna?
A. I don't understand your question.
Q. Okay. What about Martha?
A. What would you like to know?
Q. You all promoted to Martha, didn't you?
A. No, we did not promote to Martha.
Q. You promoted to Donna, didn't you?

Bandick, Michael (June 9, 2006)
236:10-237:8
Issues: 01 Plaintiff's Trial Designation

236:10 Are you married?
11 A. Yes.
12 Q. Your wife is Mary?
13 A. Marcie.
14 Q. Marcie. That's my
15 handwriting I can't read.
16 Can you tell the jury where
17 Marcie works?
18 A. Marcie works for Eli Lilly
19 and Company.
20 Q. How long has Marcie worked
21 for Eli Lilly?
22 A. Approximately, 15 years.
23 Q. What department is she in?
24 A. Human resources.
237: 1 Q. And what's her title in human
2 resources?
3 A. She is a Human Resources
4 Director.
5 Q. And is she therefore, in
6 management?
7 A. Yes, I think you can
8 characterize that as a management role.

Bandick, Michael (June 9, 2006)

242:12-16

Issues: 01 Plaintiff's Trial Designation

242:12 Okay. You left your
13 employment with Lilly. How would you
14 characterize you leaving, did you resign or
15 were you fired?
16 A. I resigned.

Bandick, Michael (June 9, 2006)

244:24-245:22

Issues: 01 Plaintiff's Trial Designation

244:24 Q. You said you resigned, right?
245: 1 A. I did.
2 Q. Did somebody ask you to
3 resign?
4 A. I was given the choice.
5 Q. Of resign or be fired?
6 A. Or -- yes.
7 Q. Okay. Who gave you the
8 choice of either resigning or being fired?
9 A. Diedre Connelly and Dan
10 Hasler.
11 Q. Tell me -- I didn't hear the
12 name?

A. Diedre Connelly and Dan Hasler.
Q. Tell the jury Diedre Connelly's title, please?
A. She was the head of the human resources function. I don't know her exact title.
Q. And who is Dan Hasler?
A. He is VP of Global Marketing.
Q. Why were you fired?

Bandick, Michael (June 9, 2006)
246:5-247:8
Issues: 01 Plaintiff's Trial Designation

246:
Q. Why were you given this option of resigning or being fired?
A. The company felt that my involvement in some activities with a third-party consultant had been handled inappropriately and concluded that that was grounds for the decision that I reached.
Q. Who was the third-party consultant?
A. It was a communications vendor that we had used as part of our activities.
Q. Who's the communications vendor?
A. The name of the company is Nichols Dezzinhall.
Q. And you used them as part of your activities. Are you saying you used them as part of your activities in relation to Zyprexa?
247:
A. Yes.
Q. And what activity did you engage in with this communications company, and tell me their name again, Nichols -- see, I didn't get it. Can you tell this jury and me again, please, the name of this communications company?
A. Nichols Dezzinhall.

Bandick, Michael (June 9, 2006)
247:19-22
Issues: 01 Plaintiff's Trial Designation

247:19
Where's Nichols Dezzinhall located? Where are they located?
A. I believe Nichols Dezzinhall is headquartered in Washington, D.C.

Bandick, Michael (June 9, 2006)
248:8-16
Issues: 01 Plaintiff's Trial Designation

248: 8 Q. What did Nichols Dezzinhall
9 from Washington, D.C., do for Lilly with
10 regard to Zyprexa?
11 A. They helped to identify
12 people who wrote articles that were then
13 offered for the lay media print and
14 electronic that were consistent with the
15 views that the Zyprexa team had on various
16 subjects.

Bandick, Michael (June 9, 2006)
250:7-253:1
Issues: 01 Plaintiff's Trial Designation

250: 7 Q. I'm going to find out what
8 Dezzinhall did. I'm trying to find out. I
9 have no idea what you just said. I want you
10 to explain to me and this jury what it is
11 Dezzinhall did for Zyprexa?
12 A. We used them to identify
13 individuals who would author articles,
14 typically, op ed types of articles, that
15 would be offered for placement in the lay
16 media, print and electronic, on subjects that
17 we, that were views that were consistent with
18 what Lilly held on certain subjects. Issues
19 in the marketplace that I can try to describe
20 for you. But I just want to make sure I'm
21 giving you enough clarity with that part and
22 if you are clear there then I can go on.
23 Q. Yeah, I'm clear so far I
24 think. But let's go on. Then what else did
251: 1 they do?
2 A. Well, it was in that context
3 that they, like I said, they found
4 individuals who would write articles and,
5 typically, these would be on marketplace
6 issues that were germane to Zyprexa and the
7 marketing of antipsychotics.
8 Q. So all Dezzinhall, am I
9 pronouncing that correctly?
10 A. Dezzinhall.
11 Q. All Dezzinhall did was just
12 locate authors for these articles? That's
13 all they did?
14 A. They were also involved in
15 the actual offering of the pieces. They

worked directly with the media. That's not something that we did.

Q. Well, did Dezzinhall, actually, write the pieces and then try to find a person who would put their name on it as the author?

A. No, it was the other way around. They found the individuals who would author the articles.

Q. Is there a Dezzinhall file that you kept there at Lilly?

A. There may be. It wasn't something that I would have a lot of content for. There was a short time that I was involved in the, in that relationship, and most of the interactions that we had were teleconferences. So there may be a file, I don't recall.

Q. Who were your Dezzinhall contacts?

A. Well, the principal, the principal's name is Eric Dezzinhall. There was an account executive, it was a woman, I'm not recalling her name.

Q. You said most of your contact with them was in teleconferences?

A. That's true.

Q. You indicated that the reason you were given this choice of resign or be fired was that these activities you described with Dezzinhall -- was it one particular event in particular, or was it a series of events that led to this choice of being fired or resigned?

Bandick, Michael (June 9, 2006)

253:3-254:7

Issues: 01 Plaintiff's Trial Designation

A. As it was explained to me, it had to do more broadly. There was not a single event that was cited.

Q. Were you the only person at Lilly that was in contact with Dezzinhall concerning the Zyprexa issue?

A. No.

Q. There's other people on these teleconferences and working with you on this Dezzinhall endeavor, weren't they?

A. Sometimes.

Q. Were they fired or had the choice to resign?

A. There were two other individuals who left the same week that I

did. I have not been in contact with them to confirm this but I believe it had to deal with the same topic.

Q. Their names are, sir?

A. Jack Jordan and Jeff Newton.

Q. Jack Jordan was your immediate supervisor in the Zyprexa chain.

A. At one time.

Q. Who is the other guy, Newton, Jack?

A. Jeff Newton.

Q. What was Jeff's title?

A. He was director in communications.

Bandick, Michael (June 9, 2006)
255:21-256:12
Issues: 01 Plaintiff's Trial Designation

Q. Okay. You were fired because of this.

A. I was not fired.

Q. I'm sorry, you resigned. What was the advantage of resigning as opposed to being fired? Was there a monetary advantage or what was the advantage?

A. It better reflected the terms on which I wanted to leave the company.

Q. Did you all have a written agreement when you left?

A. Yes.

Q. So over whatever event this is in Dezzinhall you have a written agreement with Lilly at the time you resigned as opposed to being fired, right?

Bandick, Michael (June 9, 2006)
256:14-257:10
Issues: 01 Plaintiff's Trial Designation

A. That's correct.

Q. Did it provide you compensation as part of that written agreement?

A. Yes.

Q. How much?

A. Approximately, eight months salary.

Q. How much is that?

A. Just over a hundred thousand dollars.

Q. Are you under any current

contract with Eli Lilly or any of their affiliates?
A. No.
Q. Are you being paid to be here today?
A. No, I'm not.
Q. What is it you did wrong? You described it -- what is it that they said you did wrong?

Bandick, Michael (June 9, 2006)
257:13-258:10
Issues: 01 Plaintiff's Trial Designation

257:13 A. There, as I understand it, was a, essentially, an evaluation or an assessment that that relationship had not been managed to the company's satisfaction. They felt that it, potentially, put them in an embarrassing situation, and as a result I was given that choice that I -- we talked about earlier.
Q. I understand that part of the answer. And what is it that put them in an embarrassing situation and what is it that they said you did wrong?
258: 1 A. It's difficult for me to tell you that it's not entirely clear to me, because there was not a dialog that we had about it. And so I'm generally aware of what the area was, but have not -- I don't have the specifics to share with you that -- I mean, you'd have to talk to them.
Q. I'm going to. But I'm asking you what you understand they said you did wrong?

Bandick, Michael (June 9, 2006)
258:14-18
Issues: 01 Plaintiff's Trial Designation

258:14 A. I've given you my best answer to that.
Q. You've given this jury your best answer?
A. Yes, I have.

Bandick, Michael (June 9, 2006)
259:5-20
Issues: 01 Plaintiff's Trial Designation

259: 5 Q. When you signed this deal,
6 you signed this contract that paid you just
7 over a hundred thousand dollars, you didn't
8 inquire as to what they said you did wrong?
9 A. As I indicated, it was not
10 entirely clear to me in specific terms. What
11 I can tell you is that it was evident that
12 the company had lost confidence in me, and at
13 that point it was in my best interest to move
14 on.
15 Q. I hear you. Let me ask you
16 this: Before that happened, had anybody at
17 any time come to you before you were asked to
18 either resign or be fired and ever complain
19 to you that you had done anything wrong in
20 your role in marketing Zyprexa?

Bandick, Michael (June 9, 2006)

260:1-261:17

Issues: 01 Plaintiff's Trial Designation

260: 1 A. I mean in terms of
2 materiality, I mean, I've got lots of
3 feedback there were certain things I could
4 have done better. I think the spirit of your
5 question is, is that had I done something
6 that had required disciplinary action or was
7 something of that magnitude, and the answer
8 to that is no.
9 Q. Okay. And I apologize, my
10 memory is short, you left in 2004, is it
11 April, you said?
12 A. Yes.
13 Q. And I appreciate the prior
14 answer about materiality. So what you were
15 saying to me is, "Mr. Allen, from 1995 when I
16 became involved in Zyprexa until April
17 of 2004 I was never disciplined or informed
18 by anybody at Eli Lilly that anything
19 material or important that I had ever done in
20 relation to my activities was wrong or
21 improper." Correct?
22 A. Yes, that's correct.
23 Q. And so it was in April
24 of 2004 that you were first informed from any
261: 1 source at Eli Lilly that you had allegedly
2 done anything wrong, right?
3 A. That's correct.
4 Q. And the person who first
5 informed you was named who?
6 A. There were two people, it was
7 Diedre Connelly and Dan Hasler.
8 Q. You said Diedre. Diedre,

probably, works for your wife?
A. No, she doesn't.
Q. She works in the same department?
A. She did.
Q. I don't want to talk about Diedre. But Diedre, that's human resources, they're always kind of their when you resign or get fired. It was this guy named Don?

Bandick, Michael (June 9, 2006)
261:20-262:1
Issues: 01 Plaintiff's Trial Designation

261:20 Q. Don or Dan -- what was his name?
A. The other person's name is Dan Hasler.
Q. Dan, he was the boss that was giving you your discipline, wasn't he?

Bandick, Michael (June 9, 2006)
262:4-12
Issues: 01 Plaintiff's Trial Designation

262: 4 THE WITNESS: I don't understand what you mean by "discipline."
QUESTIONS BY MR. ALLEN:
Q. Let me tell you, when Dan came to your office with the lady, Diedre, from human resources, did this come out of the clear blue to you or did you have some warning it was coming?

Bandick, Michael (June 9, 2006)
262:18-263:10
Issues: 01 Plaintiff's Trial Designation

262:18 Q. I'm sorry. Where did this meeting take place?
A. It took place in the conference room.
Q. You were summoned to the conference room?
A. I was.
263: 1 Q. On -- here at Eli Lilly?
A. It was at Lilly headquarters, yes.
Q. Okay. Did you have some

warning that you were fixing to have this choice or did it come out of the clear blue to you?

A. I did not know what the meeting was going to be about.

Q. And I understand that. But

Bandick, Michael (June 9, 2006)
265:4-21
Issues: 01 Plaintiff's Trial Designation

Q. Okay. Well, wow, my only question was before that meeting -- what day was that meeting? I bet you can give us the very day in April 2004 that meeting took place, can't you?

A. It was in the second week of April, I don't remember the exact date.

Q. What date day of the week?

A. A Monday.

Q. Okay. So it was the second Monday in April of 2004?

A. Presumably.

Q. Okay. Prior to the second Monday in April 2004, had you had any indication from any source at Eli Lilly that any of your activities surrounding Zyprexa were wrong or you were about to be fired or asked to resign?

Bandick, Michael (June 9, 2006)
266:3-18
Issues: 01 Plaintiff's Trial Designation

A. No, I was not.

Q. Okay. So when you were summoned to that conference room and they told you that you had this choice to get fired or resign, it came out of the clear blue to you?

A. It was a surprise.

Q. When did you resign, that day?

A. Two days later.

Q. Did you, after you left the meeting in the conference room, did you return to your office and go back to work or did you go home?

A. I collected my things and I went home.

Bandick, Michael (June 9, 2006)
267:22-268:8
Issues: 01 Plaintiff's Trial Designation

267:22 Q. Okay. And I understand. So
23 you went, how long did this meeting last?
24 A. About 20 minutes.
268: 1 Q. You had been working at Eli
2 Lilly in one capacity or another since 1991.
3 You're called in on what you recall to be the
4 second Monday in April, 2004, after 13 years
5 of work. You had no indication you had ever
6 been in trouble. And they gave you this
7 choice and you had gone out of the conference
8 in 20 minutes; is that right?

Bandick, Michael (June 9, 2006)
268:13-16
Issues: 01 Plaintiff's Trial Designation

268:13 Q. Is that right what I said?
14 A. It's accurate.
15 Q. I mean, that's got to come as
16 a big shock to somebody. Did it?

Bandick, Michael (June 9, 2006)
268:23-269:1
Issues: 01 Plaintiff's Trial Designation

268:23 A. I was not expecting it.
24 Q. Did you ask for a written
269: 1 explanation?

Bandick, Michael (June 9, 2006)
269:4-15
Issues: 01 Plaintiff's Trial Designation

269: 4 A. No, I didn't.
5 Q. Did they provide you with
6 some, did they provide you with any documents
7 or any writings, or show you any materials?
8 A. They read from a statement
9 and I was not provided that document.
10 Q. They read from a prepared
11 statement; is that correct?
12 A. They read from a statement.
13 Q. Who read it?
14 A. I believe, Diedre did.
15 Q. What did Don say to you?

Bandick, Michael (June 9, 2006)
269:19-23
Issues: 01 Plaintiff's Trial Designation

269:19 What did Dan Hasler say to
20 you?
21 A. I don't recall his comments
22 in that meeting.
23 Q. They couldn't have lasted

Bandick, Michael (June 9, 2006)
270:5-11
Issues: 01 Plaintiff's Trial Designation

270: 5 Q. Have you ever talked to Dan
6 ever again?
7 A. I think I saw him once
8 outside of Lilly.
9 Q. Did you ever ask him what
10 happened --
11 A. No.

Bandick, Michael (June 9, 2006)
312:18-22
Issues: 01 Plaintiff's Trial Designation

312:18 Q. Okay. You told us that it
19 would be against federal regulations and the
20 law for Eli Lilly to promote Zyprexa for
21 indications that are not within the approved
22 label; is that correct?

Bandick, Michael (June 9, 2006)
313:1-15
Issues: 01 Plaintiff's Trial Designation

313: 1 A. It would be inconsistent with
2 company policy to do that.
3 Q. Is it also against FDA
4 regulation?
5 A. I'm not an expert in FDA
6 regulation. That's my understanding.
7 Q. It's your understanding it's
8 against FDA regulation, right?
9 A. To promote outside of
10 approved indications, yes.

Q. Okay. Now can you -- so Lilly cannot, is not supposed to promote outside the label, but can Lilly use third party intermediaries to conduct such activities? Sir?

Bandick, Michael (June 9, 2006)

313:18-314:5

Issues: 01 Plaintiff's Trial Designation

A. Not promotional activities.
Q. No. So in other words, if Lilly can't promote outside of the label Lilly cannot hire third parties and pay them money to promote outside the label either, can they?
A. No. Lilly cannot hire third parties to promote outside the label.
Q. Did Lilly ever hire third parties to assist in promotion of Zyprexa outside the indications on the label?
A. No.

Bandick, Michael (June 9, 2006)

314:19-315:16

Issues: 01 Plaintiff's Trial Designation

Q. Lilly's a member of PhRMA, are they not?
A. Yes, I believe so.
Q. Have you ever served in any capacity on the PhRMA board or any committees?
A. No, I haven't.
(Whereupon, Deposition Exhibit(s) 4 duly received, marked and made a part of the record.)
QUESTIONS BY MR. ALLEN:
Q. I'm going to hand you what's been marked as Bandick Exhibit No. 4. Copies for your counsel. And I will admit it's a poor copy. You can look at mine, all highlighted if you like.
That's a statement by PhRMA concerning the marketing and promotion of pharmaceuticals from PhRMA's website. Do you recognize that?
A. Let me take a look at it and I'll let you know.

Bandick, Michael (June 9, 2006)
317:1-318:24
Issues: 01 Plaintiff's Trial Designation

317: 1 Q. Now you gave me my
2 highlighted copy back. It's got some
3 questions on there. I'm not trying to hide
4 anything from you. What that thing says in
5 sum -- you've now read it, right?
6 A. Yes, I have.
7 Q. I'm going to paraphrase what
8 I think it says and you let me know if you
9 agree or disagree with my characterization.
10 PhRMA has taken the position that
11 pharmaceutical marketing must be accurate, it
12 must be balanced, and it must be, have full
13 disclosure. Doesn't it say that right there?
14 I highlighted it on there, I think, right?
15 Do you see where I
16 highlighted "full disclosure"? I think I
17 underlined it in red.
18 A. I'm looking for that. Yes, I
19 see that now.
20 Q. Okay. That's the second
21 paragraph. It says -- the title of this
22 document, Bandick, is it No. 3?
23 A. 4.
24 Q. Bandick 4, comes from PhRMA.
318: 1 It says Marketing and Promotion of
2 Pharmaceuticals, that's the title, correct?
3 A. Yes.
4 Q. Then you can look at my
5 highlighted and underlined red copy, the
6 second paragraph, it says: "The vast
7 majority of the amount spent by
8 pharmaceutical companies on medical marketing
9 is on substantive information provided to
10 physicians." Do you see that?
11 A. Yes.
12 Q. Is that what you did in your
13 role as marketing Zyprexa?
14 A. "The vast majority of the
15 amount spent on medical marketing is on
16 substantive information." Yes, I would say
17 that's true.
18 Q. The second sentence of that
19 paragraph: "All of it -- every word -- is
20 regulated by the FDA to assure accuracy,
21 balance, and full disclosure." Did I read
22 that correctly?
23 A. That's what it says.
24 Q. Is that true?

319:4-23
Issues: 01 Plaintiff's Trial Designation

319: 4 A. I can't speak to everything
5 that the FDA does or doesn't review. I would
6 say that, certainly, we had mechanisms
7 internally to ensure that things were in
8 compliance with what we understood the
9 regulations to be.
10 Q. It doesn't say the FDA
11 reviews it. It says, all of it, I'll read
12 the second sentence: "All of it -- every
13 word -- is regulated by the FDA to assure
14 accuracy, balance and full disclosure." Do
15 you understand that statement to be true?
16 A. I've no reason to think that
17 it's not.
18 Q. All right. So you understood
19 that your marketing and promotion, and the
20 materials that were prepared for marketing
21 and promotion, needed to be accurate,
22 balanced and constitute full disclosure about
23 Zyprexa --

Bandick, Michael (June 9, 2006)
320:1-1
Issues: 01 Plaintiff's Trial Designation

320: 1 Q. -- is that true?

Bandick, Michael (June 9, 2006)
320:10-321:1
Issues: 01 Plaintiff's Trial Designation

320:10 THE WITNESS: Can you repeat
11 your question, please?
12 Q. Yes, I'm going to just read
13 the entire second paragraph put out by PhRMA.
14 Paragraph: "The vast
15 majority of the amount spent by
16 pharmaceutical companies on medical marketing
17 is on substantive information provided to
18 physicians. All of it -- every word -- is
19 regulated by the FDA to assure accuracy,
20 balance and full disclosure."
21 Did I read that correctly,
22 first of all?
23 A. Yes.
24 Q. Do you agree with that,
321: 1 second of all?

Jack E. Jordan

Bandick, Michael (June 9, 2006)
321:5-322:10
Issues: 01 Plaintiff's Trial Designation

321: 5 A. The promotion of products,
6 which is different from a broader concept of
7 marketing, I would certainly agree with that.
8 I can't speak to every
9 possible thing that could be under the
10 umbrella of marketing. The way we worked at
11 Lilly was to work in that regard,
12 particularly, around promotional activities.
13 Q. Okay. Now I'm not going to
14 read every word of this entire rest of the
15 document because we have other documents we
16 need to discuss. But let's read the first
17 sentence of the third paragraph.
18 "Pharmaceutical marketing serves the
19 following positive purposes for physicians;
20 it enables physicians to learn quickly and
21 accurately about new therapies and diagnostic
22 tools." Do you agree with that?
23 A. I do.
24 Q. Continuing in the third
322: 1 paragraph: "Pharmaceutical markets serves
2 the following positive purposes for
3 physicians," skipping down, "it provides
4 FDA-regulated information that must be
5 balanced and disclose all risks." Did I read
6 that correctly?
7 A. You did.
8 Q. And I think, my copy I
9 highlighted the word "all" and underlined it
10 in red, didn't I?

Bandick, Michael (June 9, 2006)
322:14-18
Issues: 01 Plaintiff's Trial Designation

322:14 A. Yes, you did.
15 Q. Okay. And I want to direct
16 your attention to the word "all." It says
17 "the information must be balanced and
18 disclose all risk." Do you agree with that?

Bandick, Michael (June 9, 2006)
323:3-5
Issues: 01 Plaintiff's Trial Designation

323: 3 Q. My question is: Do you agree

that your marketing documents must be balanced and disclose all risk?"

Bandick, Michael (June 9, 2006)
323:12-17
Issues: 01 Plaintiff's Trial Designation

323:12 A. Again, because I'm not in the position to be a subject matter expert on those risks or their disclosure, I would say that we followed company policies that were very clear in terms of how to use subject matter experts to address those concerns.

Bandick, Michael (June 9, 2006)
324:16-325:21
Issues: 01 Plaintiff's Trial Designation

324:16 Q. In promotional material for Zyprexa did you disclose all of Zyprexa's risks?
A. We provided information that would have disclosed all risks, yes.
Q. All risk?
A. To the best of my knowledge.
Q. And was it fair and balanced? Was it fair and balanced?
325: 1 A. Yes, that was the assessment of the members of our team.
Q. Did it constitute full disclosure as is reflected in Paragraph No. 2?
A. To the best of my knowledge it did.
Q. The last sentence of this entire document Marketing and Promotion of Pharmaceuticals it says: "More importantly it -- well, let me just read the entire last paragraph, two sentences.
"We regard pharmaceutical marketing as an essential part of the research process that brings new products into medical practice. More importantly, it serves a critical educational role in our health care delivery system."
First of all, did I read that correctly?
A. You did.

Bandick, Michael (June 9, 2006)

325:24-326:8
Issues: 01 Plaintiff's Trial Designation

325:24 Q. Marketing performs and serves
326: 1 as a critical educational role.
2 A. Among other things, yes.
3 Q. And so you knew when you
4 prepared promotional and/or nonpromotional
5 marketing materials concerning Zyprexa they
6 would be utilized to educate both doctors,
7 patients, third-party payors, and regulators,
8 about your product; is that correct?

Bandick, Michael (June 9, 2006)

326:13-20
Issues: 01 Plaintiff's Trial Designation

326:13 A. Not all the materials that we
14 created would be designed to go to all of
15 those audiences.
16 Q. I understand. But those
17 materials that were prepared and intended to
18 reach those audiences, you understood would
19 perform an educational function that is
20 critical to our health care system?

Bandick, Michael (June 9, 2006)

327:2-328:4
Issues: 01 Plaintiff's Trial Designation

327: 2 A. I would say that in all of
3 the materials that we had, both promotional
4 and nonpromotional, there was an element of
5 educational value in them, yes.
6 Q. And do you agree with PhRMA
7 that that educational element performed a
8 critical role in delivery of health care in
9 the health care system?
10 A. That's really beyond my scope
11 of being able to answer that.
12 Q. Can you hand me my copy of
13 that back? Thank you sir.
14 You've heard the term "fair
15 and balanced" before have you not, in regard
16 to marketing documents?
17 A. I've heard the term "fair
18 balance."
19 Q. What does that mean to you?
20 A. That there is an appropriate
21 balance between what would be considered
22 advantages or disadvantages, efficacy,

safety.
Q. For example, you cannot, you, being the marketing department, in order to reach fair balance, you cannot overemphasize the benefits of Zyprexa and underemphasize the risk of Zyprexa?

Bandick, Michael (June 9, 2006)
328:11-24
Issues: 01 Plaintiff's Trial Designation

A. That's my understanding of the term fair balance.
Q. Thank you. At Lilly, in order to have fair balance can you spin the data on Zyprexa?
A. I don't know what you mean.
Q. You ever heard the term "spin the data?"
A. I'm familiar with the term "spinning." I'm not sure I understand "spinning the data."
Q. Do you think -- in your opinion, can you spin the data when marketing Zyprexa?

Bandick, Michael (June 9, 2006)
329:3-7
Issues: 01 Plaintiff's Trial Designation

A. The way we treated clinical data you would not be in a position to quote/unquote spin the data.
Q. And you should not spin the data?

Bandick, Michael (June 9, 2006)
329:10-330:2
Issues: 01 Plaintiff's Trial Designation

A. Let me be clear about what I define as spinning the data.
Q. Yes, sir.
A. If by spinning you mean to mislead or to provide an untrue characterization of the data, that would be inappropriate.
I've also heard the use of the word spin more loosely in a way that would suggest to try to make things appear

positive without compromising the integrity of those data.

So I want to be clear that my definition covers both of those.

Q. Okay. In marketing, be it promotional or nonpromotional materials, can you torture the data --

Bandick, Michael (June 9, 2006)
330:5-6
Issues: 01 Plaintiff's Trial Designation

Q. -- presented concerning the safety or efficacy of Zyprexa?

Bandick, Michael (June 9, 2006)
330:10-14
Issues: 01 Plaintiff's Trial Designation

A. That's not a phrase that I would use to characterize the way that we produced marketing materials at Lilly.

Q. You would agree you should not be permitted to torture the data?

Bandick, Michael (June 9, 2006)
330:19-24
Issues: 01 Plaintiff's Trial Designation

A. I'm not sure I understand what you mean by quote/unquote torturing the data, so I can't answer your question.

Q. Okay. When Lilly speaks about Zyprexa is it giving answers that matter?

Bandick, Michael (June 9, 2006)
331:4-21
Issues: 01 Plaintiff's Trial Designation

A. Answers that matter is a tag line that Lilly adopted as a corporation some years ago. That's not the context in which we created our materials. It's not a tag line that meant something to me while I was creating those materials. That was something I felt represented more of a corporate

messaging campaign.
Q. Yeah. And you're a marketing professional, it was a corporate message, it's on the documents. It's Lilly, you see Lilly, and underneath it you always see "answers that matter," do you not?
A. Some of them.
Q. Yes. What is the message that the phrase, the slogan that Lilly, answers that matter, what message does that send to the consumers of Lilly's products?

Bandick, Michael (June 9, 2006)
332:15-24
Issues: 01 Plaintiff's Trial Designation

A. The reason that you'll find it on a lot of documents is that was part of a Lilly corporate branding campaign. If you're asking me to interpret "answers that matter," to me that would imply that it's information that is relevant to the audience.
Q. Right. And, in fact, didn't Lilly represent itself in response to questions involving Zyprexa at times as being the world leaders in diabetes treatment?

Bandick, Michael (June 9, 2006)
333:3-7
Issues: 01 Plaintiff's Trial Designation

Q. Do you recall that?
A. Lilly has a long history in that disease state. I don't recall Lilly characterizing itself as such regarding matters around Zyprexa.

Bandick, Michael (June 9, 2006)
334:5-8
Issues: 01 Plaintiff's Trial Designation

Q. Is there a higher standard in the marketing and manufacturing of drug products required as opposed to, let's say, ordinary consumer products such as soap?

Bandick, Michael (June 9, 2006)
334:12-19

Jack E. Jordan

Issues: 01 Plaintiff's Trial Designation

334:12 A. I don't know what the
13 standards are around consumer products. I
14 can only speak to what I know about
15 pharmaceutical marketing.
16 Q. Do you think there should be
17 a higher standard applied to the marketing of
18 drug products such as Zyprexa as opposed to
19 consumer products such as soap?

Bandick, Michael (June 9, 2006)

334:22-335:2
Issues: 01 Plaintiff's Trial Designation

334:22 A. That's a hypothetical
23 question that I've never considered before.
24 Q. Okay. Did Lilly have a
335: 1 problem of being overly aggressive to the
2 point of greed in promoting Zyprexa?

Bandick, Michael (June 9, 2006)

335:7-16
Issues: 01 Plaintiff's Trial Designation

335: 7 THE WITNESS: Is there an
8 example that you'd like me to react
9 to?
10 Q. Do you know of any examples?
11 A. No, I don't.
12 Q. Okay. So the answer to my
13 question was did Lilly have a problem with
14 being overly aggressive to the point of greed
15 in promoting Zyprexa, is your answer yes or
16 no?

Bandick, Michael (June 9, 2006)

335:19-336:4
Issues: 01 Plaintiff's Trial Designation

335:19 A. My answer would be no.
20 Q. Was Lilly spinning the
21 medical facts and data and presenting biased
22 information in order to beat the competition
23 when it promoted Zyprexa?
24 A. No.
336: 1 Q. Did Lilly have a quote -- let
2 me rephrase. Did Lilly have a quote
3 "spinning mentality," close quote, in its

4 promotional efforts on behalf of Zyprexa?

Bandick, Michael (June 9, 2006)
336:7-9
Issues: 01 Plaintiff's Trial Designation

336: 7 A. No. In fact, great care was
8 taken to provide accurate data and in
9 appropriate context.

Bandick, Michael (June 9, 2006)
347:9-348:4
Issues: 01 Plaintiff's Trial Designation

347: 9 MR. ALLEN: Here's Bandick
10 Exhibit No. 6. I have copies for
11 your counsel.
12 QUESTIONS BY MR. ALLEN:
13 Q. Do you know Alan Breier?
14 A. Yes, I do.
15 Q. Tell the jury who Alan Breier
16 is?
17 A. Currently, he is Lilly's
18 Chief Medical Officer.
19 Q. Chief Medical Officer. Let
20 me go down to the third paragraph of -- so
21 it's Dr. Alan Breier; is that correct?
22 A. Yes, he is a physician.
23 Q. This is an e-mail he wrote to
24 US Medical, Medical US, Subject: 2004
348: 1 Medical Objectives. Attaching 2004 Medical
2 Objectives, Power Point Principles.
3 Do you agree with that so
4 far?

Bandick, Michael (June 9, 2006)
349:2-5
Issues: 01 Plaintiff's Trial Designation

349: 2 Q. Sir, do you agree that is to
3 US Medical Medical and it's from Dr. Alan
4 Breier?
5 A. As far as I can tell.

Bandick, Michael (June 9, 2006)
349:17-350:7
Issues: 01 Plaintiff's Trial Designation

349:17 Q. Sir, I want to direct your
18 attention to the third paragraph under
19 principles. Do you see the bold word
20 Principles?
21 A. I do.
22 Q. Hear what Dr. Breier says in
23 Bandick No. 6: Making medicine for people
24 facing illness is a much different and higher
350: 1 calling than making consumer products for
2 other markets. We do not sell soap. It,
3 therefore, requires a different and a higher
4 code for conducting our business."
5 Did I read that correctly?
6 A. That's what it says in this
7 document.

Bandick, Michael (June 9, 2006)
350:11-11
Issues: 01 Plaintiff's Trial Designation

350:11 Q. -- philosophy expressed by

Bandick, Michael (June 9, 2006)
354:2-355:13
Issues: 01 Plaintiff's Trial Designation

354: 2 Q. All right, sir, you reviewed
3 this document, have you not, now?
4 A. Yes, I have.
5 Q. Okay. Do you see within this
6 document that Dr. Breier, who you said you
7 understand to be Director of Global Medical
8 Affairs in the company, correct?
9 A. I believe his current role is
10 Chief Medical Officer.
11 Q. Is there any higher doctor in
12 the whole company?
13 A. Not based on Lilly structure,
14 no.
15 Q. Based on what structure?
16 A. Not based on Lilly structure.
17 Q. So he's the highest medical
18 doctor in the whole company, right?
19 A. As far as I can tell.
20 Q. Okay. He writes this e-mail.
21 And I'm going down the third paragraph,
22 bolded sentence: "Principles. Making
23 medicine for people facing illness is a much
24 different and higher calling than making
355: 1 consumer products for other markets. We do
2 not sell soap, exclamation point." Did I

read that correctly?
A. Yes.
Q. Do you agree with Dr. Breier?
A. I agree it's much different, and my own opinion is that it is a higher calling.
Q. So, therefore, there is a higher standard required for the marketing and promotion of drugs as opposed to other ordinary consumer products such as detergent, do you agree?

Bandick, Michael (June 9, 2006)
355:17-22
Issues: 01 Plaintiff's Trial Designation

A. I'm not aware what Dr. Breier meant by that statement. And as we were talking about earlier, I don't know enough about the regulations in other areas. I know what the regulations are for pharmaceutical marketing.

Bandick, Michael (June 9, 2006)
356:2-11
Issues: 01 Plaintiff's Trial Designation

Q. Dr. Breier is not referring to regulations. He's referring, as I understand it to an issue of ethics and standards; would you agree with that?
A. I don't know what he intended by that statement.
Q. Okay. So you're not willing to concede for this jury that the marketing of drug products requires a higher standard than as opposed to Tide detergent?

Bandick, Michael (June 9, 2006)
356:14-357:2
Issues: 01 Plaintiff's Trial Designation

A. I'm not in a position to pass judgment on that.
Q. You're not in a position to pass judgment on that. Weren't you the Brand Manager and the Director of Marketing Management for Zyprexa?
A. Yes, I was.
Q. Did you consider your

marketing activities and the statements that would be made in the promotion and nonpromotional materials to be more significant than that which would entail in the marketing of Camay soap?

Bandick, Michael (June 9, 2006)

357:5-16

Issues: 01 Plaintiff's Trial Designation

A. As I indicated to you, I do agree with the comment it is a higher calling but I have no way of comparing what the, what the parameters are for commercializing soap. What I do know is what the parameters are for commercializing medications and pharmaceutical products and that's what we adhere to.

Q. Are those standards for manufacturing and marketing drugs higher than those for marketing soap?

A. I don't know.

Bandick, Michael (June 9, 2006)

357:19-359:11

Issues: 01 Plaintiff's Trial Designation

Q. Dr. Breier goes on: "It therefore requires a different and higher code for conducting our business." First, did I read that correctly?

A. You did.

Q. Do you agree with Dr. Breier?

A. I don't know the context in which he intended that statement.

Q. So you can't answer my question?

A. I can't answer your question.

Q. Dr. Breier goes on: "The principles of medical research, parens, PMR, close parens, provide the road map to guide all human research at Lilly. PMR has been fully endorsed by all key governance bodies and including the Corporate Policy Committee and are now the law of the land. To make the principles live in our culture requires all of us to understand and put into action their underlying intent. We are particularly challenged when it comes to presenting our data in a completely objective, unbiased manner because of our passion for our

molecules and the belief that, quote, "spinning" data is sometimes necessary to gain a competitive advantage. If we do not abandon the quote "spinning," close quotes, mentality, we will not restore confidence in our medical research and rebuild the public trust our industry has compromised."

First of all, did I read that correctly?

A. Yes.

Q. You agree with Dr. Breier?

A. I don't understand all the things that he is communicating in those sentences.

Q. But what you understand do you agree with Dr. Breier?

Bandick, Michael (June 9, 2006)
359:14-21
Issues: 01 Plaintiff's Trial Designation

A. I don't know where he is differentiating between Lilly and the rest of industry. I don't know which, if any, specific products he's referring to. I'm generally able to understand the comment but I don't know the full context of it. I wasn't part of the audience for this e-mail.

Q. Do you agree with Dr. Breier?

Bandick, Michael (June 9, 2006)
360:2-13
Issues: 01 Plaintiff's Trial Designation

A. I don't think I know enough about the context to be able to answer your question.

Q. Well, when Dr. Breier says: "We are particularly challenged when it comes to presenting our data in a completely objective, unbiased manner because of our passion for our molecules, and the belief that "spinning" data is sometimes necessary to gain a competitive advantage," does it appear he's talking about Eli Lilly and their products?

Bandick, Michael (June 9, 2006)
360:18-361:6
Issues: 01 Plaintiff's Trial Designation

Jack E. Jordan

360:18 A. It's not clear to me. And
19 the next sentence he uses the same pronoun
20 "we, and attaches that to the public trust
21 that our industry has compromised. So it's
22 not clear to me that he's speaking about
23 Lilly or if he's speaking more broadly about
24 the industry.
361: 1 Q. Okay. So when he says "the
2 belief that "spinning" data is sometimes
3 necessary to gain a competitive advantage,"
4 are you saying he's saying spinning the data
5 for the drug industry to gain a competitive
6 advantage over the cereal industry?

Bandick, Michael (June 9, 2006)
361:9-14
Issues: 01 Plaintiff's Trial Designation

361: 9 A. No, I don't think he meant
10 that.
11 Q. No. What he means is, he's
12 saying when we spin our data to gain a
13 competitive advantage over another drug
14 company, isn't that what he's saying?

Bandick, Michael (June 9, 2006)
361:18-363:18
Issues: 01 Plaintiff's Trial Designation

361:18 A. As I said a couple of
19 questions ago, it's not clear to me from that
20 sentence whether he's speaking about Lilly,
21 specifically, or about the industry.
22 Q. Did you reach all these
23 conclusions here in the last five minutes?
24 A. It's the first time I've seen
362: 1 it.
2 Q. Okay. Why don't we go up to
3 the very first paragraph of this document and
4 let me read it to you. Dr. Breier says:
5 "Greetings, Medical Colleagues, Early in
6 January, the extended Medical Lead team,
7 which comprises 25 cross functional leaders
8 from our Component, gathered to discuss our
9 2004 challenges and define a set of
10 objectives for 2004," period. Did I read
11 that correctly?
12 A. Yes.
13 Q. Who is he talking about, the
14 industry or is he talking about Eli Lilly?

A. I take that to mean Lilly.
Q. Okay. He says: "These objectives, which are organized around 5 Ps -- Patients, Principles, Pipeline, Productivity and People, were presented at the Medical Town Hall on January the 27th." Period. Did I read that correctly?
A. Yes.
Q. Is he talking about the industry or is he talking about Eli Lilly?
363: 1 A. I presume that to be a Lilly reference.
Q. "I have attached the objectives along with our strategic intent statement, parens, also known as the medical component mantra, close parens, below and would like to share some additional thoughts about them now," period. Did I read that correctly?
A. Yes.
Q. Is he talking about the industry or is he talking about Eli Lilly?
A. I presume that's a Lilly reference.
Q. And then he goes down and he says, I'm going to provide you the Lilly principles, right?
MR. FAHEY: Objection to

Bandick, Michael (June 9, 2006)
363:22-364:5
Issues: 01 Plaintiff's Trial Designation

363:22 A. Those are the objectives for the Medical Lead team.
Q. Of what company?
364: 1 A. Lilly.
Q. Okay. So this document is not dealing with the industry, this document's dealing with Lilly practices and procedures, is it not?

Bandick, Michael (June 9, 2006)
364:10-365:7
Issues: 01 Plaintiff's Trial Designation

364:10 A. The document, as I understand it, has to do with Lilly medical objectives. There are other references that are broader than simply Lilly medical.
Q. What are objectives that are broader than Lilly medical?

A. No, I said there are references that are broader than Lilly medical. References like in that last sentence of the paragraph entitled Principles.

Q. Okay. Anyhow, this is what Dr. Breier says. "Below I'd like to share some additional thoughts about them now," referring to the medical component mantra. Is No. 1 Patients?

A. Yes.

Q. Now here's how I read it. I come from Houston now, you understand, so I'm going to have a hard time with this French word. He says, "The raison d'être for our industry;" is that right?

Bandick, Michael (June 9, 2006)
365:13-366:14
Issues: 01 Plaintiff's Trial Designation

A. I'm not in a position to address your French pronunciation.

Q. You know what that means? Doesn't that mean "the reason?"

A. The reason for being.

Q. The reason for our industry and why most of us chose to work at Lilly is to serve patients. While we have other important customers, parens, e.g., meaning for example, doctors, payors and regulators, close parens, we make medicines for only one customer." Did I read that correctly?

A. Yes.

Q. Who is that one customer that Dr. Breier says we make these medicines for?

A. The document says the patient.

Q. I asked you about that about the first 20 minutes this morning. Do you recall that?

A. I do.

Q. And do you agree with Dr. Breier here that the first and most important customer Eli Lilly has is not the doctor, it's not the payor, it's not the regulator, it's the patient?

Bandick, Michael (June 9, 2006)
366:19-368:6
Issues: 01 Plaintiff's Trial Designation

366:19 A. The context in which we were
20 talking earlier this morning had to do with
21 marketing. I would agree that from a medical
22 standpoint the patient would be at the very
23 top of the list. Within marketing I put
24 patients and physicians co-No. 1.
367: 1 Q. Good we got that agreement.
2 In your view in marketing patients and
3 doctors are co-No. 1s, right?
4 A. Yes.
5 Q. All right. Is there anytime
6 where the patient is not No. 1 at Eli Lilly?
7 A. There are times when a
8 patient wouldn't be the primary audience for
9 a particular message, but in terms of
10 priority, patient safety would be at the top
11 of the list.
12 Q. Now it goes on to say: "Thus
13 the patient is our primary customer. We in
14 medical are in the process of affirming a
15 patient centered culture where the needs of
16 patients are well understood and take top
17 priority in all of what we do. Integral to a
18 patient centered culture is putting patients
19 in the heart of our business process. In our
20 daily work we are faced with making decisions
21 based on a set of priorities. Putting
22 patients at the top of the priority list will
23 lead to the right decisions and the most
24 robust business results. As I have often
368: 1 said, quote, what is good for patients is
2 good for business, close quotes." Did I read
3 that correctly?
4 A. Yes.
5 Q. Is the converse true, what is
6 bad for patients is bad for business?

Bandick, Michael (June 9, 2006)
368:9-21
Issues: 01 Plaintiff's Trial Designation

368: 9 A. It certainly can be.
10 Q. Right. For example, if in
11 marketing to the customer you started
12 informing doctors and patients that Zyprexa
13 carried with it an increased risk of diabetes
14 different, separate and apart, from other
15 antipsychotic medications, that you need to
16 monitor your glucose levels because you can
17 develop diabetes, diabetic ketoacidosis and
18 go into a diabetic coma and die, if you relay
19 that information about your product that
20 would be bad information concerning the
21 health of the patient, would you agree?

Jack E. Jordan

Bandick, Michael (June 9, 2006)
369:3-23
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: That's a very long question. Could you break it up or rephrase it?
Q. Yeah. Let me say, Dr. Breier says "what's good for patients is good for business," right?
A. He did.
Q. I'm asking is the converse true, what's bad for patients is bad for business?
A. I think that's often the case.
Q. Okay. So, therefore, if you're marketing a product such as Zyprexa -- we're here to talk about Zyprexa.
A. Right.
Q. And you start telling people, we believe that there is an increased risk of diabetes, diabetic coma, and diabetic ketoacidosis, that would be a bad medical condition, right?

Bandick, Michael (June 9, 2006)
370:2-15
Issues: 01 Plaintiff's Trial Designation

A. There are two parts to your question; one, is that a bad medical condition. And I think an MD would be in a better position than me but based on what I know, yes, that would be a bad medical condition.

But if the question is would telling audiences about that risk be a bad thing? I would say no.
Q. If a drug in a class has an increased risk over other drugs in a class, do you have an opinion as a marketing professional, as to how that would affect the sales of the product with the increased risk?

Bandick, Michael (June 9, 2006)
370:18-23
Issues: 01 Plaintiff's Trial Designation

Jack E. Jordan

370:18 A. It depends on the risk, it
19 depends on the difference, it depends on the,
20 on other factors, such as relative
21 differences in efficacy. I mean, the whole
22 risk/benefit balance is a pretty complicated
23 thing.

Bandick, Michael (June 9, 2006)
371:2-10
Issues: 01 Plaintiff's Trial Designation

371: 2 Q. Explain to the jury since you
3 used that term "risk/benefit balance", why
4 don't you explain what you meant to the jury,
5 please?
6 A. I didn't go to medical school
7 but my understanding is that MDs are educated
8 as to how to perform a risk/benefit analysis
9 with their patients, and try to optimize that
10 balance to favor the patient.

Bandick, Michael (June 9, 2006)
372:10-13
Issues: 01 Plaintiff's Trial Designation

372:10 Q. Mr. Bandick, I handed you at
11 the break what's been marked as Bandick
12 Exhibit No. 7. Do you recognize this
13 document?

Bandick, Michael (June 9, 2006)
372:23-375:8
Issues: 01 Plaintiff's Trial Designation

372:23 A. Yes, I do.
24 Q. And how is it you recognize
373: 1 this document? How is it you recognize this
2 document?
3 A. I am familiar with the,
4 generally familiar with the content. It's
5 been a while since I've seen it. And I was
6 aware of when it was published.
7 Q. It is a document entitled the
8 "Consensus Development Conference on
9 Antipsychotic Drugs and Obesity and
10 Diabetes." And it's published by the
11 American Diabetes Association, the American
12 Psychiatric Association, the American
13 Association of Clinical Endocrinologists and
14 the North American Association for the Study

Jack E. Jordan

of Obesity, in 2004; is that correct?
A. It was published in Diabetes Care and those four associations are associated with it.
Q. And you read this in your role at Eli Lilly before you left your employment, did you not?
A. Yes, that's true.
Q. And just for the record, as reflected in this exhibit, this is a consensus development document involving a conference that was held in November of 2003; is that correct?
A. Yes, I believe it is.
Q. And individuals as reflected in this document, individuals from Eli Lilly made a presentation at that conference, correct?
A. That is correct.
Q. Along with other drug company representatives and individuals from the FDA, among others?
A. Yes, that's correct.
Q. And some of the drug companies that made presentations included were AstraZeneca, Janssen and Pfizer?
A. Those are the three I recall.
Q. By the way, did you attend this conference?
A. Yes, I did.
Q. So you were, actually, there at the conference itself; is that right?
A. Yes, I attended.
Q. Where was that conference held?
A. It was in -- in Virginia.
Q. Why did you attend this conference?
A. I was part of a Lilly group most of whom are in medical, but then I also was attending for my own education.
Q. What was the Lilly group's

Bandick, Michael (June 9, 2006)
375:19-378:22
Issues: 01 Plaintiff's Trial Designation

375:19 Q. Did they have a name for this Lilly group?
A. No.
Q. Why were you selected to attend?
A. Many of the things that we did involved a collaboration between

Jack E. Jordan

marketing and medical.
Q. So when you told me earlier "I'm not a doctor," and then you gave an answer, do you recall starting an answer "I'm not a doctor" and then you started answering the question?
A. I believe I did say that, yes.
Q. But you have throughout the entire experience in marketing drug products, in particular Zyprexa, worked on committees and teams at Eli Lilly which they call cross-functional teams, and you've worked with the medical affairs department, have you not?
A. I have worked with medical on a number of occasions.
Q. Okay. Now, this conference was convened to answer several questions, was it not?
A. Yes, it was.
Q. Okay. I'm just going to have you skip over to Page 597 of Bandick Exhibit No. 7, the consensus statement, and you see question three?
A. Yes.
Q. The question is: "What is the relationship between the use of these drugs and the incidence of obesity and diabetes, question mark." Did I read that correctly?
A. Yes.
Q. And when we're talking about "these drugs," this conference was looking at second generation antipsychotics; is that correct?
A. Primarily.
Q. Okay. Including Risperdal, Zyprexa, Seroquel, Geodon, is it Abilify?
A. Yes, is it.
Q. And Clozaril?
A. Yes.
Q. Those are the second generation antipsychotics that were evaluated in this consensus statement, right?
A. That's correct.
Q. The question is: What is the relationship in the use of these drugs and the incidences of obesity or diabetes?
A. That is correct.
Q. The first heading, the bold heading, obesity, do you see that?
A. Yes, I do.
Q. It says under there: "There is considerable evidence, particularly in patient with schizophrenia, that treatment with the second general antipsychotics can

cause a rapid increase in body weight in the first few months of therapy that may not reach a plateau even after one year of treatment. There is, however, considerable variability in weight gain among the various second generation antipsychotics." And it references Table 2. Did I read that correctly?

A. Yes.

Q. And you see table two underneath that statement?

A. Yes, I do.

Bandick, Michael (June 9, 2006)
379:14-380:17
Issues: 01 Plaintiff's Trial Designation

379:14 Q. According to table two, which is directly in front of you, at a conference you attended, what second generation antipsychotics carried the largest risk of weight gain and risk for diabetes according to Table 2?

A. According to this panel, clozapine and olanzapine, Clozaril and Zyprexa, had a higher relative risk for weight gain.

Q. And for diabetes?

380: 1 A. And to answer the other part of your question, according to this table they also identify clozapine and olanzapine as having a relatively higher risk for diabetes.

Q. And when we say olanzapine, so olanzapine being Zyprexa, for example, has a greater risk for causing weight gain and diabetes than Risperdal, Seroquel, Abilify and Geodon, correct?

A. That's what it says in this table.

Q. According to Table No. 2?

A. Yes.

Q. Of course, you'd known about that for a long, long, time before this consensus statement, right?

Bandick, Michael (June 9, 2006)
380:22-22
Issues: 01 Plaintiff's Trial Designation

380:22 A. I don't agree with that.

Bandick, Michael (June 9, 2006)
381:19-382:1
Issues: 01 Plaintiff's Trial Designation

381:19 Q. The marketing department and
20 the medical affairs department at Eli Lilly
21 had known for years prior to the consensus
22 statement conference that you attended that
23 Zyprexa carried a greater risk for weight
24 gain than Seroquel, Risperdal or traditional
382: 1 neuroleptics; isn't that true?

Bandick, Michael (June 9, 2006)
382:4-383:24
Issues: 01 Plaintiff's Trial Designation

382: 4 A. I'm trying to recall the
5 launch date of Seroquel, but for Risperdal,
6 yes, it was well characterized that Zyprexa
7 resulted in more weight gain than the other
8 products.
9 Q. And let me hand you what's
10 been marked as --
11 A. I just want to note, though,
12 my source for disagreement in your previous
13 statement had to do with your question about
14 also knowing about the increased risk of
15 diabetes and that's the part I disagreed
16 with.
17 (Whereupon, Deposition
18 Exhibit(s) 8 duly received, marked
19 and made a part of the record.)
20 QUESTIONS BY MR. ALLEN:
21 Q. Okay. I've handed you what's
22 been marked as Bandick Exhibit No. 8. It's
23 an e-mail from Alan Breier, you've already
24 told us who Dr. Breier is, to various people
383: 1 including individuals within the marketing
2 department; is that correct?
3 A. I don't know. I'll need to
4 take a minute. I've not seen this before.
5 Q. Just look at the two cc's.
6 My question right now is are people in the
7 marketing department included in this e-mail?
8 A. The names in the, to whom
9 this was addressed are senior leadership that
10 I wouldn't characterize as marketing
11 leadership. I would characterize them as
12 corporate leadership.
13 Q. Okay. That's better. This
14 e-mail was sent to corporate leadership in
15 November of '99, right?

Jack E. Jordan

A. Apparently.
Q. Do you see where Dr. Breier says in the first sentence: "John asked me to overview the topic of olanzapine-associated weight changes, parens, OWC, close parens, period?"
A. Yes, I see that.
Q. Who's "John"?
A. I don't know yet.

Bandick, Michael (June 9, 2006)

384:5-7

Issues: 01 Plaintiff's Trial Designation

Q. My question is: The only John I see in there is John Lechleiter, is that how you pronounce his name?

Bandick, Michael (June 9, 2006)

384:11-24

Issues: 01 Plaintiff's Trial Designation

Q. Assume with me the only John referenced in this e-mail is John Lechleiter.
Who is John Lechleiter?
A. I can't assume that that's the only John that could be referenced.
John Lechleiter, currently, I believe, he's the President and Chief Operating Officer of the company. He did not have that role in 1999.
Q. Okay. Anyhow, the e-mail says "John asked know the overview the topic of olanzapine-associated weight changes, parens, OWC, close presents, period.
I read that correctly, right?

Bandick, Michael (June 9, 2006)

385:8-386:9

Issues: 01 Plaintiff's Trial Designation

Q. Did I read that sentence correctly?
A. It appears that you did.
Q. Okay. Skipping down in this paragraph to the third sentence says, "Although," and I'll read it out loud. "Although it is a significant issue for us, perhaps our only/major clinical Achilles heel, and our competitors have robustly

Jack E. Jordan

focused on it, parens, reminiscent of anxiety and, redacted, close parens, the fact is Zyprexa offers the best combination of efficacy, safety, and ease of use of any available treatment for psychosis and acute mania. The most critical immediate issue is to keep the focus where it belongs -- superior treatment and outcome -- an arena where we have no peer. What follows is a high level review."

Did I read that portion of the e-mail correctly?

A. Yes.

Q. And wasn't it always the position of the Zyprexa marketing department that Zyprexa provided superior treatment and outcome and Zyprexa had no peer?

Bandick, Michael (June 9, 2006)
386:18-21
Issues: 01 Plaintiff's Trial Designation

A. I would like to take a moment to review the rest of the document.

Q. My question, sir. You can put the document down, sir.

Bandick, Michael (June 9, 2006)
386:24-387:11
Issues: 01 Plaintiff's Trial Designation

Q. I'm not asking about the document. Take the document, flip it over, and I'm not going to ask you about the document, okay. Do you agree to do that?

A. As you wish.

Q. All right, sir. Let me ask you, was it the position of the Zyprexa marketing team, the Zyprexa brand team and the marketing efforts for Zyprexa, that Zyprexa provided superior treatment and outcome and in the antipsychotic market you had no peer?

Bandick, Michael (June 9, 2006)
387:14-21
Issues: 01 Plaintiff's Trial Designation

A. That's not language that I used in characterizing the brand in our

Jack E. Jordan

marketing.
Q. So you disagree with that statement?
A. That's not what I said.
Q. Do you agree with that statement?

Bandick, Michael (June 9, 2006)

387:24-388:11

Issues: 01 Plaintiff's Trial Designation

387:24 A. Without knowing the context
388: 1 of what Dr. Breier intended in thinking about
2 it in 1999, I don't really have a basis to
3 agree or disagree with that.
4 Q. I'm not asking about
5 Dr. Breier now. Let me ask this question.
6 Do you agree that when you were marketing
7 Zyprexa was it your position in your role in
8 marketing that Zyprexa offers the best
9 combination of efficacy, safety, and ease of
10 use, of any available treatment for
11 psychosis?

Bandick, Michael (June 9, 2006)

388:14-389:22

Issues: 01 Plaintiff's Trial Designation

388:14 A. That's not a verbatim for our
15 promotional marketing. It does represent, I
16 believe, a summary in 1999 of how we felt
17 Zyprexa compared to other second generation
18 antipsychotics.
19 Q. How about in 2000?
20 A. I would still say that
21 represented, in general, our characterization
22 of the brand.
23 Q. How about 2001?
24 A. Nothing would have changed.
389: 1 Q. How about 2002?
2 A. Nothing would have changed.
3 Q. How about 2003?
4 A. Nothing would have changed.
5 Q. How about 2004?
6 A. I left the team at that point
7 and was no longer involved in the marketing.
8 Q. How about prior to the time
9 you left in 2004?
10 THE WITNESS: In January
11 of 2004?
12 MR. ALLEN: Yes, sir.
13 A. It still represented a

general summary of how we felt the brand compared.

Q. So in marketing, the general summary of how you felt the brand compared to the other anti second generation antipsychotics, would accurately state that Zyprexa offers the best combination of efficacy, safety, and ease of use; is that correct? True?

Bandick, Michael (June 9, 2006)

390:1-8

Issues: 01 Plaintiff's Trial Designation

390:

A. It's a very broad statement. We wouldn't -- we wouldn't hold that position for every single patient. In comparing the major drugs out there it's generally a reasonable statement, again, not a verbatim that we would use in our promotion.

Q. Well, isn't it a fact that's exactly what you told doctors and patients?

Bandick, Michael (June 9, 2006)

390:13-391:6

Issues: 01 Plaintiff's Trial Designation

390:

A. I'm not aware of that language.

Q. Remember -- now I'm going back to number 8, sir. I'm going to refer you back to Exhibit 8, now.

A. Then I will ask for a few moments to review the document in its entirety.

Q. Don't you want to hear a question I have first?

A. No. Actually, we've been asking a lot of questions about it and I'm

391:

feeling that I'm not going to be able to answer your question very well unless I've read the document.

Q. So before you hear a question you want to review the entire document?

A. Yes, sir.

Bandick, Michael (June 9, 2006)

391:23-392:16

Issues: 01 Plaintiff's Trial Designation

Jack E. Jordan

391:23 Q. While you you're reviewing
24 the document, sir, I want you to keep this
392: 1 question in mind. Sir? Sir? Here's the
2 question I want you to consider while you're
3 reviewing this document.
4 In November of '99, as you
5 said, the corporate -- what do you call these
6 people, the corporate what?
7 A. I referred to them as
8 corporate leadership.
9 Q. The corporate leadership of
10 Lilly knew as a fact that among the
11 antipsychotics Zyprexa carried a greater risk
12 of weight gain than Seroquel, Risperdal, and
13 the other traditional neuroleptics. Now the
14 question's on the table as you review this
15 document?
16 A. I will keep that in mind.

Bandick, Michael (June 9, 2006)
392:22-393:6
Issues: 01 Plaintiff's Trial Designation

392:22 Q. And the answer to my question
23 is what, sir?
24 THE WITNESS: Could you
393: 1 repeat your question?
2 Q. Corporate leadership at Lilly
3 had known since at least November of '99 as a
4 fact that Zyprexa carried a greater risk of
5 weight gain than Seroquel, Risperdal, and the
6 traditional neuroleptics?

Bandick, Michael (June 9, 2006)
393:9-12
Issues: 01 Plaintiff's Trial Designation

393: 9 A. That's true.
10 Q. And in fact, in this
11 document, Exhibit No. 8, it states that that
12 is a fact, correct?

Bandick, Michael (June 9, 2006)
393:14-394:4
Issues: 01 Plaintiff's Trial Designation

393:14 A. Yes.
15 Q. Did you tell, you in
16 marketing, in your promotional activities,
17 subsequent to, at least -- let me rephrase

the question.

The date of Exhibit No. 8 is November 24, 1999; is it not?

A. Yes, it is.

Q. Did you in the marketing department then begin to promote Zyprexa and tell the patients and doctors and your customers and your audience that it was a fact that Zyprexa carried a greater risk of weight gain than Seroquel, Risperdal and traditional neuroleptics?

Bandick, Michael (June 9, 2006)
394:7-15
Issues: 01 Plaintiff's Trial Designation

A. At that point I would say that we'd already been doing that for more than three years.

Q. Your position is you'd been telling doctors and patients for three years, since 1996, it was a fact, it was a fact that Zyprexa carried a greater risk of weight gain than Seroquel, Risperdal and traditional neuroleptics?

Bandick, Michael (June 9, 2006)
394:18-395:1
Issues: 01 Plaintiff's Trial Designation

A. Going back to 1996 when Zyprexa was launched Seroquel was not yet on the market so we didn't state it. And I don't know that we used that exact language saying it is a fact. But we did disclose and describe the clinical trial data that demonstrated that weight gain was higher on Zyprexa than on the other products.

Bandick, Michael (June 9, 2006)
395:5-396:4
Issues: 01 Plaintiff's Trial Designation

Q. Let's read the statement in Bandick Exhibit No. 8 under Market Research and go down to one, two, three, four, five, six bullet points. Do you see that?

A. I do.

Q. It says: "Olanzapine is viewed to have more associated weight gain

Jack E. Jordan

than risperidone, Seroquel and traditional neuroleptics, Parens, Facts: The order of weight gain among antipsychotics is Clozapine is greater than olanzapine, which is Zyprexa, which is greater than Seroquel, which is greater than risperidone, which is greater than traditional neuroleptics, close parens, period." Right?

A. That's what it says.

Q. And it uses the word that's a fact, F-A-C-T, right?

A. Yes, it does.

Q. Do you recall as of November 1999, whether or not you were using and promoting Zyprexa and telling people, your audience that it was a fact that Zyprexa carried a greater risk of weight gain?

Bandick, Michael (June 9, 2006)

396:20-397:8

Issues: 01 Plaintiff's Trial Designation

A. I don't recall that we used that exact language the way that you just suggested, but continued to disclose the fact that Zyprexa did have clinically significant weight gain and that weight gain was, in fact, greater than on other second generation antipsychotics.

Q. Do you see how in Exhibit No. 8 it just says "fact," it's a fact for Zyprexa?

A. Yes.

Q. Do you ever recall using that terminology in the promotion of Zyprexa?

Bandick, Michael (June 9, 2006)

397:12-398:1

Issues: 01 Plaintiff's Trial Designation

A. I don't recall using that exact terminology, no.

Q. You think that terminology is rather clear and unambiguous? It's a fact. That's a pretty unambiguous term, is it not?

A. I think it's fairly clear.

Q. And if you were trying to effectively communicate whether or not Zyprexa carried a greater risk of weight gain than other second generation antipsychotics or traditional antipsychotics, wouldn't the best and easiest and straightforward fashion

Jack E. Jordan

to do is is say "it's a fact Zyprexa carries a greater risk of weight gain"?

Bandick, Michael (June 9, 2006)

398:4-7
Issues: 01 Plaintiff's Trial Designation

A. That would be one way to do it.
Q. Wouldn't it be the best way to do it?

Bandick, Michael (June 9, 2006)

398:10-399:5
Issues: 01 Plaintiff's Trial Designation

A. I don't know.
Q. Why don't you turn, now, sir, to Page 598 in Bandick Exhibit No. 7, which is the consensus statement, and go to question No. 4. Do you see that?
A. Yes.
Q. The question No. 4 reads: Given the above risks, how should patients be monitored for the development of significant weight gain dyslipidemia, and diabetes, and how should they be treated if diabetes develops, question mark."
Did I read that correctly?
A. Yes.
Q. The answer says: "Given the serious health risks, patients taking SGAs should receive appropriate baseline screening and ongoing monitoring." Did I read that correctly?
A. Yes.

Bandick, Michael (June 9, 2006)

399:14-400:18
Issues: 01 Plaintiff's Trial Designation

Q. Do you agree with that?
A. Based on my conversations with Lilly clinicians I believe that would be reasonable.
Q. And when did you form that belief?
A. I don't recall.
Q. What year?
A. Probably, 2003.

Jack E. Jordan

Q. Isn't there a -- what do you recall about what month you reached that conclusion based on your conversations with Lilly medical people?

A. I don't.

Q. Do you recall the context in which you reached that conclusion?

A. No.

Q. You just recall that you reached that conclusion after talking to Lilly medical people?

A. That's what I've said.

Q. Okay. Well, did any letters go out from the medical affairs departments to your customers, be it hospitals, third party payors, patients or doctors, informing them that Lilly believed as of 2003 that given the serious health risks patients taking SGAs should receive appropriate baseline screening and ongoing monitoring?

Bandick, Michael (June 9, 2006)
400:21-402:8
Issues: 01 Plaintiff's Trial Designation

A. There were materials that went out in the fall of 2003 with those directions.

Q. What materials would those be?

A. Those materials were associated with the label change that occurred for all second generation antipsychotics regarding association with hyperglycemia and appropriate screening and treatment of patients.

Q. Tell the jury what the PDR is?

A. PDR stands for Physician's Desk Reference. It is a compendium of all major pharmaceutical products -- not even major -- all pharmaceutical products that are available with a list of their indications, warnings, dosing, other considerations. It's an encyclopedia, if you will, of clinical information.

(Whereupon, Deposition Exhibit(s) 9 duly received, marked and made a part of the record.)

QUESTIONS BY MR. ALLEN:

Q. I've handed you what I've marked as Bandick Exhibit No. 9, which I'll represent to you is a 2005 PDR reference on Zyprexa.

Jack E. Jordan

Do you have that in front of you?

A. It appears that I do.

Q. Okay. You know the precaution section, you know where that is, don't you? You've seen this document a lot of times, haven't you?

Bandick, Michael (June 9, 2006)

402:10-403:24

Issues: 01 Plaintiff's Trial Designation

402:10 A. I said I'm generally familiar with the Zyprexa label.

Q. Sir?

A. I said I'm generally familiar with the Zyprexa label.

Q. Tell the jury what a precaution section is?

A. A, well, there are experts that can describe it better than me. Precaution generally is noted as something that a physician should take into account when they're considering prescribing the drug for a patient.

Q. And, of course, as we saw in the PhRMA documents or web page earlier, 403: 1 every single -- let me ask it this way.

This label is federally regulated by the Food and Drug Administration, correct?

A. I don't know that to be a fact.

Q. Okay. Look at the precaution section which begins on the fourth page of Bandick Exhibit No. 9.

Are you there with me?

A. I believe so.

Q. Then the precaution section goes to the next page.

Can you turn the page for me, please?

A. Yes.

Q. And there's a section in the precaution section entitled "Laboratory Tests," isn't there?

A. Yes, there is.

Q. Is there any recommendation in the precaution section of the label in 2005 suggesting that doctors or physicians monitor fasting plasma glucose?

404:4-5
Issues: 01 Plaintiff's Trial Designation

404: 4 A. If you could just give me a
5 moment.

Bandick, Michael (June 9, 2006)
404:24-405:7
Issues: 01 Plaintiff's Trial Designation

404:24 A. No, there's language,
405: 1 however, that's in the warning section which
2 is elevated, which would reflect even a
3 greater level of awareness, that patients
4 with an established diagnosis of diabetes
5 mellitus who are started on an atypical
6 antipsychotic should be monitored regularly
7 for worsening of glucose control.

Bandick, Michael (June 9, 2006)
405:12-406:5
Issues: 01 Plaintiff's Trial Designation

405:12 Q. My simple question was: In
13 the precaution section of the label is there
14 any laboratory testing recommended for
15 patients who take second generation
16 antipsychotics to have their fasting plasma
17 glucose monitored?
18 A. Not under laboratory tests in
19 the precaution section.
20 Q. Right. Now, if you go back
21 to the consensus statement, which is Exhibit
22 No. 8, is that correct, sir?
23 A. Consensus statement is
24 Exhibit No. 7.
406: 1 Q. I'm sorry, sir. Exhibit
2 No. 7. If you look at Page 598, and go to
3 599, the monitoring that is recommended
4 includes monitoring of fasting plasma
5 glucose; isn't that correct?

Bandick, Michael (June 9, 2006)
406:12-14
Issues: 01 Plaintiff's Trial Designation

406:12 A. Yes, that is one of the items
13 lifted under baseline monitoring.
14 Q. And what is it about the

Jack E. Jordan

Bandick, Michael (June 9, 2006)
406:19-407:7
Issues: 01 Plaintiff's Trial Designation

406:19 Q. Thank you.
20 Isn't it a fact, sir, that in
21 the marketing and promotional materials
22 related to Zyprexa, Eli Lilly touted as a
23 benefit and a safety message to consumers the
24 lack of a need to conduct ongoing monitoring
407: 1 including plasma glucose levels?
2 A. I'm not aware of any
3 communication to consumers on that topic.
4 Q. So it was never a safety
5 message to the audience for Zyprexa
6 marketing?
7 MR. HAMMERLE: I object to

Bandick, Michael (June 9, 2006)
407:9-409:23
Issues: 01 Plaintiff's Trial Designation

407: 9 A. As we discussed, the primary
10 audience for those message, clinical
11 messages, would be physicians.
12 Q. And you never used the lack
13 of ongoing monitoring as a safety and
14 efficacy message?
15 A. There are different kinds of
16 monitoring. And there, when Zyprexa was
17 launched in 1996 one of the things that
18 differentiated it from Clozaril was that
19 there was not required blood monitoring for
20 the risk of agranulocytosis.
21 So we did indicate in that
22 time frame and for some time after, that no
23 need for blood monitoring related to
24 agranulocytosis was one of Zyprexa's safety
408: 1 features.
2 Q. Did you ever indicate --
3 we'll show those documents in a minute.
4 Sir, let's go to the summary
5 of the consensus statement, Exhibit No. 7, on
6 Page 600. Do you see the summary, sir?
7 A. Yes, I do.
8 Q. I'm going to read it out loud
9 as follows: "The SGAs are of great benefit
10 to a wide variety of people with psychiatric
11 disorders. As with all drugs, SGAs are
12 associated with undesirable side effects.
13 One constellation of adverse effects is an

Jack E. Jordan

increased risk for obesity, diabetes, and dyslipidemia." Did I read that correctly?
A. Yes.
Q. I'm going to skip down to the next paragraph, it says: "These three adverse conditions are closely linked, and their prevalence appears to differ depending on the second generation antipsychotic used. Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia." Did I read that correctly?
A. That's what it says in this document.
Q. As the Brand Manager and the Director of Marketplace Management for Zyprexa in the years you have indicated, do you agree with that statement?
A. Lilly disagreed with that statement.
Q. Do they agree with it now?
A. I don't know.
Q. Did they agree with it the last time you checked when you were at Eli Lilly?
A. No.
Q. They did not agree with it?
A. They did not agree with it.
Q. But the fact of the matter is the consensus statement has reached a conclusion that Zyprexa is associated with the greatest weight gain and the highest occurrence of diabetes and dyslipidemia, correct?

Bandick, Michael (June 9, 2006)
410:2-8
Issues: 01 Plaintiff's Trial Designation

A. That was one of the conclusions of this group.
Q. Now, of course, you in marketing, and Eli Lilly, had known about this potential for a considerable amount of time before the release of this consensus statement, had you not?

Bandick, Michael (June 9, 2006)
410:20-411:6
Issues: 01 Plaintiff's Trial Designation

A. Lilly's conclusion, at least

Jack E. Jordan

up through the time that I was still with the company, was that that was not borne out by the data.

(Whereupon, Deposition Exhibit(s) 10 duly received, marked and made a part of the record.)

QUESTIONS BY MR. ALLEN:

Q. Sir, I'm going to hand you what has been marked as Bandick Exhibit No. 10. I have a copy for your counsel.

Bandick, Michael (June 9, 2006)
411:8-412:6
Issues: 01 Plaintiff's Trial Designation

Q. Do you have Exhibit No. 10 in front of you?

A. I do.

Q. You have seen this document before, have you not?

A. I have.

Q. When did you see this document?

A. I first saw this document when it was published in April 2002.

Q. This document, it's dated April 2002. It's Exhibit No. 10.

Can you briefly describe for the jury what it is?

A. This is the English translation of a Dear Health Care Professional letter that was distributed to physicians in Japan following a label change for Zyprexa in Japan.

Q. And what did Japan do, in summary for the jury, just to educate them, in regard to the label change on Zyprexa in April 2002?

Bandick, Michael (June 9, 2006)
415:5-416:24
Issues: 01 Plaintiff's Trial Designation

A. The Japanese regulatory agency affected a label change for Zyprexa that limited the eligible patient population for use of Zyprexa, including patients who either had diabetes or a history of diabetes.

There were some other guidelines as well. I'd say a clinician or regulatory person could give you better detail on that.

Exhibit 7
Jack E. Jordan

Q. What the Japanese government did is they put a black box warning on Zyprexa in Japan, didn't they?
A. It was comparable to what in the U.S. we would call a black box warning.
Q. And what they said -- and let me read a portion of this exhibit -- it says: "Emergency safety information regarding diabetic ketoacidosis and diabetic coma due to increased blood glucose during administration of an antipsychotic agent, Zyprexa tablets, olanzapine. Since the marketing of this product in June 2001, nine serious cases, parens, including two cases of death, close parens, with hyperglycemia, diabetic ketoacidosis and diabetic coma have been reported for which causal relationship with this product cannot be denied, parens, estimated number of patients treated with this product 137,000 as of the end of December 2001."
Did I read that correctly, sir?
A. Yes.
Q. So at least according to the Japanese government, the Ministry of Government, Zyprexa was marketed in Japan beginning in June 2001, correct?
A. I believe that's true.
Q. And they had seen enough evidence of serious adverse consequences related to diabetes, diabetic ketoacidosis and diabetic coma to recommend and, in fact, require, the equivalent of a black box label on Zyprexa in Japan --

Bandick, Michael (June 9, 2006)
417:3-3
Issues: 01 Plaintiff's Trial Designation

Q. -- did they not?

Bandick, Michael (June 9, 2006)
418:11-420:9
Issues: 01 Plaintiff's Trial Designation

A. What this document reflects is that the Japanese regulatory agency had decided, based on what they believed were cases of hyperglycemia, diabetic ketoacidosis and diabetic coma that such an action was warranted.

Exhibit 7
Jack E. Jordan

Q. "Such an action" being the placing of a black box, correct?
A. The equivalent in Japanese regulatory, yeah.
Q. The black box said, among other things, "Do not administer to patients with diabetes mellitus and those who have a history of diabetes mellitus.
No. 2. During administration of this product, observe sufficiently with such as measurement of blood glucose.
No. 3. Explain sufficiently to the patient and family members.
And it goes on to say, "Upon administration of this product, explain sufficiently to the patient and family members possible occurrence of serious adverse reactions, such as diabetic ketoacidosis and diabetic coma, et cetera. Provide guidance to them to see a physician suspending administration if such symptoms as thirst, polydipsia, polyuria, or frequent urination, et cetera, appear."
Did I read that correctly?
A. Yes.
Q. Did Lilly change its label for Zyprexa in the United States consistent with what was required by Japan in April of 2002?
A. No, it did not.
Q. Did Lilly get its sales force together and inform the sales force of the need to inform doctors, patients, third party payors and regulatory agencies -- let me rephrase the question.
Did Lilly, in its marketing and/or sales department, inform its sales representatives that they needed to tell doctors and patients of the equivalent of a black box warning being placed on Zyprexa in Japan?

Bandick, Michael (June 9, 2006)
420:14-21
Issues: 01 Plaintiff's Trial Designation

A. Lilly did provide background information to the U.S. sales organization for use in discussions with physicians if the question arose. Lilly sales representatives were not in direct contact with patients.
So to answer your question, information was made available through the sales organization for physicians.

Jack E. Jordan

Bandick, Michael (June 9, 2006)
421:17-20
Issues: 01 Plaintiff's Trial Designation

421:17 Q. Did Lilly send doctors in the
18 United States a Dear Doctor letter informing
19 them about the equivalent of a black box
20 warning on the Japanese label in April 2002?

Bandick, Michael (June 9, 2006)
421:23-422:9
Issues: 01 Plaintiff's Trial Designation

421:23 A. I don't recall a Dear Health
24 Care Professional letter being distributed on
422: 1 that topic.
2 Q. Once this, the equivalent of
3 a black box label was put on the Japanese
4 label for Zyprexa in April of 2002, shouldn't
5 Eli Lilly, in the interest of accuracy, fair
6 balance, and full disclosure, let its primary
7 care physicians and/or psychiatrists who were
8 one of its markets, know as quickly as
9 possible about this black box label in Japan?

Bandick, Michael (June 9, 2006)
422:14-20
Issues: 01 Plaintiff's Trial Designation

422:14 A. Lilly strongly disagreed with
15 the regulatory outcome in Japan based on
16 Lilly's analysis of the data. What it
17 provided its sales organization was
18 background information to be able to respond
19 to questions from physicians if it did come
20 up.

Bandick, Michael (June 9, 2006)
422:24-423:14
Issues: 01 Plaintiff's Trial Designation

422:24 Q. My question is assuming that
423: 1 a doctor in Cincinnati, Ohio, had no idea
2 what the Japanese regulatory authorities had
3 done in Japan concerning the equivalent of a
4 black box. You follow me?
5 A. Yes.

Exhibit 7
Jack E. Jordan

Q. And you did promote Zyprexa to doctors in Ohio, did you not?
A. I believe we did.
Q. And wouldn't it be incumbent upon you as a company to, as quickly as possible, inform the doctors in Ohio and all across the United States about the Japanese regulatory action, whether they asked about it or not?

Bandick, Michael (June 9, 2006)
423:17-424:1
Issues: 01 Plaintiff's Trial Designation

A. I'm uncomfortable speaking for people with a much deeper clinical background than me. But at the time, as I understand the decision, it was rooted in the fact because we didn't agree with the interpretation of the data, we didn't feel that it represented, we didn't feel that it represented actionable information for physicians in other countries.

Bandick, Michael (June 9, 2006)
424:9-13
Issues: 01 Plaintiff's Trial Designation

Q. What you just said is Lilly didn't agree with Japan so we thought we didn't have to tell doctors in the United States about Japan's actions; is that what you're saying?

Bandick, Michael (June 9, 2006)
424:17-425:7
Issues: 01 Plaintiff's Trial Designation

A. I think that oversimplifies what I said.
Q. How did I oversimplify it?
A. It's not a question of because we didn't agree. It was a question of because we didn't feel that the data reflected that interpretation. We were consistent in our communications with physicians about what we believe the data did represent.
Q. Who should make the decision about whether or not the, what the doctors

Exhibit 7
Jack E. Jordan

are going to do with this information or the patients, should it be Lilly, or should it be the doctors and the patients?

Bandick, Michael (June 9, 2006)
425:10-23
Issues: 01 Plaintiff's Trial Designation

A. I don't think I can answer your question.
Q. Didn't you just tell me Lilly didn't agree with the Japanese Ministry of Health concerning the addition of the equivalent of a black box?
A. That's correct.
Q. Lilly didn't agree. That's clear as a bell, right?
A. Lilly did not agree.
Q. Right. But Lilly was informed and was able to look at what Japan did and reach its own judgment; is that correct?

Bandick, Michael (June 9, 2006)
426:17-23
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: And what do you mean by "reach its own judgment?"
MR. ALLEN: About whether it agreed or disagreed with the Japanese Ministry of Health's decision to put the equivalent of a black box.

Bandick, Michael (June 9, 2006)
427:3-5
Issues: 01 Plaintiff's Trial Designation

Q. Lilly was able to look at it and make its own judgment about whether it agreed or disagreed with Japan, right?

Bandick, Michael (June 9, 2006)
427:8-14
Issues: 01 Plaintiff's Trial Designation

Exhibit 7
Jack E. Jordan

427: 8 A. As we said, yes, Lilly
9 disagreed with that outcome, disagreed with
10 that analysis, disagreed with that
11 interpretation.
12 Q. Right. But they were able to
13 look at what Japan did and make their own
14 judgment, right?

Bandick, Michael (June 9, 2006)
427:17-21
Issues: 01 Plaintiff's Trial Designation

427:17 THE WITNESS: Make their own
18 judgment regarding?
19 MR. ALLEN: Whether or not
20 they agreed or disagreed with
21 Japan's action?

Bandick, Michael (June 9, 2006)
427:24-428:4
Issues: 01 Plaintiff's Trial Designation

427:24 A. I'm sorry, I feel like we're
428: 1 in circles here.
2 Q. Oh, I know we're in circles,
3 you're doing it on purpose, but I'm going to
4 keep on asking you the question.

Bandick, Michael (June 9, 2006)
429:6-19
Issues: 01 Plaintiff's Trial Designation

429: 6 Q. Mr. Bandick, I'm discussing
7 with you, I believe, is it Bandick Exhibit
8 No. 10, the emergency safety information and
9 the equivalent of a black box in Japan; is
10 that correct?
11 A. Yes, is it.
12 Q. You testified a minute ago,
13 and I'm paraphrasing, that Lilly looked at
14 the data, they looked at the conclusions,
15 they looked at the information that Japan
16 had, they looked at the Japanese action, and
17 made a determination that they disagreed with
18 Japan. Is that a fact? Is that what you
19 said?

Bandick, Michael (June 9, 2006)

Exhibit 7
Jack E. Jordan

430:1-8
Issues: 01 Plaintiff's Trial Designation

A. Lilly medical had analyzed and made the determination that they felt it was an incorrect decision or an incorrect analysis.
Q. And Lilly got to look at the information and reach its own conclusion, right?
THE WITNESS: Which data?

Bandick, Michael (June 9, 2006)

430:11-23
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: The cases?
MR. ALLEN: The Japanese action and the reasons for it.
A. Lilly was aware of the data, Lilly was aware of the cases, and, yes, they had a chance to reach their own conclusion.
Q. Don't you think that immediately upon reaching that conclusion that you should have informed the United States doctors and United States consumers, the patients, of the Japanese action and allow the doctors and the patients to reach their own conclusion?

Bandick, Michael (June 9, 2006)

431:4-9
Issues: 01 Plaintiff's Trial Designation

A. That decision would not be mine to make, but I can tell you the policy that Lilly had to provide data that was accurate and truthful was something that we consistently applied before and after the Japanese regulatory change.

Bandick, Michael (June 9, 2006)

431:13-18
Issues: 01 Plaintiff's Trial Designation

Q. My only question is: Don't you think United States doctors and United States patients should have been told by Lilly about what happened in Japan and allow

Exhibit 7
Jack E. Jordan

the doctors and the patients to reach their own conclusion?

Bandick, Michael (June 9, 2006)
431:22-432:9
Issues: 01 Plaintiff's Trial Designation

A. That was not my decision to make.
Q. Understanding it was not your decision to make. As the Director of Marketplace Management and as the former Brand Manager for Zyprexa who communicates with the audience, including doctors and patients, don't you think that Lilly should have told U.S. doctors and U.S. patients of the Japanese action and allowed the doctors and the patients to reach their own conclusion?

Bandick, Michael (June 9, 2006)
432:14-433:3
Issues: 01 Plaintiff's Trial Designation

A. Lilly continued to provide data, and I would say that it was consistent before and after the label change. I'm not in a position to answer a should or should not question. I can tell you what we did.
Q. Well, sir, you, for one, certainly if you wanted to, as the director of, and I've all of a sudden blanked out, Director of Marketplace Management for Zyprexa, you certainly could have, on your own initiative, informed the sales force, and asked them to inform the doctors about the Japanese equivalent of a black box. You could have done that had you wanted?

Bandick, Michael (June 9, 2006)
433:6-16
Issues: 01 Plaintiff's Trial Designation

A. Those decisions don't take place in a vacuum and that's not something that I would have or could have done unilaterally.
Q. Isn't it true, sir, as the Director of Marketplace Management for Zyprexa that's exactly what you can do is you

Exhibit 7
Jack E. Jordan

can inform the sales force of a black box warning in a foreign country and ask the sales force to inform the doctors. Isn't that something you can do yourself?

Bandick, Michael (June 9, 2006)
433:22-434:9
Issues: 01 Plaintiff's Trial Designation

A. What I did in that role was to share content that was carefully reviewed and considered by members of all areas, as opposed to me making a decision one off as to what I thought might make the most sense.
Q. The Japanese action, Exhibit No. 10, had you wanted to, as the Director of Marketplace Management for Zyprexa, you could have sent that document, itself, to every sales representative in the United States and ask them to inform their doctors who they detailed, true?

Bandick, Michael (June 9, 2006)
434:16-20
Issues: 01 Plaintiff's Trial Designation

A. I stand by my earlier answer.
Q. Well, you only inform the sales force of regulatory actions in foreign countries if it helps Zyprexa but don't inform the sales force if it hurts Zyprexa?

Bandick, Michael (June 9, 2006)
434:24-435:4
Issues: 01 Plaintiff's Trial Designation

A. That's not the way we look at it.
Q. Have you ever informed the sales force of foreign regulatory action concerning a black box on antipsychotics?

Bandick, Michael (June 9, 2006)
435:10-22
Issues: 01 Plaintiff's Trial Designation

A. I don't recall an example.

Exhibit 7
Jack E. Jordan

Bruce Kinon, M.D.

(Whereupon, Deposition Exhibit(s) 11 duly received, marked and made a part of the record.)

QUESTIONS BY MR. ALLEN:

Q. Well, let me see if I can refresh your recollection. I'm going to hand you what's been marked as Bandick Exhibit No. 11. Provide it to your counsel. This is an e-mail you wrote, is it not? Sir, that's just a simple question, this is an e-mail that you wrote, is it not?

Bandick, Michael (June 9, 2006)
436:14-437:11
Issues: 01 Plaintiff's Trial Designation

436:14 A. Yes, it is.
15 Q. Okay. Can you tell the jury
16 the date of this e-mail that you wrote?
17 A. October 18, 2002.
18 Q. Can you tell the jury the
19 subject of the e-mail as reflected on
20 Exhibit 11 that you wrote?
21 A. The subject is Risperidone
22 Cerebrovascular Warning in Canada.
23 Q. What's risperidone?
24 A. It's the molecule for
437: 1 Risperdal.
2 Q. Who manufactured Risperdal?
3 A. Janssen manufactures
4 Risperdal.
5 Q. Was Risperdal a competitor to
6 Zyprexa?
7 A. Yes.
8 Q. Were you trying to beat the
9 competition in sales of Zyprexa over
10 Risperdal at the time you were marketplace
11 manager?

Bandick, Michael (June 9, 2006)
437:14-19
Issues: 01 Plaintiff's Trial Designation

437:14 THE WITNESS: Were we trying
15 to beat the competition in sales of
16 Zyprexa over Risperdal?
17 MR. ALLEN: Sure.
18 THE WITNESS: Is that your
19 question?

Exhibit 7
Jack E. Jordan

Bruce Kinon, M.D.

Bandick, Michael (June 9, 2006)
437:20-20
Issues: 01 Plaintiff's Trial Designation

437:20 MR. ALLEN: Yes, it is.

Bandick, Michael (June 9, 2006)
437:23-438:8
Issues: 01 Plaintiff's Trial Designation

437:23 A. In any marketplace where
24 Zyprexa competed our goal would have been to
438: 1 realize the full commercial potential of the
2 molecule, and that would involve, at times,
3 differentiating it from other antipsychotics.
4 Q. Who is this e-mail to? You
5 don't need to read everybody's name but can
6 you be fair and accurate to the jury and
7 balanced and tell the jury who the recipients
8 of this e-mail represent?

Bandick, Michael (June 9, 2006)
438:17-439:9
Issues: 01 Plaintiff's Trial Designation

438:17 A. Generally, this is an
18 internal memo to members and other
19 affiliates, which we discussed earlier were
20 other countries where Zyprexa was marketed,
21 as well as to some internal Zyprexa
22 personnel.
23 Q. You sent this e-mail around
24 the world, in essence?
439: 1 A. That's true.
2 Q. And the subject is
3 risperidone, which is Risperdal, Cerebral
4 Vascular Warning in Canada, right?
5 A. Yes.
6 Q. Why would you want to be
7 informing -- and were some of these people
8 you sent the e-mail to involved in the issue
9 of marketing and sales for Zyprexa?

Bandick, Michael (June 9, 2006)
439:12-441:18
Issues: 01 Plaintiff's Trial Designation

439:12 A. Yes. Some of these people
13 were involved with the marketing and sales of

Exhibit 7
Jack E. Jordan

Bruce Kinon, M.D.

Zyprexa.

Q. Okay. Let me read the e-mail for you out loud and for the jury.

From Michael Bandick, 10/18/2002. Subject Risperidone Cerebral Vascular Warning in Canada. Yesterday some of you may have received a document containing a Dear Doctor letter that was recently issued by Janssen in Canada. The purpose of this e-mail is to provide some background and recommendations regarding this letter.

Background: Earlier this year Health Canada requested all antipsychotic manufacturers, parens, including Lilly, to provide safety data regarding cerebrovascular, parens, for example, stroke, close parens, adverse events, CVAEs. Upon review of all of the information provided, Health Canada required that Janssen and only Janssen update their label. Janssen and Health Canada are still negotiating final details of the label change and Health Canada has requested that Janssen issue a Dear Doctor letter, attached, in the interim. It is likely that the Risperdal label will now contain a black box warning pertaining to CVAEs. In addition, physicians are advised to assess the risks of using Risperdal in elderly patients with dementia. Risperdal has an indication for this in Canada."

Did I read that correctly?

A. Yes.

Q. Now, do you then give instructions to the recipients as to how they're supposed to share the Dear Doctor letter from Canada with the doctors to whom Zyprexa is marketed in the United States?

THE WITNESS: I'm sorry, could you repeat your question?

MR. ALLEN: Yes.

QUESTIONS BY MR. ALLEN:

Q. Let me just get straight and to the point. When Canada took regulatory action against Risperdal and required them to send out a Dear Doctor letter addressing the risk of cerebrovascular disease, didn't you ask that the sales force for Zyprexa in the United States make this fact known to the doctors in the United States as a selling point against Risperdal and in favor of Zyprexa?

441:21-445:9
Issues: 01 Plaintiff's Trial Designation

441:21 A. The direction that was given
22 in this note is that the attached letter is
23 not approved for use in the field. This was
24 to provide information to affiliates around
442: 1 the world to keep them apprised of important
2 regulatory events.
3 Q. Didn't you say under do's,
4 "share this information selectively as
5 appropriate?"
6 A. Yes.
7 Q. And didn't you say in this
8 e-mail that it would be appropriate to make
9 mention of this information when confronted
10 with speculation and allegations regarding
11 our label?
12 A. The context for that remark
13 is that all manufacturers were required to
14 provide data on that topic and Janssen and
15 risperidone were the only ones who were
16 required to make a label change. Sometimes
17 there can be speculation that if one company
18 has made that change it must apply to all
19 products in the class. We felt it was
20 important, from a safety standpoint to
21 provide truthful and balanced information,
22 that that did not apply to Zyprexa.
23 Q. Doesn't your e-mail say "it
24 would be appropriate to make mention of this
443: 1 information when confronted with speculation
2 and allegations regarding our own label.
3 While we do not want to speculate on
4 potential label changes, ours or competitors,
5 we would like to point out actual label
6 changes, such as the recent addition of a
7 black box warning, pending finalization of
8 language to the Risperdal label in Canada
9 regarding CVAE."
10 Did I read that correctly?
11 A. That's what it says.
12 Q. And it says: "We would like
13 to point out actual label changes such as the
14 recent addition of a black box warning
15 pending to the Risperdal label in Canada."
16 A. And the context for that
17 remark the first part of the sentence is
18 avoiding speculation on potential label
19 changes, because we thought that would be
20 inappropriate. However, if there was an
21 actual label change that that would be
22 something that would potentially be
23 appropriate. And as you pointed out under do
24 was to share information selectively as
444: 1 appropriate. That does not represent a

proactive tell-every-customer-you've-got. If it came up that was something that could be cited as a fact.

Q. It says "we would like," sir, do you see the phrase "we would like to point out actual label changes such as the recent addition of a black box warning pending finalization of language to the Risperdal label in Canada regarding CVAE."

Did I read that correctly?

A. Yes. It's the second part of the sentence that begins by saying we shouldn't be speculating.

Q. But if a label change is made we'd like to point it out?

A. If appropriate to that situation.

Q. Yeah, okay. So it says if a label change is made, and this is your words, "we with like to point out actual label changes," right?

A. In the context of doing it selectively as appropriate as it says at the very bottom.

Q. Okay. Was an actual label change on Zyprexa made in Japan in April of 2002?

A. Yes.

Q. Would you like to point that out?

THE WITNESS: What do you mean?

Bandick, Michael (June 9, 2006)
445:14-18
Issues: 01 Plaintiff's Trial Designation

Q. Did you send out an e-mail to the same recipients or their colleagues as reflect in Bandick No. 11, and say we'd like to point out the black box label change in Japan? Did you say that?

Bandick, Michael (June 9, 2006)
445:21-446:8
Issues: 01 Plaintiff's Trial Designation

A. We did not send out a document that said we would like to point out the label change in Japan.

Q. Did you send out a document that says, while we do not want to speculate

on potential label changes, ours or competitors, we would like to point out actual label changes such as the recent addition of the equivalent of a black box warning in Japan to the Zyprexa label regarding diabetic ketoacidosis, coma and death. Did you say that?

Bandick, Michael (June 9, 2006)
446:17-447:15
Issues: 01 Plaintiff's Trial Designation

446:17 A. We did not send out a document that said we would like to point out that an actual label change occurred with the equivalent of a black box for Zyprexa in Japan.

The reason for that was that we didn't believe the data warranted that outcome.

447: 1 Q. Did you evaluate the data concerning the changes in the Risperdal label in Canada and reach a conclusion you agreed with?

A. We had clinical personnel who were responding to Health Canada's request for that data. And we were very familiar with the interpretation and analysis that Health Canada used.

Q. Let's look at what you did. When a label change was made in Japan concerning the Zyprexa label and diabetic ketoacidosis, coma and death, you did not send out an e-mail asking that this news be shared with doctors, correct?

Bandick, Michael (June 9, 2006)
447:18-448:2
Issues: 01 Plaintiff's Trial Designation

447:18 Q. Correct, sir?

A. That's correct.

Q. But when a label change was made to your competition, Risperdal in Canada, with a black box concerning CVAE, cerebrovascular events, you sent out a world wide e-mail and said to the recipients we'd like to share the black box warning on the Risperdal label? Isn't that what happened?

Bandick, Michael (June 9, 2006)
448:9-12
Issues: 01 Plaintiff's Trial Designation

448: 9 A. I can go back to the earlier
10 answer that I gave you to a similar question.
11 Q. Just answer my last question,
12 please?

Bandick, Michael (June 9, 2006)
448:15-449:4
Issues: 01 Plaintiff's Trial Designation

448:15 THE WITNESS: If you can read
16 back his last question I'll do my
17 best to answer it.
18 (The Court Reporter read the
19 requested material, as set forth
20 herein:
21 "QUESTION: But when a label change was
22 made to your competition, Risperdal in
23 Canada, with a black box concerning CVAE,
24 cerebrovascular events, you sent out a
449: 1 world wide e-mail and said to the
2 recipients we'd like to share the black box
3 warning on the Risperdal label? Isn't that
4 what happened?")

Bandick, Michael (June 9, 2006)
449:16-450:7
Issues: 01 Plaintiff's Trial Designation

449:16 Q. I mean, can you answer that
17 question? There wasn't an answer on the
18 record to that one? What was the answer to
19 that question?
20 A. We did not intend, nor did we
21 communicate broadly to physicians about the
22 Risperdal label change in Canada on CVAE. We
23 informed members of sales and marketing in
24 other markets of the change. We advised them
450: 1 to share the information selectively as
2 appropriate, and similarly, we provided
3 background information to the U.S. sales
4 organization and to other affiliates on the
5 label change in Japan, and provided them with
6 Lilly's view on why we felt the decision was
7 inappropriate.

Bandick, Michael (June 9, 2006)
450:11-17
Issues: 01 Plaintiff's Trial Designation

450:11 Q. Do you see any hypocrisy in
12 the action you took regarding the changes to
13 the label made in Japan on Zyprexa versus the
14 actions you took concerning the black box
15 addition of the warning in Canada on the
16 Risperdal label? Do you see any hypocrisy in
17 that action?

Bandick, Michael (June 9, 2006)
450:21-451:4
Issues: 01 Plaintiff's Trial Designation

450:21 A. No.
22 Q. You think the actions
23 concerning the black box label change, the
24 equivalent of a block box label change in
451: 1 Japan on Zyprexa, do you see any
2 inconsistency in your action concerning that
3 action in Japan versus what you did
4 concerning the Risperdal label in Canada?

Bandick, Michael (June 9, 2006)
451:7-10
Issues: 01 Plaintiff's Trial Designation

451: 7 A. I see them as very different
8 situations.
9 Q. Do you see any inconsistency
10 in what you did, sir, Mr. Bandick?

Bandick, Michael (June 9, 2006)
451:13-20
Issues: 01 Plaintiff's Trial Designation

451:13 A. I can't evaluate the
14 consistency or inconsistency, I see them as
15 different situations.
16 Q. Thank you, sir.
17 (Whereupon, Deposition
18 Exhibit(s) 12 duly received, marked
19 and made a part of the record.)
20 QUESTIONS BY MR. ALLEN:

Bandick, Michael (June 9, 2006)
452:21-454:8
Issues: 01 Plaintiff's Trial Designation

452:21 Q. Sir, you recognize this
22 document, Exhibit 12, do you not?
23 A. Yes, I do.
24 Q. You wrote it?
453: 1 A. Yes, I did.
2 Q. When did you write it?
3 A. August of 2000.
4 Q. Okay. Sir, this document,
5 read the title to the jury, please.
6 A. Zyprexa Primary Care Strategy
7 and Implementation Overview.
8 Q. Why did you write this?
9 A. This was about one month into
10 my role as Brand Manager for Zyprexa in
11 primary care, and I believe this was a, an
12 overview for an internal audience, probably
13 other members of the Zyprexa Marketing Team
14 and, perhaps, other internal audiences.
15 Q. Zyprexa, had been on the
16 market since 1996; is that correct?
17 A. Yes.
18 Q. Why were you considering
19 expanding the market to primary care
20 physicians?
21 A. In studying where
22 antipsychotics were used, and understanding
23 where patients with schizophrenia and bipolar
24 disorder, or in this case bipolar mania
454: 1 presented, we determined that there was
2 significant unmet need in the primary care
3 setting and that we would be able to meet
4 some of those unmet medical needs by
5 promoting the drug in the primary care
6 segment.
7 Q. Is that a long way of saying
8 you wanted to make more money?

Bandick, Michael (June 9, 2006)
454:14-21
Issues: 01 Plaintiff's Trial Designation

454:14 Q. Sir?
15 A. It's not a way of saying
16 anything other than what I said. There was
17 unmet medical need. It's where those
18 patients presented and it's where a lot of
19 antipsychotic prescribing was already taking
20 place.
21 Q. Isn't it true that Zyprexa's

Bandick, Michael (June 9, 2006)
455:5-10
Issues: 01 Plaintiff's Trial Designation

455: 5 Q. You know what year X is,
6 don't you, sir?
7 A. I do.
8 Q. Isn't it true that Zyprexa
9 success was critical to Lilly's corporate
10 performance with the advent of Year X?

Bandick, Michael (June 9, 2006)
457:19-458:10
Issues: 01 Plaintiff's Trial Designation

457:19 Q. Okay, sir, now let's look at
20 Exhibit No. 12 which this is your document,
21 you did draft it in August of 2000; is that
22 right?
23 A. Yes.
24 Q. I'll read the background.
458: 1 "Background: Following several months of
2 study by the Lilly USA Zyprexa Brand Team the
3 affiliate approved the recommendation that
4 Lilly actively promote Zyprexa to selected
5 current primary care prescriber targets."
6 Did I read that correctly?
7 A. Yes.
8 Q. But, of course, sir, in order
9 to do that you would have to face several
10 challenges, would you not?

Bandick, Michael (June 9, 2006)
458:13-14
Issues: 01 Plaintiff's Trial Designation

458:13 THE WITNESS: What challenges
14 are you referring to?

Bandick, Michael (June 9, 2006)
459:1-10
Issues: 01 Plaintiff's Trial Designation

459: 1 Q. Sir, my question on the table
2 is in order to actively promote Zyprexa to
3 selected current primary care prescriber
4 targets you would face many challenges, isn't

that true?
A. There are challenges in every product launch and, yes, I've indicated a few that were specific to this launch.
Q. One of the challenges was very difficult to overcome, wasn't it, sir?

Bandick, Michael (June 9, 2006)

459:13-460:4
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: Is there a specific one you had in mind?
MR. ALLEN: Yes, sir. Let's go to challenge.
QUESTIONS BY MR. ALLEN:
Q. Tell the jury what a challenge is?
A. A challenge, in this context, would be to understand where extra care or effort might be taken so as to increase your probability of having a successful launch.
Q. Okay. Was it one of the challenges that Zyprexa's primary indications, schizophrenia and bipolar, are not viewed as primary care physician treated conditions?

Bandick, Michael (June 9, 2006)

461:7-463:23
Issues: 01 Plaintiff's Trial Designation

A. Yes, we had learned in market research that primary care physicians didn't acknowledge that there were patients who suffered from schizophrenia and bipolar disorder in their practice. Yet when we described how those patients presented, we learned there were, in fact, those patients in their practice who were either being undiagnosed or underdiagnosed or misdiagnosed.
Q. Okay, sir, why don't you look at your challenges section of your memo Exhibit 12, okay? Do you have it there in front of you?
A. I do.
Q. Why don't you read it out loud to the jury, please.
THE WITNESS: The whole section?
MR. ALLEN: Yes, sir?

A. Most PCPs currently prescribe a low volume of antipsychotics and mood stabilizers.

Q. Can you read it very slowly and distinctly so the jury can hear you when they hear the tape back.

A. Certainly.

Q. Go ahead.

A. "Most PCPs currently prescribe a low volume of antipsychotics and mood stabilizers. Many PCPs will refer patients in need of psychotropic treatment to a specialist rather than treat that patient. Key barriers to uptake include PCPs lack of training in this category, limited time with patients, and an aversion to perceived risk. Zyprexa's primary indications, schizophrenia and bipolar, are not viewed as PCP treated conditions so there's not a specific indication for Lilly reps to promote in the PCP segment."

Q. Let's stop right there. These are your words: "Zyprexa's primary indications, schizophrenia and bipolar, are not viewed as PCP treated conditions, so there's not a specific indication for Lilly reps to promote in the PCP segment." Did I read that correctly?

A. Yes.

Q. I want to break this sentence down. This is your sentence, you wrote it, right?

A. Yes, I did.

Q. Let's look at the first part, "Zyprexa's primary indications, schizophrenia and bipolar." Aren't those the only indications for Zyprexa at that time?

A. Yes, that's correct.

Q. So when you said "Zyprexa's primary indications, schizophrenia and bipolar, are not viewed as PCP treated conditions," it would be more accurate to say that Zyprexa's only indications, schizophrenia and bipolar, are not viewed as PCP treated conditions?

Bandick, Michael (June 9, 2006)
464:4-17
Issues: 01 Plaintiff's Trial Designation

A. That, probably, would have been a better way to say that phrase.

Q. Okay. Then I'm going to read it like that and we're going to continue.

Exhibit 7
Jack E. Jordan

Bruce Kinon, M.D.

Continuing: Zyprexa's only indications, schizophrenia and bipolar, are not viewed as PCP treated conditions. so there's not a specific indication for Lilly reps to promote in the PCP, primary care physician segment; is that correct?

A. That's what's written there.

Q. You wrote it, didn't you?

A. Yes, I did.

Q. Did you agree with it?

Bandick, Michael (June 9, 2006)
464:20-465:6
Issues: 01 Plaintiff's Trial Designation

A. Putting this document in context, as I mentioned, I had been in the role for about a month. As I look at it now, and even as I look at materials that were then sent to the sales organization in part of our implementation, I would agree that this is not the clearest language. However, as we got more educated about the segment and understood what the opportunities were this doesn't reflect the kind of language that we supplied to our sales organization.

Bandick, Michael (June 9, 2006)
465:11-466:12
Issues: 01 Plaintiff's Trial Designation

Q. Sir, you've already told us in this document you had reached the conclusion already you were going to market to PCPs. That's the whole point of Exhibit No. 12, isn't it? You'd already reached that conclusion?

A. That's not the point of that document.

Q. Doesn't it say here? "Following several months of study by Lilly USA Zyprexa Brand Team, the affiliate approved the recommendation that Lilly actively promote Zyprexa to selected current primary care prescribers targets," Isn't that what this says?

A. Yes.

Q. You had already reached that conclusion. And then you go down and say in the challenges, after reaching the conclusion you're going to market to PCPs, that Zyprexa's primary indications, which you now

admit is the only indications, schizophrenia and bipolar are not viewed as PCP treated conditions so there's not a specific indication for Lilly reps to promote in the PCP segment. Isn't that what you said?

Bandick, Michael (June 9, 2006)
466:17-467:10
Issues: 01 Plaintiff's Trial Designation

A. What I wrote in this document, specifically the phrase "there's not a specific indication for Lilly reps to promote in the PCP segment," is, as I said, a less clear -- is a less clear way to convey what we ended up training our sales reps on.
Q. An indication, as you told me at the very beginning of this deposition, is a term of art. And that's an FDA approved indication and that's the only indication you can promote Zyprexa for, correct?
A. I don't recall using the phrase term "of art" but it is true that the promotion was limited to approved indications.
Q. And your memo here, Exhibit 12, says there is not an indication for Lilly reps to promote in the PCP segment, correct?

Bandick, Michael (June 9, 2006)
467:14-468:1
Issues: 01 Plaintiff's Trial Designation

A. Admittedly, that's not the clearest sentence, and certainly was better informed as I spent more time in the role. When we launched the product there was a great deal of clarity on the indications and how we were going to be communicating with physicians.
Q. Well, at least at the time you wrote this memo, you said "there's not an indication to market to primary care physicians." When you wrote it that's what you said?

Bandick, Michael (June 9, 2006)
468:7-22
Issues: 01 Plaintiff's Trial Designation

468: 7 Q. Right?
8 A. I would link this sentence
9 back to the earlier comment about primary
10 care physicians didn't acknowledge
11 schizophrenia and bipolar as a -- those
12 patients weren't frequently part of their
13 practice.
14 So in trying to make the
15 connection between what PCPs acknowledged, a
16 challenge for anyone marketing Zyprexa in
17 that segment would be to overcome the fact
18 that they didn't acknowledge that there were
19 a lot of patients with those diseases in
20 their practice.
21 Q. That's your best answer to my
22 question?

Bandick, Michael (June 9, 2006)
469:7-21
Issues: 01 Plaintiff's Trial Designation

469: 7 A. Yes, is it.
8 Q. Okay. The first sentence in
9 challenges says -- and we're going to move
10 on -- says: "Most PCPs currently prescribe a
11 low volume of antipsychotics and mood
12 stabilizers." Was Zyprexa a mood
13 stabilizers?
14 A. Mood stabilizer commonly
15 refers to drugs used to treat bipolar and
16 Zyprexa, had an indication for bipolar mania.
17 Q. Now, you figured out a way,
18 and this is your document, to get around this
19 problem of not having a specific indication
20 for Lilly reps to promote in the PCP segment.
21 Didn't you figure out a way to do that?

Bandick, Michael (June 9, 2006)
470:1-471:21
Issues: 01 Plaintiff's Trial Designation

470: 1 A. We promoted Zyprexa in the
2 primary care segment based on approved
3 indications.
4 Q. What's positioning?
5 A. Positioning refers in a
6 marketing context to the relative position
7 that one product has to another. You could
8 use a number of different axes to measure
9 that.
10 Q. Why don't you go down, after
11 challenges, which we just read, there's a

segment on position, right?
A. Um-hum.
Q. Sir?
A. Yes, that's true.
Q. You underlined this sentence, do you not, the first sentence under position?
A. I did underline the first sentence in that section.
Q. And you say this: "Position: Zyprexa. The safe, proven solution in mood, thought, and behavioral disorders."
Did I read that correctly?
A. You did.
Q. Didn't you tell me hours ago in this deposition that there was no indication for Zyprexa for the treatment of mood?
A. That's correct.
Q. Didn't you tell me hours ago there was no indication, approved indication, for Zyprexa for the treatment of thought disorders?
A. That's correct.
Q. Didn't you tell me hours ago that there was no approved indication for Zyprexa for the treatment of behavioral disorders?
A. Yes, that's true.
Q. Yet, when you wrote this e-mail or this document, Exhibit No. 12, you intended to position Zyprexa as a safe, proven solution in mood, thought and behavioral disorders; is that correct, sir?

Bandick, Michael (June 9, 2006)
472:1-6
Issues: 01 Plaintiff's Trial Designation

A. A position is not the same as a verbatim. It's not the same as a message to physicians. So it is, in fact, inappropriate to compare a desired position in a prelaunch planning document to what we ultimately promoted to physicians.

Bandick, Michael (June 9, 2006)
472:10-14
Issues: 01 Plaintiff's Trial Designation

Q. My only question was: When you prepared Exhibit No. 12, you wrote that

you intended to position Zyprexa as a safe, proven solution in mood, thought, and behavioral disorders?

Bandick, Michael (June 9, 2006)
472:19-473:12
Issues: 01 Plaintiff's Trial Designation

A. As I indicated, a position and a desired position in a prelaunch planning document, does not represent the same as a verbatim to a sales organization or a promotion to a customer.
Q. Is that your best answer to my question?
A. Yes, it is.
(Whereupon, Deposition Exhibit(s) 13 duly received, marked and made a part of the record.)
QUESTIONS BY MR. ALLEN:
Q. Sir, you've seen Exhibit No. 13, haven't you, Bandick?
A. Give me a moment with it please.
Q. The Viva Zyprexa, document? My question is: Have you seen this before?

Bandick, Michael (June 9, 2006)
474:2-4
Issues: 01 Plaintiff's Trial Designation

A. I'm refamiliarizing myself with it.
Q. So the answer's yes?

Bandick, Michael (June 9, 2006)
475:15-22
Issues: 01 Plaintiff's Trial Designation

Q. My question on the table is you have reviewed and seen this document before, haven't you, sir?
A. I have seen it and I'm almost done reviewing it.
Q. Tell the jury what the Viva Zyprexa launch meeting was without reference to that document.

Bandick, Michael (June 9, 2006)
476:8-477:16
Issues: 01 Plaintiff's Trial Designation

476: 8 A. Viva Zyprexa launch meeting
9 referred to the initial launch in primary
10 care in October of 2000.
11 Q. And that was a launch in
12 Orlando, Florida, right?
13 A. Yes, I believe so.
14 Q. Did you speak at that launch?
15 A. Yes, I did.
16 Q. Now, I'm confused. You're
17 launching Zyprexa in October of 2000 but
18 Zyprexa had been on the market since 1996,
19 right?
20 A. In psychiatry, yes.
21 Q. So from '96 to October of
22 2000, Zyprexa had been launched in
23 psychiatry, and psychiatry alone; is that
24 correct?
477: 1 A. Yes. With the neuroscience
2 sales organization and their call targets,
3 primarily, psychiatrists.
4 Q. And the approved indications
5 on the label in '96 and in the fall of 2000
6 were psychiatric conditions, schizophrenia
7 and bipolar mania, correct?
8 A. The bipolar approval came in,
9 I believe, March of 2000.
10 Q. So what I said was correct?
11 A. No. You said that in '96 as
12 in 2000 those two indications were approved.
13 The second one came in March of 2000.
14 Q. Doesn't this document,
15 Exhibit number, what number is -- 12, sir, or
16 13?

Bandick, Michael (June 9, 2006)
477:18-21
Issues: 01 Plaintiff's Trial Designation

477:18 Q. Thirteen. The Zyprexa launch
19 meeting Viva Zyprexa, doesn't this document
20 expressly tell us Lilly's motive for entering
21 the primary care physician market?

Bandick, Michael (June 9, 2006)
477:24-481:3
Issues: 01 Plaintiff's Trial Designation

477:24 Q. Doesn't it answer that very
478: 1 question?
2 A. Well, as you pointed out
3 there are a hundred pages. I wouldn't
4 characterize this document as simply
5 explaining the motive.
6 Q. I didn't say it simply
7 explained the motive.
8 Isn't one of the things this
9 document did is answer the question why you
10 were entering the primary care physician
11 market, you, being Lilly?
12 A. Yes, that is one of the
13 questions that it answers.
14 Q. You're right there on the
15 page I see. You're on Page 68, aren't you?
16 A. Yes, I am.
17 Q. You helped prepare this
18 slide, didn't you?
19 A. Yes, I believe I did.
20 Q. And by the way, wasn't this
21 launch meeting videotaped?
22 A. Parts of it, I believe.
23 Q. Including your presentation?
24 A. I don't know that I've ever
479: 1 viewed that. I don't know.
2 Q. Did you all get up -- did you
3 all have a song that was created for this
4 presentation?
5 A. Yes.
6 Q. Jail House Rock?
7 A. No, it wasn't called Jail
8 House Rock.
9 Q. Oh, Viva Las Vegas but you
10 all changed the words to Viva Zyprexa, right?
11 A. Yes.
12 Q. We're going to get to the --
13 by the words, when you created the song Viva
14 Zyprexa, those words were intended to convey
15 a message, weren't they, sir?
16 A. To an internal audience, yes.
17 Q. To an internal audience they
18 were intended to convey a message, right,
19 that song Viva Zyprexa?
20 A. Yes.
21 Q. Did you sing the song Viva
22 Zyprexa at the launch meeting?
23 A. I did not.
24 Q. Okay. Now I want to go back
480: 1 to this question of why Lilly entered the
2 primary care physician market, that's on
3 Page 68, and it says right here, "Zyprexa,
4 primary care, why are we entering this
5 market, question mark?" Right?
6 A. Yes.
7 Q. I don't have time to read
8 every bullet point but go one, two, three,

four, five bullet points down. Can you read to the jury what you said as to why Lilly was entering the primary care market for Zyprexa?

A. One of several reasons on this page reads: "Zyprexa's success is crucial to corporate performance. PCPs represent last major untapped segment."

Q. Zyprexa's success is crucial to corporate performance was one of the reasons listed as to why Lilly was entering this market, right?

Sir?

A. The context for this document was that this was a sales organization audience and we were providing motivation for them to understand how they fit into the bigger picture.

Q. You were telling the truth to the sales reps, weren't you?

Bandick, Michael (June 9, 2006)
481:4-4
Issues: 01 Plaintiff's Trial Designation

481: 4 A. We were.

Bandick, Michael (June 9, 2006)
489:3-9
Issues: 01 Plaintiff's Trial Designation

Q. Sir, the Viva Zyprexa song, the first two lines: "The whole new purpose gonna set my soul, set my soul on fire." Did I read that correctly?

A. Yes.

Q. There was a whole new purpose for Zyprexa in the fall of 2000?

Bandick, Michael (June 9, 2006)
489:12-15
Issues: 01 Plaintiff's Trial Designation

A. I didn't write the lyrics to the song, I don't know what the lyricist had in mind with "whole new purpose."

Q. Sir, by the way, you didn't

Bandick, Michael (June 9, 2006)

490:9-9
Issues: 01 Plaintiff's Trial Designation

490: 9 THE WITNESS: I'm sorry?

Bandick, Michael (June 9, 2006)

490:12-23
Issues: 01 Plaintiff's Trial Designation

490:12 Q. Wasn't this launch for every
13 single Zyprexa sales rep in the country?
14 A. No.
15 Q. For primary care physicians.
16 A. For primary care, that's
17 correct.
18 Q. How many sales reps attended?
19 A. Approximately, 550.
20 Q. I'm going to skip down. It
21 says "a whole new purpose going to set my
22 soul." Was there a whole new purpose for
23 Zyprexa in the fall of 2000?

Bandick, Michael (June 9, 2006)

491:2-4
Issues: 01 Plaintiff's Trial Designation

491: 2 A. I didn't look at it that way.
3 Q. So you don't think there was
4 a whole new purpose?

Bandick, Michael (June 9, 2006)

491:7-492:11
Issues: 01 Plaintiff's Trial Designation

491: 7 A. That's not how I would
8 characterize it. We were launching the
9 product into the primary care segment.
10 Q. Let's go down to the third
11 versus: "Yeah, we're helping patients, Viva
12 Zyprexa, many wonderful indications, Viva
13 Zyprexa."
14 Did I read that correctly?
15 A. You did.
16 Q. Many wonderful indications.
17 There was only two indications, weren't
18 there, sir?
19 A. That's correct.
20 Q. Schizophrenia and manic,
21 mania related to bipolar disorder disease,

Exhibit 7
Jack E. Jordan
Bruce Kinon, M.D.

right?
A. That's correct.
Q. So there wasn't many
492: 1 wonderful indications, were there, sir?
A. I assume this had more to do
with getting the right number of syllables
into that line.
Q. You don't think it had
something to do with mood, thought,
irritability and anxiety?
A. I'm quite certain the person
who wrote the lyrics to this song was not
aware of our strategy or our promotional
message.

Bandick, Michael (June 9, 2006)
493:3-494:3
Issues: 01 Plaintiff's Trial Designation

493: 3 Q. Last, lyrics of the last
stanza: "Can't rest now I've got to run, I'm
gonna tell everyone, might tell a doctor 50
times, give a perfect message on every shot,
keep Zyprexa at the top, Viva Zyprexa, Viva
Zyprexa."
Did I quote from the lyrics
correctly?
A. You left out a couple of
lines in that stanza, but yes.
Q. "Might tell a doctor 50
times, give a perfect message on every shot,
keep Zyprexa on top." Right?
A. As you just said, you left a
few lines out of that stanza but the other
lines were correct.
Q. Okay. By leaving the lines
out did I misrepresent the song in any way?
A. I don't know how you intend
to represent the song.
Q. Never mind, sir. Heck,
you're smarter than me.
494: 1 (Whereupon, Deposition
Exhibit(s) 17 duly received, marked
and made a part of the record.)

Bandick, Michael (June 9, 2006)
494:12-17
Issues: 01 Plaintiff's Trial Designation

494:12 Q. -- Bandick Exhibit No. 17.
You know what this is, don't you?
Well, I'll tell the jury what

Exhibit 7
Jack E. Jordan

Bruce Kinon, M.D.

15 it is and see if you agree. This is the
16 June 2002 Zyprexa Primary Care Sales Force
17 Resource Guide, right?

Bandick, Michael (June 9, 2006)
494:22-23
Issues: 01 Plaintiff's Trial Designation

494:22 Q. What number is it?
23 A. It says 17.

Bandick, Michael (June 9, 2006)
495:15-21
Issues: 01 Plaintiff's Trial Designation

495:15 Q. Sir, I didn't ask you the
16 read every page. You recognize this as the
17 Primary Care Sales Resource Guide for
18 June 2002?
19 A. I'm taking a look through the
20 document because I was no longer in the
21 primary care role in June of 2002.

Bandick, Michael (June 9, 2006)
496:9-497:13
Issues: 01 Plaintiff's Trial Designation

496: 9 Q. Can you turn to Page 77 of
10 the Primary Care Sales Force Resource Guide?
11 A. Yes.
12 Q. Exhibit 17. Who's the
13 patient profile No. 1?
14 A. It says Donna is a --
15 Q. No. Who's the patient
16 profile No. 1? Who?
17 A. I'm not sure what you mean.
18 Q. The person's name, patient
19 profile No. 1, who is that?
20 A. In this particular case the
21 patient profile is symbolized by the name
22 Donna.
23 Q. Right. Let's go ahead to
24 patient profile number on page 9, patient
497: 1 profile No. 2. Who's that?
2 A. This patient profile is
3 symbolized by the name Mark.
4 Q. Back to Donna, did she have
5 either schizophrenia or bipolar mania? On
6 Page 7.
7 Let me read: "Understanding

Donna's needs. Understanding needs. Donna is a single mom in her mid-30s appearing in your office in drab clothing and seeming somewhat ill at ease. Her chief complaint is I feel so anxious and irritable lately."
Did I read that correctly?

Bandick, Michael (June 9, 2006)
497:17-17
Issues: 01 Plaintiff's Trial Designation

497:17 Q. Did I read that correctly?

Bandick, Michael (June 9, 2006)
498:22-500:9
Issues: 01 Plaintiff's Trial Designation

498:22 Q. Sir, listen to my question, listen to my question I withdraw the last question. Sir, the fact of the matter is you
499: 1 at Lilly used illustrative metaphors, that's what you called them, and you prepared --
A. No, I didn't.
Q. At Lilly, didn't you call them illustrated metaphors?
A. No.
Q. You didn't?
A. I've not used that phrase today and that's not a phrase I remember using.
Q. Did anybody at Lilly use that phrase?
A. I don't know.
Q. Okay. Do you recall marketing to Donna, Mark and Martha?
A. You'd asked me that earlier and I didn't know what you meant then and I'm still not sure what you mean.
(Whereupon, Deposition Exhibit(s) 15 duly received, marked and made a part of the record.)
QUESTIONS BY MR. ALLEN:
Q. Okay, sir. By the way, we'll get off that document.
500: 1 Bandick Exhibit 15, wasn't it your goal in regard to the issue of weight gain to minimize the liability of weight gain while at the same time increasing the focus on Zyprexa's superior efficacy. Wasn't that your goal?
A. If you have a document that you're reading from I'd like to take a look

9 at it.

Bandick, Michael (June 9, 2006)
500:20-501:1
Issues: 01 Plaintiff's Trial Designation

500:20 Q. My question to you simply is,
21 without reference to any particular document,
22 sir, wasn't it Lilly's position to minimize
23 the liability of weight gain while at the
24 same time increasing the focus on Zyprexa's
501: 1 superior efficacy?

Bandick, Michael (June 9, 2006)
501:10-17
Issues: 01 Plaintiff's Trial Designation

501:10 Q. Sir, can you answer my
11 question?
12 A. I would like to take a look
13 at the document. There are a lot of ways to
14 interpret what you just read.
15 Q. Didn't Lilly try to, what was
16 the words here, minimize the risk and
17 accentuate the benefit?

Bandick, Michael (June 9, 2006)
501:24-502:6
Issues: 01 Plaintiff's Trial Designation

501:24 A. Those are very general terms
502: 1 so I can't answer the question the way you've
2 posed it.
3 Q. Without reading from a
4 document isn't it true that Lilly tried to
5 eliminate the risk of diabetes from the
6 risk/benefit equation?

Bandick, Michael (June 9, 2006)
502:9-14
Issues: 01 Plaintiff's Trial Designation

502: 9 A. No.
10 Q. No. Okay, sir.
11 (Whereupon, Deposition
12 Exhibit(s) 16 duly received, marked
13 and made a part of the record.)

14 QUESTIONS BY MR. ALLEN:

Bandick, Michael (June 9, 2006)
503:2-504:15
Issues: 01 Plaintiff's Trial Designation

503: 2 Q. Sir, you recognize the
3 Exhibit No. 16, Issue Management Planning on
4 Diabetes. Lilly Answers That Matter?
5 A. There are aspects of it that
6 are familiar. I'm not sure that I recall
7 this exact document.
8 Q. Okay. Why don't we go to
9 Page 2?
10 A. Okay.
11 Q. Diabetes. What is a
12 position, sir? A position as used in
13 marketing?
14 A. Well, in the context of this
15 document it would be similar to saying our
16 point of view.
17 Q. Okay. And isn't it, in
18 fact -- this document is a marketing
19 document, is it not?
20 A. This document would have come
21 from a marketing source.
22 Q. Okay. Our position would be
23 our point of view. "Our position: Diabetes
24 hyperglycemia may appear in patients taking
504: 1 antipsychotics and/or mood stabilizers
2 including Zyprexa at comparable rates with
3 the possible exception of Clozapine."
4 Did I read that correctly?
5 A. Yes.
6 Q. We saw earlier today the
7 consensus statement from April 2004, says
8 that diabetes occurs in a greater rate in
9 Zyprexa than it does in the other second
10 generation antipsychotics, correct?
11 A. That is the conclusion that
12 that group drew.
13 Q. Right. So right here your
14 position in this document, Exhibit 16, is
15 contrary to the consensus statement, correct?

Bandick, Michael (June 9, 2006)
504:18-21
Issues: 01 Plaintiff's Trial Designation

504:18 A. Well, this took place in 2000
19 and the consensus statement was three years
20 later, but taken on its face, yes, they are

21 in conflict.

Bandick, Michael (June 9, 2006)
505:3-6
Issues: 01 Plaintiff's Trial Designation

505: 3 Q. I'm saying your position on
4 diabetes in this document, Exhibit No. 16, is
5 contrary to the consensus statement
6 conclusions, correct?

Bandick, Michael (June 9, 2006)
505:9-506:12
Issues: 01 Plaintiff's Trial Designation

505: 9 A. I would agree with that.
10 Q. Now, you know what as
11 rationale is. Rationale means reason,
12 correct?
13 A. Yes.
14 Q. So your position is, we've
15 just read it: "Diabetes, hyperglycemia, may
16 occur in patients taking antipsychotics
17 and/or mood stabilizers including Zyprexa at
18 comparable rates with the possible exception
19 of Clozapine."
20 Skipping down: "To rationale
21 for the position," which means reason for the
22 position. You agreed with that, right?
23 A. I agree that rationale means
24 reason.
506: 1 Q. Okay. The reason for the
2 position that's reported in your marketing
3 document Exhibit 16 is as follows, follow
4 along with me: "Showing that diabetes is a
5 common occurrence for all antipsychotics and
6 not just Zyprexa will help reduce the
7 perception that diabetes is linked to,
8 specifically, to Zyprexa, and in turn, will
9 help to eliminate this risk from the
10 risk/benefit equation."
11 Did I read that correctly?
12 A. Yes, you did.

Bandick, Michael (June 9, 2006)
507:10-15
Issues: 01 Plaintiff's Trial Designation

507:10 Q. The stated reason in
11 Exhibit 16 for stating that diabetes risk is

comparable to other antipsychotics was in order to eliminate the diabetes risk from the risk/benefit equation?

MR. HAMMERLE: And I object

Bandick, Michael (June 9, 2006)
507:17-24
Issues: 01 Plaintiff's Trial Designation

Q. Correct, sir?
A. No. I disagree with that.
Q. Doesn't -- the document says this will help eliminate this risk from the risk/benefit equation?
A. Yes, that document says that.
Q. And if the document is true -- is that document false, Exhibit 16?

Bandick, Michael (June 9, 2006)
508:3-15
Issues: 01 Plaintiff's Trial Designation

Q. Is it false, sir?
A. It doesn't characterize the way that I saw that issue nor the way that we worked with it in the years that I was in the marketplace management role.
The date of this document is about the time that I was joining that area. I did not author it, so I can't speak for what the author of this document had in mind.
Q. You can't read it and see the purpose and the reason and you can't interpret what that means as a marketing professional?

Bandick, Michael (June 9, 2006)
508:19-509:1
Issues: 01 Plaintiff's Trial Designation

A. You asked me if I agreed and I disagreed with it.
Q. My question is: At least the marketing document concerning Diabetes, Issue Management Planning in November of 2001 was that we will try to eliminate the risk of diabetes from the risk/benefit equation?

Bandick, Michael (June 9, 2006)
509:4-510:22
Issues: 01 Plaintiff's Trial Designation

509: 4 A. Again, I can't speak to what
5 the author of this document had in mind, so,
6 no, I can't answer the question.
7 Q. Why don't you read out loud
8 for the jury the rationale for the position.
9 Read it out loud.
10 A. In this document it says:
11 "Showing that diabetes is a common occurrence
12 for all antipsychotics and not just Zyprexa
13 will help reduce the perception that diabetes
14 is linked, specifically, to Zyprexa and in
15 turn" -- spelled wrong -- "will help to
16 eliminate this risk from the risk/benefit
17 equation."
18 Q. That's at least what the
19 author of the document in the marketing
20 department wrote?
21 A. That's correct.
22 Q. Issues Management Planning
23 Weight Gain, Exhibit 15, November 2001.
24 You've seen that document before, haven't
510: 1 you?
2 A. As with the last document
3 which was dated one day differently from this
4 one, I'm familiar with much of the content,
5 I'm not sure I recall the specific document.
6 Q. Okay. This is the Issues
7 Management Planning Weight Gain, Lilly
8 Answers That Matter. Our Position is on
9 Page 2. You following me?
10 A. Yes.
11 Q. Our position: Weight gain
12 can occur with Zyprexa as with other
13 antipsychotics and mood stabilizers. For
14 most patients this can be managed allowing
15 them to receive the overwhelming benefits
16 Zyprexa offers."
17 Did I read that correctly?
18 A. Yes, you did.
19 Q. So it's your position that
20 the benefits of Zyprexa overwhelmingly
21 outweigh any alleged risk of weight gain,
22 correct?

Bandick, Michael (June 9, 2006)
511:1-18
Issues: 01 Plaintiff's Trial Designation

511: 1 A. No, I wouldn't interpret it

the way that you just paraphrased.
Q. Okay. What is the rationale for the position as contained in this exhibit --
A. It says --
Q. -- No. 15?
A. In this document it says: "To minimize the liability of weight gain while at the same time increasing focus on Zyprexa's superior efficacy."
Q. At least as stated in Lilly's document produced in this case from November of 2001, the rationale for your position on weight gain was to minimize the liability of weight gain while at the same time increasing focus on Zyprexa's superior efficacy, correct?

Bandick, Michael (June 9, 2006)
511:21-23
Issues: 01 Plaintiff's Trial Designation

A. That is what I read in this document, yes.
Q. Okay.

Bandick, Michael (June 9, 2006)
512:19-513:5
Issues: 01 Plaintiff's Trial Designation

(Whereupon, Deposition Exhibit(s) 18 duly received, marked and made a part of the record.)
QUESTIONS BY MR. ALLEN:
Q. I'm going to hand you Bandick No. 18. You've seen this, haven't you? My question is you've seen this before, haven't you?
A. Not that I'm aware of.
Q. Let me read it out loud. What's the number again, 18?

Bandick, Michael (June 9, 2006)
513:6-515:1
Issues: 01 Plaintiff's Trial Designation

MR. FAHEY: Eighteen.
Q. Sir?
A. Eighteen.
Q. It's to Jack Jordan. That

was your boss, right?
A. Yes, that's true.
Q. And it's dated February 14th, Valentine's day, 2000, right?
A. Yes, it is. And he was not my boss at that time.
Q. Okay. He was your boss at one time. From John Richards, who's John Richards?
A. John Richards was a member of the Zyprexa Brand Team in the U.S.
Q. Same team you were on, right?
A. That I later joined, yes.
Q. What were you doing in February 2000?
A. I was a sales manager.
Q. For what?
A. In the neuroscience group.
Q. Including Zyprexa?
A. That's right.
Q. Okay. So you were in the Zyprexa business in the marketing department, right?
A. No, that was in the sales organization.
Q. Sales organization, even better. Let's go back to Exhibit 18. From Jack, to Jack from John: "Jack, Attached as we discussed. As you can see we have been driving the depression story with Zyprexa in our DTP program since quarter three, 1998." Did I read that correctly?
A. Yes.
Q. What's DTP program?
A. DTP refers to direct-to-physician.
Q. Did you know that Lilly had been driving the depression story to physicians in the third quarter, since the third quarter of 1998?

Bandick, Michael (June 9, 2006)
515:6-18
Issues: 01 Plaintiff's Trial Designation

Q. Sir, did you know that?
A. I don't know the context of this specific e-mail but I do know that at that particular point in time there was data suggesting that use of Zyprexa in schizophrenia also had a corresponding effect on coexisting depression.
Q. Okay, sir. While my able associate is looking for another document,

I'm going to mark this one.
You all marketed and sold Zyprexa to the elderly for dementia, didn't you?

Bandick, Michael (June 9, 2006)

515:21-517:15
Issues: 01 Plaintiff's Trial Designation

A. No.
(Whereupon, Deposition Exhibit(s) 19 duly received, marked and made a part of the record.)
QUESTIONS BY MR. ALLEN:
Q. What's Exhibit 19, do you recognize that? My question is do you recognize the document, sir?
A. No, I don't.
Q. You don't? Why don't we just turn to Page 7 of this document, okay? Page 7. Are you with me?
A. Yes, I am.
Q. Let me just read into the record -- by the way, the title of this document is Controlling Crisis Can Lead to Connection; is that right?
A. That's what it says on this document.
Q. It has an illustration, looks like a doctor and an older person, right?
A. It's a doctor, and from the sketch that could potentially be an older person, I'm not sure.
Q. Turn to Page 7, will you please, sir?
A. Um-hum, yes.
Q. And on Page 7 it says: "Zyprexa IntraMuscular olanzapine for injection. Safety in agitation associated with dementia in a clinical trial."
Did I read that correctly?
A. Yes.
Q. Then you go: "In patients up to 97 years old, mean age of 77, favorable adverse event profile, the most common treatment-emergent adverse event in dementia patients was somnolence 4 percent versus 3 percent with placebo."
Did I read that correctly?
A. Yes.
Q. Weren't you all marketing Zyprexa to dementia patients?

Bandick, Michael (June 9, 2006)
518:23-24
Issues: 01 Plaintiff's Trial Designation

518:23 Isn't it true Lilly marketed
24 Zyprexa for dementia patients?

Bandick, Michael (June 9, 2006)
519:3-7
Issues: 01 Plaintiff's Trial Designation

519: 3 A. No.
4 Q. Okay. Well let me ask you
5 another question, isn't it true Lilly
6 marketed Zyprexa for depressive symptoms
7 related to dementia?

Bandick, Michael (June 9, 2006)
519:10-13
Issues: 01 Plaintiff's Trial Designation

519:10 A. Not that I'm aware.
11 Q. Isn't it true that Lilly
12 marketed Zyprexa for depressive symptoms
13 period?

Bandick, Michael (June 9, 2006)
519:16-21
Issues: 01 Plaintiff's Trial Designation

519:16 A. By themselves, no.
17 Q. Why don't you turn to
18 Page 18. What's the title of that page?
19 A. Improves depressive symptoms.
20 Q. Okay. Let's go to the page
21 20?

Bandick, Michael (June 9, 2006)
521:13-522:13
Issues: 01 Plaintiff's Trial Designation

521:13 Q. What's the title of Page 20?
14 A. Zyprexa Safely Stabilizes
15 Behavioral Symptoms.
16 Q. Zyprexa Safely Stabilizes
17 Behavioral Symptoms. That's what you just

said, right?
A. You asked me to read what was at the top of the page.
Q. Didn't you market Zyprexa for the treatment of symptoms?
A. No.
Q. Why don't you go down to the third section on this page where it says: "Zyprexa IntraMuscular, olanzapine for injection." You follow me?
A. Yes.
Q. Read out loud what it says right there?
A. "First and only psychotropic indicated for the treatment of agitation associated with dementia."
Q. First of only psychotropic indicated for the treatment of agitation associated with dementia, right?
A. That's what it says.

Bandick, Michael (June 9, 2006)
528:8-14
Issues: 01 Plaintiff's Trial Designation

Q. Sir, DTP programs, that means direct-to-physician programs, right?
A. Yes.
Q. Didn't you at Eli Lilly market directly to physician for the treatment of depressive symptoms in relation to Zyprexa?

Bandick, Michael (June 9, 2006)
528:17-20
Issues: 01 Plaintiff's Trial Designation

A. The only marketing to physicians through DTP that I'm aware of that included depressive symptoms were those symptoms within the context of schizophrenia.

Bandick, Michael (June 9, 2006)
528:24-529:3
Issues: 01 Plaintiff's Trial Designation

Q. My only question to you was: Didn't Lilly market Zyprexa directly to physicians for the treatment of depressive symptoms?

Bandick, Michael (June 9, 2006)
529:7-530:18
Issues: 01 Plaintiff's Trial Designation

529: 7 A. We did not promote Zyprexa
8 for the treatment of depressive symptoms.
9 (Whereupon, Deposition
10 Exhibit(s) 22 duly received, marked
11 and made a part of the record.)
12 QUESTIONS BY MR. ALLEN:
13 Q. Can you read to the jury the
14 title of Bandick Exhibit No. 22?
15 A. It's entitled 1999 DTP
16 Programs.
17 Q. There's a little bit more of
18 the title, isn't there?
19 A. I'm sorry, Programs
20 Emphasizing Zyprexa's Efficacy for Depressive
21 Symptoms.
22 Q. And then it lists Programs
23 Emphasizing Zyprexa's Efficacy For depressive
24 Symptoms, does it not?
530: 1 A. Yes, that's what I just read.
2 Q. And are these Lilly programs?
3 A. I assume so.
4 Q. Are Doctors Keck or Shelton
5 or Zajecka, are they Lilly speakers, sir?
6 A. All three of them are
7 psychiatrists who did do speaking for Lilly,
8 among other companies.
9 Q. They were paid honoraria and
10 money by Lilly?
11 A. They were compensated for
12 their time and service.
13 Q. So the physicians listed here
14 on Exhibit 22 were paid money by Lilly to
15 participate and give the programs listed on
16 this exhibit; is that correct?
17 A. Yes.
18 (Whereupon, Deposition

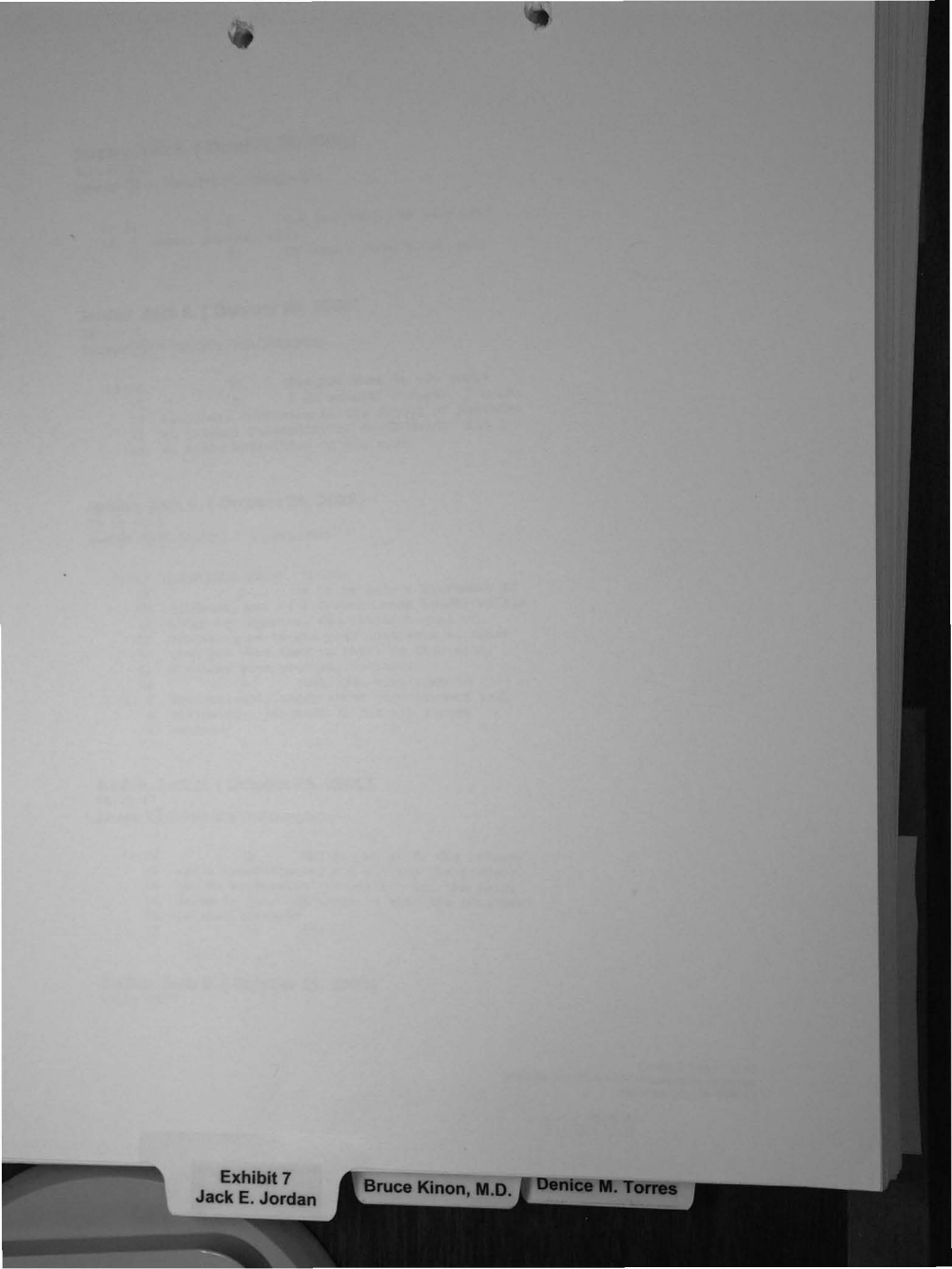


Exhibit 7
Jack E. Jordan
Bruce Kinon, M.D.
Denice M. Torres

Jordan, Jack E. (October 26, 2006)
21:24-22:2
Issues: 01 Plaintiff's Trial Designation

21:24 Q. Can you tell the jury your
22: 1 name, please, sir?
2 A. My name's Jack E. Jordan.

Jordan, Jack E. (October 26, 2006)
22:10-14
Issues: 01 Plaintiff's Trial Designation

22:10 Q. And for whom do you work?
11 A. I do several things. I'm an
12 Associate Professor at the School of Business
13 at Indiana University of South Bend. And I
14 do other activities on the side.

Jordan, Jack E. (October 26, 2006)
43:17-44:3
Issues: 01 Plaintiff's Trial Designation

43:17 QUESTIONS BY MR. ALLEN:
18 Q. As an Associate Professor of
19 Business, and as a former brand leader at Eli
20 Lilly for Zyprexa, the ultimate goal of
21 marketing is to get your customers to think
22 what you want them to think so they will
23 purchase your product, correct?
24 A. Yeah, you want them to
44: 1 appropriately think about your product and,
2 ultimately, purchase it for the target
3 market.

Jordan, Jack E. (October 26, 2006)
48:12-17
Issues: 01 Plaintiff's Trial Designation

48:12 Q. And as you said, the company
13 who's manufacturing and selling the product
14 has to synthesize information for the sales
15 force so they can share it with the customer;
16 is that correct?
17 A. Yes.

Jordan, Jack E. (October 26, 2006)
49:24-50:7

Issues: 01 Plaintiff's Trial Designation

49:24 Q. You said that where the sales
50: 1 force gets this information that's
2 synthesized comes from the marketing
3 department, correct?
4 A. Yeah. It ultimately comes
5 from the medical department but it goes
6 through a process and then marketing rolls it
7 out to sales within Lilly, yes.

Jordan, Jack E. (October 26, 2006)

52:12-15
Issues: 01 Plaintiff's Trial Designation

52:12 Q. Yes, sir. And you said,
13 though, that the marketing department
14 synthesizes this information and passes it on
15 to the sales force, right?

Jordan, Jack E. (October 26, 2006)

53:3-55:13
Issues: 01 Plaintiff's Trial Designation

53: 3 A. The process is that the
4 medical group gets the studies, gets the
5 data, analyzes it, and determines, along with
6 the regulatory group, what's medically useful
7 and what's in the context of Lilly's label,
8 and passes that information off to marketing
9 to make materials to communicate with
10 customers through various venues, one of
11 which is the sales force.
12 Q. Okay. So -- and you used the
13 term, and I'm just trying to find out when
14 you used the term, the record will reflect
15 you used the term "synthesize the data and
16 information." You recall that?
17 Synthesization? Synthesize them?
18 A. I did use that term and I
19 want to be clear on the process. It's the
20 medical department, along with the regulatory
21 group, that does the analysis, determines
22 what the data's actually saying, and leads
23 the marketing department on what's
24 appropriate to communicate to physicians. So
54: 1 I just want to make sure the process is
2 clear.
3 Q. Yes, sir. I apologize. And
4 I thank you for your help.
5 You said the medical and

regulatory take the information and give it to the marketing department to determine what's proper to communicate to the physicians?

A. No. There's a whole process that determines what's proper to communicate to physicians. It's called a, it's called, actually, it's a standardized process, it's called the ELMR process, which stands for --ELMR process.

Q. Can you spell that for me?

A. E-L-M-R. It's an acronym for the editor, legal, medical and regulatory.

Q. What's the E stand for, I'm sorry?

A. The editor.

Q. Okay. Go ahead, I'm sorry. Go ahead.

A. Editor, legal, medical and regulatory approve everything that goes out. And then the marketing department takes that approved information for promotional items and communicates it to customers.

Q. And the marketing department also takes this approved information and communicates it to the sales force to help train them so they can appropriately communicate, as you said, good and useful information to the customer?

A. Yes. It goes through the process and is approved and, for promotional activities through the sales force, yes.

Jordan, Jack E. (October 26, 2006)
59:18-20
Issues: 01 Plaintiff's Trial Designation

Q. And you worked for Eli Lilly from 1988 until when, sir?

A. Until April of 2004.

Jordan, Jack E. (October 26, 2006)
60:22-61:1
Issues: 01 Plaintiff's Trial Designation

Q. What was your title at the time you left Eli Lilly in April of 2004?

A. I was a sales director for the northeast part of the country.

Jordan, Jack E. (October 26, 2006)
61:14-63:4
Issues: 01 Plaintiff's Trial Designation

61:14 Q. Prior to the time you were
15 Sales Director for the Gamma Division for the
16 northeastern portion of the United States,
17 what was your job at Eli Lilly?
18 A. I was the Brand Leader for
19 Zyprexa.
20 Q. You were the Brand Leader for
21 the drug Zyprexa for Eli Lilly from when to
22 when?
23 A. From May of 1998 until about
24 August of 2003.
62: 1 Q. We will, of course, explore
2 it in some detail, but can you tell us as an
3 executive, as a Brand Leader for Zyprexa from
4 May of 1988 until August of 2003, can you
5 tell this jury in layman's terms what it
6 means to be a brand leader in that position?
7 A. It's really two areas of
8 responsibility: One was to be responsible
9 for the marketing strategy for the U.S., and
10 the second area was to make sure there was
11 alignment across the organization around that
12 strategy.
13 Q. And when you said "alignment
14 across the organization," is that correct?
15 A. Yes.
16 Q. Tell this jury what you mean
17 when you say "alignment across the
18 organization?"
19 A. To make sure that those folks
20 that are responsible to communicate data,
21 such as the sales organization, such as, such
22 as the -- we had business-to-business people
23 who would communicate clinical data to
24 customers, we had organizations that would do
63: 1 promotional mailings out to customers -- to
2 make sure that they were aligned with our
3 strategy and with the approved data for that
4 strategy.

Jordan, Jack E. (October 26, 2006)
65:20-66:9
Issues: 01 Plaintiff's Trial Designation

65:20 Q. Okay. Let's get back to your
21 job title; it was Brand Leader for Zyprexa,
22 is that correct, from May of 1998 to August
23 of 2003?
24 A. They would change back and

66: 1 forth between that and Marketing Director for
2 Zyprexa for the U.S.
3 Q. Okay. So, just so the jury
4 understands who we're talking to today, we're
5 talking to Mr. Jack Jordan, the Brand Leader
6 or the Marketing Director for the entire
7 United States of America for the product
8 Zyprexa from Eli Lilly from 1998 till August
9 of 2003; is that correct?

Jordan, Jack E. (October 26, 2006)
66:11-11
Issues: 01 Plaintiff's Trial Designation

66:11 A. That was my title, yes.

Jordan, Jack E. (October 26, 2006)
105:6-22
Issues: 01 Plaintiff's Trial Designation

105: 6 Q. Right. Your activities
7 concerning the marketing of Zyprexa were
8 known by senior management and senior
9 executives and it was done on a consensus
10 environment, on a consensus basis?
11 A. It was.
12 MR. GOLD: Objection as to
13 form.
14 Q. Sir? Your testimony was?
15 A. It was, yes.
16 Q. Thank you, sir.
17 During the entire time you
18 were Brand Leader and Marketing Director for
19 Zyprexa, from 1998 until 2003, were you ever
20 reprimanded, disciplined, in any regard for
21 any of your activities as Marketing Manager
22 or Brand Leader for Zyprexa?

Jordan, Jack E. (October 26, 2006)
106:1-1
Issues: 01 Plaintiff's Trial Designation

106: 1 A. No.

Jordan, Jack E. (October 26, 2006)
107:8-10
Issues: 01 Plaintiff's Trial Designation

107: 8 a rating scale. How were you rated in your
9 role as Brand Leader and Marketing Director
10 for Zyprexa from 1998 until 2003?

Jordan, Jack E. (October 26, 2006)
107:13-13
Issues: 01 Plaintiff's Trial Designation

107:13 A. Most years was exemplary.

Jordan, Jack E. (October 26, 2006)
115:20-116:3
Issues: 01 Plaintiff's Trial Designation

115:20 Q. From May of 1998 until August
21 of 2003, the only Eli Lilly drug product that
22 was then on the market that you were
23 Marketing Director for and/or Brand Leader
24 was Zyprexa?
116: 1 A. Yes.
2 Q. Okay. That was -- so Zyprexa
3 was your sole job during that time period?

Jordan, Jack E. (October 26, 2006)
116:6-6
Issues: 01 Plaintiff's Trial Designation

116: 6 A. Yes.

Jordan, Jack E. (October 26, 2006)
123:1-12
Issues: 01 Plaintiff's Trial Designation

123: 1 Q. What other departments did
2 you work with?
3 A. I had frequent interaction
4 with the Medical Group, with the Product
5 Team, with the Regulatory Group, with the
6 Legal Group, with the Business-to-Business
7 Group, with the Sales Organization, with the
8 Market Research Group, the PR Department,
9 with the Health Outcomes Department, with the
10 Medical Liaison Group, the Health Outcomes
11 Group, and there's a number of others. At
12 one point I had 20 or 30 groups.

Jordan, Jack E. (October 26, 2006)
125:20-126:1
Issues: 01 Plaintiff's Trial Designation

125:20 Now you left Zyprexa Brand
21 Leadership and Marketing Director in August
22 of 2003?
23 A. It was, again, most
24 transitions weren't -- it was the August-ish
126: 1 time frame.

Jordan, Jack E. (October 26, 2006)
157:4-6
Issues: 01 Plaintiff's Trial Designation

157: 4 Q. Right. How was the
5 performance of Zyprexa sales in the United
6 States between 1998 and 2003?

Jordan, Jack E. (October 26, 2006)
157:9-22
Issues: 01 Plaintiff's Trial Designation

157: 9 A. They were fine.
10 Q. Didn't they go up every year
11 while you were a Marketing Manager and Brand
12 Leader until the time you left in the summer
13 of 2003, when it began to fall?
14 A. Yeah. I was never a
15 marketing manager but --
16 Q. Marketing Director. I
17 apologize, sir.
18 A. But it was -- it did go up
19 every year, yes.
20 Q. I mean sales, as I recall it,
21 were, approximately, over $2 billion, for
22 example, in the year 2000, right?

Jordan, Jack E. (October 26, 2006)
158:1-19
Issues: 01 Plaintiff's Trial Designation

158: 1 A. I think that's correct.
2 Q. And then sales increased
3 above that level in 2001, did they not?
4 A. They did, yes.
5 Q. And what was the approximate
6 of the dollar value in sales in the United

States in 2001 of Zyprexa?
A. Boy, that's been a while ago. 2.2, 2.3, I don't recall the exact number.
Q. 2.2 or 2.3 what?
A. Billion.
Q. What, sir?
A. Billion.
Q. Billion. And then in 2002, the sales of Zyprexa even, in the United States went higher than that, did they not?
A. Yes, they did.
Q. What were they in that year, approximately, as you recall?

Jordan, Jack E. (October 26, 2006)
158:22-159:1
Issues: 01 Plaintiff's Trial Designation

158:22 A. Well, it went up another couple hundred million, as I recall.
Q. Almost $3 billion in 2002; is that correct?

Jordan, Jack E. (October 26, 2006)
159:4-14
Issues: 01 Plaintiff's Trial Designation

159: 4 A. We monitored net sales. So net sales were, the highest they ever got while I was there was, I believe, 2.4 or 2.6 billion, I just can't remember.
Q. That's net sales not gross sales, correct?
A. Yeah. I never tracked gross sales.
Q. Okay. Net sales is less than gross sales.
A. It is, yes.

Jordan, Jack E. (October 26, 2006)
163:9-164:4
Issues: 01 Plaintiff's Trial Designation

163: 9 Q. Sir, can you testify whether or not, in your opinion as the Marketing Director and Brand Leader for Zyprexa, as to whether or not Zyprexa was the single most important product for Eli Lilly from at least the fall of 2000 until the time you left in 2003?

A. Our CO had highlighted, I believe, it was four or five products that were going to be the priority during those years.
Q. Did any product take a priority over Zyprexa?
A. Not that I know of.
Q. What product, what drug product for Eli Lilly, during the time of at least the fall of 2000 until the time you left in the summer of 2003, what drug product for Eli Lilly created Eli Lilly's greatest profit?

Jordan, Jack E. (October 26, 2006)
164:13-19
Issues: 01 Plaintiff's Trial Designation

A. Zyprexa was the, was the answer to that. Zyprexa.
Q. Zyprexa was the biggest profit maker for Eli Lilly from at least the fall of 2000 until the time you left; is that correct?
A. Yes.

Jordan, Jack E. (October 26, 2006)
189:17-191:7
Issues: 01 Plaintiff's Trial Designation

Q. Can you market a product -- can you promote a product off-label?
A. No.
Q. Why can't you promote a product off-label?
A. The regulatory environment in the U.S. is that you need to do studies, and get them approved by the FDA, and then your promotion needs to be consistent with the label that's granted by the FDA.
Q. And when you say "consistent with the label," your promotional activities cannot exceed the indications on the label, can it?
A. There's nonpromotional activity and promotional activity. And promotional activity need to be consistent with the label.
Q. I know, sir. And I heard that. But when you say "it needs to be consistent with the label," can you promote for anything other than the specific

indications in the label in the indications section?
A. No.
Q. Okay. So all promotional activities have to be only for those specific written indications in the indications section of the label, correct?
A. In the label for the U.S.
Q. Right. Is that correct?
A. It is.
Q. During the time you were Marketing Director, let's take 2000, let's take the fall of 2000, do you recall what the indications in the label were for Zyprexa?
A. The fall of 2000, would have been a schizophrenia indication and a bipolar mania indication.

Jordan, Jack E. (October 26, 2006)

192:14-193:19
Issues: 01 Plaintiff's Trial Designation

Q. Did you have any other indications for Zyprexa besides bipolar mania and schizophrenia?
A. There was an indication for combination therapy using Zyprexa with lithium or Depakote for bipolar disorder. I can't remember the exact words there.
Q. For bipolar what?
A. I think it was bipolar mania. And then there was an indication for bipolar maintenance after I left the job.
Q. After you left the job?
A. Yes.
Q. So during the entire time you were on the job as Brand Leader and Marketing Director, there was only, according to your testimony, three labeled indications for Zyprexa?
A. Yes.
Q. Those were schizophrenia, No. 1, correct?
A. Yes.
Q. Bipolar mania, No. 2?
A. Yes.
Q. The third indication, which was later added, that you were Zyprexa Brand Leader Marketing Director of, was this combination therapy, right?
A. Yes.

Jordan, Jack E. (October 26, 2006)
211:2-8
Issues: 01 Plaintiff's Trial Designation

211: 2 Q. Concerning nonpromotional
3 activities, can sales representatives and/or
4 the medical department, or anybody employed
5 by Eli Lilly go to a doctor's office or call
6 a doctor's office and affirmatively discuss
7 uses of Zyprexa that are not indicated in the
8 label?

Jordan, Jack E. (October 26, 2006)
211:11-18
Issues: 01 Plaintiff's Trial Designation

211:11 A. I can't think of a situation
12 outside of answering a particular clinician's
13 question.
14 Q. So it would be wrong for a
15 sales representative, for example, to
16 affirmatively go to a doctor's office and
17 affirmatively discuss off-label uses of
18 Zyprexa. That would be wrong?

Jordan, Jack E. (October 26, 2006)
211:21-212:3
Issues: 01 Plaintiff's Trial Designation

211:21 A. I mean affirmatively? I just
22 want to be clear --
23 Q. Yes, sir.
24 A. They can't promote off-label
212: 1 indications in a doctor's office, "they"
2 being a sales rep, medical department, et
3 cetera, yes.

Jordan, Jack E. (October 26, 2006)
223:13-224:4
Issues: 01 Plaintiff's Trial Designation

223:13 Let me, before I do that, let
14 me ask this: The on-label indication of
15 schizophrenia is a diagnosis, is it not?
16 Schizophrenia is a diagnosis?
17 A. It is, yes.
18 Q. It is a defined disease; is
19 it not?
20 A. I'm not a medical doctor but

I've always interpreted it that way, yes.
Q. Okay. Bipolar mania is a diagnosis, is it not?
A. Yes, it is, yes.
Q. And those two diagnoses, schizophrenia and bipolar mania, were the two labeled indication diagnoses for Zyprexa that were indicated in the label; is that correct?

Jordan, Jack E. (October 26, 2006)
224:7-19
Issues: 01 Plaintiff's Trial Designation

A. During the time frame after the -- yeah, from March of 2000 on, yes.
Q. Okay. From March of 2000 on, the diagnoses, and the only indications in the label for Zyprexa, were the diagnosis of schizophrenia and the diagnose of bipolar mania, correct?
A. There was the combination indication as part of bipolar mania. So that was, I mean, if you look in the label, it's the third indication.
Q. Bipolar mania.
A. Yes. Combination use, yes.

Jordan, Jack E. (October 26, 2006)
235:4-19
Issues: 01 Plaintiff's Trial Designation

Q. What's a mood stabilizing drug, sir?
A. There are different classes of drugs in the treatment of severe mental health and antipsychotics are for psychotic-related disorders, which, ultimately, the FDA reclassified for schizophrenia specifically.
Mood stabilizers are a general term used for mood disorders, of which there are several classes, some are for depression, some are for bipolar disorder, et cetera. So it's just a general term.
Q. Eli Lilly's Zyprexa was never indicated for bipolar disorder, was it, sir?
A. No. No. Over time --

Jordan, Jack E. (October 26, 2006)
235:24-236:9

Issues: 01 Plaintiff's Trial Designation

235:24 A. Over time it was for
236: 1 different phases of bipolar disorder. But
2 mood stabilizer, again, is just a general
3 term that can cover a number of classes.
4 Q. Yes, sir. Just so the record
5 is clear, Zyprexa was never indicated for
6 bipolar disorder, was it, sir?
7 A. No, it wasn't. No.
8 Q. It was only indicated for
9 bipolar mania only, correct, sir?

Jordan, Jack E. (October 26, 2006)

236:12-13
Issues: 01 Plaintiff's Trial Designation

236:12 A. During the time I was there,
13 yes.

Jordan, Jack E. (October 26, 2006)

240:12-15
Issues: 01 Plaintiff's Trial Designation

240:12 Q. Did Eli Lilly ever instruct
13 its sales force when they went to doctor's
14 offices to focus on symptoms and not
15 diagnoses?

Jordan, Jack E. (October 26, 2006)

240:18-19
Issues: 01 Plaintiff's Trial Designation

240:18 A. We focused on symptoms to
19 discuss the diagnoses.

Jordan, Jack E. (October 26, 2006)

243:8-13
Issues: 01 Plaintiff's Trial Designation

243: 8 Q. Oh, symptoms. Did Eli Lilly
9 ever instruct its sales representatives,
10 either in writing or orally, to go to the
11 doctor's office and discuss symptoms and not
12 the diagnosis of schizophrenia or bipolar
13 mania?

Jordan, Jack E. (October 26, 2006)
243:16-244:11
Issues: 01 Plaintiff's Trial Designation

243:16 A. The -- I know when we did our
17 primary care research the primary care docs,
18 we learned that you talk about symptoms first
19 and then get into indications when you share
20 the studies. And so as part of the sales
21 process, we would instruct them to talk about
22 symptoms to engage the physician in the
23 indication of bipolar mania.
24 Q. So you did instruct your
244: 1 sales representatives to go to the doctors
2 and discuss symptoms and not diagnoses first;
3 is that correct?
4 A. Within the context of the
5 sales process, describing the patient up
6 front, we would talk about symptoms and then
7 get into indications when we shared the data
8 of the studies, yes.
9 Q. In fact, you told your sales
10 representatives to focus on symptoms and not
11 diagnoses, did you not?

Jordan, Jack E. (October 26, 2006)
244:14-20
Issues: 01 Plaintiff's Trial Designation

244:14 A. As part of the sales process,
15 what we learned from market research is that
16 primary care physicians thought symptoms
17 first, and so we would talk to them about
18 symptoms first but always move on to the
19 indications as you'll see in the studies.
20 I'm sure you have those documents.

Jordan, Jack E. (October 26, 2006)
245:5-14
Issues: 01 Plaintiff's Trial Designation

245: 5 Q. Hey, Mr. Jordan, you, in
6 fact, at Eli Lilly, prior to the time you
7 launched the primary care physician market
8 knew there was not a specific indication for
9 Lilly representatives to promote in the
10 primary care market, didn't you, sir?
11 A. As I recall, the early
12 research was they weren't recognizing the

13 disease of bipolar mania in their offices.
14 It was there, but it was unrecognized.

Jordan, Jack E. (October 26, 2006)
246:9-13
Issues: 01 Plaintiff's Trial Designation

246: 9 Q. My question is: You at Eli
10 Lilly knew there was not a specific
11 indication in the primary care physician
12 market to promote to primary care physicians.
13 You knew that, did you not?

Jordan, Jack E. (October 26, 2006)
246:16-247:4
Issues: 01 Plaintiff's Trial Designation

246:16 A. No. The patients were in the
17 primary care physician's office, it was they
18 were not diagnosing those patients.
19 Q. So Eli Lilly when it,
20 according to you, when it marketed Zyprexa to
21 primary care physicians was trying just to
22 help the doctors do a better job of
23 diagnosing their patients?
24 A. The research that we had, it
247: 1 was taking them, seven, eight, nine years to
2 diagnose their patients in the primary care
3 office so, yes, we did go there to help them
4 with the diagnosis.

Jordan, Jack E. (October 26, 2006)
248:8-249:16
Issues: 01 Plaintiff's Trial Designation

248: 8 Q. Sir, is it your testimony
9 that in the marketing of Zyprexa you were
10 sending sales representatives into the office
11 to discuss symptoms because the doctors were
12 not making the proper diagnoses?
13 A. Our research showed that it
14 was taking, six, seven, eight years to
15 diagnose somebody with bipolar disorder in
16 the primary care setting. So, yes, we did go
17 in and identify the symptoms that were part
18 of DSM, the bipolar mania indication, and
19 discussing bipolar mania based on those
20 symptoms, yes.
21 Q. So you said your market
22 research, is that what you called it, market

research?
A. Yes.
Q. Said that doctors were not making the diagnosis of bipolar mania for six or seven years; is that right?
A. That was what the research was indicating, yes.
Q. And you -- so, therefore, you decided to take your sales representatives -- are they generally physicians?
A. No. They aren't generally physicians, no.
Q. Okay. You decided that you would have your sales representatives go to the office and talk about symptoms and, hopefully, correct the doctors so that they would make the proper diagnosis of bipolar mania according to you?

Jordan, Jack E. (October 26, 2006)
249:20-24
Issues: 01 Plaintiff's Trial Designation

A. We did use our sales organization to talk about the symptoms associated with bipolar mania to help physicians identify that patient population, yes.

Jordan, Jack E. (October 26, 2006)
290:3-10
Issues: 01 Plaintiff's Trial Designation

Sir, you've previously told us, Mr. Jordan, that you cannot promote for nonindicated uses, right?
A. Yes. You cannot promote for nonindicated uses, yes.
Q. But didn't, in fact, Eli Lilly drive the depression story with Zyprexa in your direct-to-physician campaigns?

Jordan, Jack E. (October 26, 2006)
290:13-14
Issues: 01 Plaintiff's Trial Designation

A. I mean, I have to see what you're referring to.

Jordan, Jack E. (October 26, 2006)
291:1-4
Issues: 01 Plaintiff's Trial Designation

291: 1 Q. I'm asking you, sir, a
2 question. Isn't it true that Eli Lilly drove
3 the depression story in your
4 direct-to-physician campaigns?

Jordan, Jack E. (October 26, 2006)
291:5-14
Issues: 01 Plaintiff's Trial Designation

291: 5 A. As I recall, in the context
6 of schizophrenia and depressive symptoms
7 associated with schizophrenia, we did, yes.
8 MR. ALLEN: Okay, sir, I'm
9 going to hand you what's been marked
10 as Jordan Exhibit No. 4.
11 (Whereupon, Deposition
12 Exhibit(s) 4 duly received,
13 marked and made a part of the
14 record.)

Jordan, Jack E. (October 26, 2006)
291:17-292:7
Issues: 01 Plaintiff's Trial Designation

291:17 Q. This is an e-mail dated
18 February the 14th, 2000, addressed to you, is
19 it not?
20 A. It was February 2000.
21 Q. I'm sorry. This is an e-mail
22 dated February 14, 2000; is it not?
23 A. Yes.
24 Q. Addressed to you, correct?
292: 1 A. It is.
2 Q. From Eric Prouty or Prouty?
3 A. Prouty.
4 Q. I'm sorry. That's who it's
5 is carbon copied to.
6 It's from John Richards,
7 right?

Jordan, Jack E. (October 26, 2006)
293:3-295:24
Issues: 01 Plaintiff's Trial Designation

A. Yes, it's from John Richards.
Q. It's in regard to what, sir?
A. It's in regard to an attachment.
Q. What's the subject matter of this e-mail?
A. Depressive DTP slides.
Q. The subject is depressive, DTP stands for direct-to-physician, does it not?
A. Yes.
Q. And the attachment is the JACK file dot doc. What is the JACK file dot doc?
A. I do not know.
Q. Anyhow, who is Mr. Richards?
A. He was a manager at Lilly.
Q. A manager of what?
A. He had various titles. He's a manager on the Zyprexa team.
Q. Yes, sir. And this e-mail from Mr. Richards in February of 2000 says Jack -- and that's you, right, Jack?
A. It is.
Q. "Jack, attached as we discussed. As you can see we have been driving the depression story with Zyprexa in our DTP" -- that's direct-to-physician -- "programs since the quarter three of 1998." Did I read that correctly?
A. You did, yes.
Q. And is it true that you, at Eli Lilly, had driven the depression story with Zyprexa in your direct-to-physician campaign since the third quarter of 1998?
A. The depressive symptoms, i.e., the subject matter, part of our core strategy during that time was to differentiate on our coverage of depressive symptoms in schizophrenia. So, yes, that is true.
Q. Sir, does this e-mail refer to depressive symptoms related to schizophrenia or bipolar mania or does it say "the depressive story?"
A. Depressive is an adjective and so it was always depressive symptoms in schizophrenia. And I'm sure if I had the attachment I could point that out.
Q. Sir, let's see if you and I, see if we can read this together. Second sentence to you, "Jack, as you can see we have been driving the depression story with Zyprexa." Did I read that correctly?
A. Yeah. But you didn't read the next sentence that said "the importance of this attribute," an attribute associated

with schizophrenia. That was our core strategy during that time.
Q. Does it say anything in this e-mail about schizophrenia or bipolar mania?
A. An attribute is not a disease, it's a part of another disease. Depressive is an adjective that we used in association with schizophrenia. If you showed me the attachment I'm sure I could show you that.
Q. I don't have the attachment, sir, it's your attachment. But let me see if you concede this.

Jordan, Jack E. (October 26, 2006)
296:17-24
Issues: 01 Plaintiff's Trial Designation

296:17 Q. My question is -- My question
18 is, sir, it would be wrong to encourage
19 doctors and to drive a depression story on
20 Zyprexa unrelated to schizophrenia or bipolar
21 mania, correct?
22 A. If it's a promotional
23 activity you can't promote for a depressive
24 symptom outside of the core indications.

Jordan, Jack E. (October 26, 2006)
297:13-24
Issues: 01 Plaintiff's Trial Designation

297:13 Q. My question to you is, sir,
14 isn't it true that Eli Lilly tried to get
15 doctors to prescribe Zyprexa for depression
16 without a diagnosis?
17 A. No, that's not.
18 MR. ALLEN: Sir, I'm going to
19 hand you what's been marked as
20 Exhibit No. 5.
21 (Whereupon, Deposition
22 Exhibit(s) 5 duly received,
23 marked and made a part of the
24 record.)

Jordan, Jack E. (October 26, 2006)
300:10-301:11
Issues: 01 Plaintiff's Trial Designation

300:10 Q. Mr. Jordan, at Eli Lilly did
11 you all have product knowledge conference

calls?
A. Yeah. There were calls about various issues. That would be one of them, yes.
Q. Yes, sir. And one of the conference calls you all would have, you all called it the product knowledge conference call, did you not?
A. I'm not that familiar with that term. I guess we did have it, yes.
Q. Who's Jill Lake?
A. I do not know.
Q. Michael Bandick, at this time in December of 2000 worked for you in issues management, did he not, or Marketplace Management?
A. No. At that point he was, I believe he was the primary care manager.
Q. Okay, sir.
A. Working for me.
Q. Sir?
A. Working for me.
Q. Yes, Mr. Bandick was working for you.

Jordan, Jack E. (October 26, 2006)
301:16-302:11
Issues: 01 Plaintiff's Trial Designation

Q. Mr. Bandick and others on this e-mail were in the marketing department that worked for you; is that correct?
A. Yes.
Q. Thank you, sir.
This e-mail concerned a conference call of December the 9th, 2000, did it not? "Hi Crew, wanted to give you a summary of the Zyprexa conference call that was held today." Right?
A. Yes.
Q. If you go to the second page there's a series of questions that were asked concerning Zyprexa, and I'm going to focus on question No. 5.
You see question No. 5, after question No. 4?
A. I do not, no.
Q. Where is it?
A. It said it's been redacted.

Jordan, Jack E. (October 26, 2006)
304:18-19
Issues: 01 Plaintiff's Trial Designation

304:18 Q. Question and answer No. 5 are
19 not present, are they, sir.

Jordan, Jack E. (October 26, 2006)
304:22-306:7
Issues: 01 Plaintiff's Trial Designation

304:22 A. It is not, no.
23 Q. Question No. 7 is. What is
24 question seven?
305: 1 A. "Is Zyprexa indicated for
2 depression?"
3 Q. And the answer is what, sir?
4 A. It says, "Zyprexa is not
5 indicated for depression. We know Zyprexa
6 improves depressive symptoms in schizophrenic
7 patients" but need to think of it, "but need
8 to think of as a mood stabilizer."
9 Q. We need to think of it as a
10 mood stabilizer, is that correct? "It" is
11 not there but we need to think of it as a
12 mood stabilizer; is that correct?
13 A. Yes.
14 Q. It says, "Zyprexa is not
15 indicated for depression;" is that correct?
16 A. That's correct. It's not
17 indicated for depression.
18 Q. And that's accurate, is it
19 not?
20 A. That is accurate.
21 Q. Now schizophrenia is a
22 diagnosis. You've already told us that
23 earlier today, right?
24 A. It is, yes.
306: 1 Q. Now in this question and
2 answer document it says "What if the doctor
3 says," this is question No. 8 following
4 question seven, "what if the doctor says I
5 don't see those types of patients?" Do you
6 see that question?
7 A. I do.

Jordan, Jack E. (October 26, 2006)
307:4-9
Issues: 01 Plaintiff's Trial Designation

307: 4 Q. Sir, can you read out loud
5 the answer to the question reflected in
6 Exhibit No. 5, "what if the doctor says I
7 don't see those types of patients?" What is

the answer written on the piece of paper, Exhibit No. 5?

Jordan, Jack E. (October 26, 2006)
307:15-21
Issues: 01 Plaintiff's Trial Designation

307:15 A. Okay. "The doctor's thinking that he does not see a schizophrenic or bipolar patient."
Q. Let's stop there. The doctor is thinking that he does not see schizophrenic or bipolar patients; is that right?

Jordan, Jack E. (October 26, 2006)
308:4-8
Issues: 01 Plaintiff's Trial Designation

308: 4 Q. Is that correct?
A. That is.
Q. Okay. Continue reading slowly and distinctly so the jury can hear, please.

Jordan, Jack E. (October 26, 2006)
308:18-309:21
Issues: 01 Plaintiff's Trial Designation

308:18 Q. Okay, go ahead. The document says: "The doctor's thinking that he does not see schizophrenic or bipolar patients."
Continue with reading the document, please, sir.
A. "But he probably does see patients with symptoms of behavior, mood, and
309: 1 thought disturbances."
Q. Or thought disorders -- disturbances, right?
A. Yes.
Q. Is there a difference between schizophrenic and bipolar patients and patients with behavior, mood, or thought disturbances?
A. There might or there might not be.
Q. Okay. Continue reading the answer to the question "what if the doctor says I don't see those types of patients?"
A. "Need to focus on symptoms

and patient types of Martha, David, and Christine. Even if the doctor does not have diagnosis, he should treat anyway. He needs to treat the symptoms until a patient can see a psychiatrist. Ask him if he uses drugs like Haldol or risperidal, and Zyprexa has less side effects than either of them."

Jordan, Jack E. (October 26, 2006)
312:14-19
Issues: 01 Plaintiff's Trial Designation

312:14 Q. My question to you was: Was it your position in marketing, and when you were Brand Leader and Director of Marketing, that the sales representatives should tell doctors to prescribe Zyprexa even without a diagnosis of schizophrenia or bipolar mania?

Jordan, Jack E. (October 26, 2006)
313:2-9
Issues: 01 Plaintiff's Trial Designation

313: 2 A. It wasn't my position, no.
3 Q. And it would be wrong to
4 encourage sales representatives to instruct
5 doctors or to inform doctors that they should
6 go ahead and prescribe Zyprexa without a
7 diagnosis; that would be wrong, wouldn't it?
8 A. Well, the sales piece and the
9 training never asked them to do that, so.

Jordan, Jack E. (October 26, 2006)
313:12-314:6
Issues: 01 Plaintiff's Trial Designation

313:12 Q. My question wasn't what you
13 say a sales piece says. We're going to get
14 to them later. My question: Would it be
15 wrong from a marketing perspective for the
16 sales force to tell doctors to go ahead and
17 prescribe Zyprexa without a diagnosis of
18 schizophrenia or bipolar mania?
19 A. In a promotional setting you
20 should ask doctors to prescribe on-label.
21 Q. And, therefore, would it be
22 wrong to ask doctors to prescribe Zyprexa
23 without a diagnosis of schizophrenia or
24 bipolar mania?
314: 1 A. The reps were never trained

to do that, so, yes, it would be --
Q. Wrong.
A. -- outside their training.
Q. And, therefore, it would be wrong.

Jordan, Jack E. (October 26, 2006)
314:13-15
Issues: 01 Plaintiff's Trial Designation

314:13 Q. Would it be wrong?
A. To ask a doctor -- yeah. But I'm not sure that's what they're saying here.

Jordan, Jack E. (October 26, 2006)
318:17-23
Issues: 01 Plaintiff's Trial Designation

318:17 It would be wrong of Eli Lilly to train its sales representatives to tell doctors to go ahead and prescribe Zyprexa without a diagnosis of schizophrenia or bipolar mania. That would be wrong?
A. Anything that would be outside the label would be inappropriate.

Jordan, Jack E. (October 26, 2006)
320:22-321:5
Issues: 01 Plaintiff's Trial Designation

320:22 Q. If a doctor told a sales representative "I do not treat schizophrenia or bipolar disorder," the doctors told that
321: 1 to your sales representative, shouldn't your sales representative tell the doctor then you don't need Zyprexa because it's only indicated for schizophrenia and bipolar disorder?

Jordan, Jack E. (October 26, 2006)
321:8-16
Issues: 01 Plaintiff's Trial Designation

321: 8 A. As we did our market research around this very issue, what primary care doctors told us is that once we described the patient based on DSM, based on the given

symptoms, that many times they would, actually, come back and say they actually do have those patients and would want to potentially prescribe Zyprexa for that bipolar mania.

Jordan, Jack E. (October 26, 2006)
322:4-14
Issues: 01 Plaintiff's Trial Designation

Q. Right. So if a sales representative told a doctor "I do not treat bipolar mania and I do not treat schizophrenia," that didn't stop Eli Lilly from training its sales representatives to still sell the doctor on Zyprexa, isn't that right?
A. Our market research showed that up to a third of the patients they were treating with an antidepressant were, actually, struggling from bipolar disorder.

Jordan, Jack E. (October 26, 2006)
339:8-340:10
Issues: 01 Plaintiff's Trial Designation

was Zyprexa ever indicated for thought, mood, or behavioral disorders?
A. Those aren't indications, so, obviously, not.
Q. And, therefore, it would be wrong for Eli Lilly to promote Zyprexa for thought, mood, or behavioral disorders, since they are not indications?
A. Well, that's a different question. It's not -- those are just general terms that you can talk about with customers. And then when you talk about the indication, schizophrenia is a subset of thought disorder. It's just a categorization. It's not promoting for an indication.
Q. Wasn't -- why did you all choose that term "thought, mood, and behavioral disorders," was there a particular reason you chose that term?
A. I don't recall any particular reason, no.
Q. Wasn't the reason you chose that term because you knew it was broad and vague and it provided latitude for your sales representatives to frame the discussion around symptoms and behavior rather than

10 specific indications in the label?

Jordan, Jack E. (October 26, 2006)
340:13-23
Issues: 01 Plaintiff's Trial Designation

340:13 A. I don't recall that being the
14 case.
15 (Whereupon, Deposition
16 Exhibit(s) 8 duly received,
17 marked and made a part of the
18 record.)
19 MR. ALLEN: Okay, sir. I'm
20 going to hand you what's been marked
21 as Jordan Exhibit No. 8, a document
22 I'll provide to counsel. I'll hold
23 it up --

Jordan, Jack E. (October 26, 2006)
341:4-6
Issues: 01 Plaintiff's Trial Designation

341: 4 MR. ALLEN: Okay.
5 (Document displayed to
6 the jury)

Jordan, Jack E. (October 26, 2006)
342:8-9
Issues: 01 Plaintiff's Trial Designation

342: 8 Q. Sir, do you recognize Exhibit
9 No. 8 as coming from your files?

Jordan, Jack E. (October 26, 2006)
342:11-343:24
Issues: 01 Plaintiff's Trial Designation

342:11 A. I don't know if it did or
12 didn't. My handwriting's there, so.
13 Q. Yes, sir. That is your
14 handwriting at the bottom, correct?
15 A. It is.
16 Q. Okay. You said in this -- is
17 this a positioning document or a marketing
18 document?
19 A. I'm not sure exactly what it
20 is. I don't remember it.

Q. Well, if it's in your files it has to be marketing material, is it not?
A. It could be from the product team, long-term planning document. I'm just not sure.
Q. Okay. It says: "Zyprexa is an agent of choice to help patients with debilitating thought, mood, and behavioral disorders achieve the highest level of long-term functioning." Did I read that correctly?
A. You did.
Q. Under "Behaviors," do you see "elderly?"
A. I see it.
Q. Was Zyprexa ever indicated for the treatment of Alzheimer's, dementia, or long-term care in the elderly unrelated to schizophrenia or bipolar mania?
A. As I communicated with you earlier, a positioning is a long-term objective over the life of the molecule. And I don't see what the time frame is on this, but we had an extensive research program for indications for the elderly: Agitation, we had a cognition studies underway. So in the long-term, yes, we did have research going on for the elderly.

Jordan, Jack E. (October 26, 2006)
344:5-10
Issues: 01 Plaintiff's Trial Designation

Q. Was Zyprexa, when you were Brand Leader and Marketing Director, ever approved for the indication for the treatment of the elderly, either in the long-term for dementia or Alzheimer's unrelated to schizophrenia or bipolar mania?

Jordan, Jack E. (October 26, 2006)
344:13-345:9
Issues: 01 Plaintiff's Trial Designation

A. It was not. But we had extensive studies for longer term indications.
Q. Sir, do you remember the primary care physician launch in October of 2000?
A. I do.
Q. Were you intimately involved

in that launch?
A. The person that reported to me, Mike Bandick, was responsible for the launch, yes.
Q. And so he had to report to you, so you had to approve his work, right?
A. Yeah. I had a good feel on what was going on, yes.
Q. You did not only have a good feel, you appeared at the launch, itself, and spoke to the audience in Orlando, Florida, correct?
A. I did.

Jordan, Jack E. (October 26, 2006)
345:18-21
Issues: 01 Plaintiff's Trial Designation

Q. Wasn't it the biggest thing you did with Zyprexa as of that time, as of October of 2000, was the primary care physician launch?

Jordan, Jack E. (October 26, 2006)
345:24-347:5
Issues: 01 Plaintiff's Trial Designation

A. No, actually it was not.
Q. Okay. Do you recall that you all did some videos and things of that nature for the launch?
A. I don't remember the specifics but we normally had videos for sessions like that.
Q. Yes, sir. And this was a big deal in your company, this primary care physician launch, wasn't it?
A. We were going to spend about 10 percent of Zyprexa's budget on it. So, I don't know if that's a big deal or small deal but --
Q. You wouldn't describe it as a big deal?
A. It's something that we saw an opportunity to help people with bipolar mania, so that's always important.
Q. So this thing was just an opportunity to help people and not help the company?
A. It was an opportunity to help the company, yes.
Q. In fact, you were trying to

help the company because Year X was upon you, wasn't it?
A. No, actually. I mean, no, we had planned it before Year X.
Q. Was Year X -- at the time of

Jordan, Jack E. (October 26, 2006)
347:6-348:18
Issues: 01 Plaintiff's Trial Designation

the primary care physician launch was Year X present?
A. It was. But we started planning for it in June of 2000 which was before we ever had any idea Prozac was going off patent.
Q. This was -- by the time of the launch of Zyprexa Year X was upon you, correct, by that time?
A. It was, yes.
Q. You had lost your patent protection on Prozac, right?
A. We had, yes.
Q. You were anticipating generic competition, correct?
A. We were.
Q. You knew you would have decreased revenues in Prozac, right?
A. We did.
Q. Prozac was your No. 1 selling multibillion dollar blockbuster as of that time, right?
A. It was.
Q. And you wanted Zyprexa to come in and take the place of Prozac at the time of the primary care physician launch and that was your company's intent, was it not?
A. No. We could never take the place of Prozac. But we did want to make sure that, with all of our products, we made sure we took advantage of the opportunities.
Q. And you were trying to take advantage of the opportunity with Zyprexa primary care physician launch in the fall of 2000, because you wanted to get dollars to the bottom line and increase your company's stock price; isn't that true?

Jordan, Jack E. (October 26, 2006)
348:20-349:10
Issues: 01 Plaintiff's Trial Designation

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

348:20 A. We certainly are in the
21 business of, of making money by helping
22 people, yes.
23 Q. Right. So you were, your
24 company was tremendously excited about the
349: 1 primary care physician launch. And, in fact,
2 it was your intent by the primary care
3 physician launch to grow Zyprexa and to grow
4 the company; isn't that true?
5 A. If you're insinuating that we
6 could make up for all of Prozac, no. But we
7 did want to increase revenues by helping
8 those folks in that marketplace, yes.
9 Q. You wanted to grow the
10 company?

Jordan, Jack E. (October 26, 2006)
349:13-13
Issues: 01 Plaintiff's Trial Designation

349:13 Q. With Zyprexa?

Jordan, Jack E. (October 26, 2006)
349:16-350:9
Issues: 01 Plaintiff's Trial Designation

349:16 Q. Is that true or not true?
17 A. That's how you make money in
18 this industry is by helping people you make
19 money, yes.
20 Q. And you did not want --
21 wouldn't a product for schizophrenia and
22 bipolar mania be a niche product?
23 A. I mean, most products in the
24 pharmaceutical industry are niche products
350: 1 because they only have one or two
2 indications.
3 Q. My question to you simply is
4 was Zyprexa, which was indicated for
5 schizophrenia and bipolar mania, a niche
6 product?
7 A. It was approved for two
8 indications, and so, yes, two niches, I
9 guess, yeah.

Jordan, Jack E. (October 26, 2006)
352:9-353:7
Issues: 01 Plaintiff's Trial Designation

352: 9 you were ecstatic at Eli Lilly for the chance

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

to make Zyprexa a multibillion dollar blockbuster, were you not?

A. I was excited about a lot of opportunities, yeah. To help undiagnosed patients, I was excited about that, yes.

Q. Was the primary goal in the primary care physician launch altruistic, that you were trying to help patients? That was your primary goal according to your testimony?

A. No, I had two primary goals. One goal was to help doctors help their patients, and the second was to increase revenue, yes.

MR. ALLEN: Why don't we -- we're going to mark the tape in a minute. We're going to put this on the conference table so the jury can see it. If you'd like to look at it, I'd ask you to look at it. Go around by your lawyer and watch this video.

Jordan, Jack E. (October 26, 2006)
355:20-356:17
Issues: 01 Plaintiff's Trial Designation

Q. Isn't it true your entire company was geared up around the Viva Zyprexa primary care physician launch? Isn't it true, sir?

A. It was an opportunity that we certainly were excited about helping that patient group and increase revenues, yes.

Q. Okay, sir. I will mark and place in the record Exhibit 9, the video that we produced that was produced to us.

(Whereupon, Deposition Exhibit(s) 9 duly received, marked and made a part of the record.)

(Whereupon, Deposition Exhibit(s) 10 duly received, marked and made a part of the record.)

MR. ALLEN: We now have Exhibit 10, this next video, sir, concerning the Viva Zyprexa launch and see if you recall this.

Jordan, Jack E. (October 26, 2006)
356:24-24
Issues: 01 Plaintiff's Trial Designation

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

356:24 (Video played.)

Jordan, Jack E. (October 26, 2006)
357:5-358:20
Issues: 01 Plaintiff's Trial Designation

357: 5 Q. Sir, were you all very
6 excited? Was that you on that video, weren't
7 you?
8 A. I was, yes.
9 Q. Were you all excited there
10 because you were getting the opportunity to
11 help patients?
12 A. Yes.
13 Q. Okay. Weren't you all
14 excited because Viva Zyprexa primary care
15 physician launch was intended to help your
16 company increase its revenue and increase the
17 stock price?
18 A. As I stated before, that's
19 the nice thing about this industry is you
20 make money by helping people, so, yeah, both
21 those, yes.
22 Q. Sir, the fact of that matter
23 was the primary care physician launch in the
24 fall of 2000 -- it was October of 2000, was
358: 1 it not?
2 A. It was, yes.
3 Q. It was an off-label launch,
4 wasn't it?
5 A. It was not, no.
6 Q. Well, you knew at the time of
7 the launch that the people you were fixing to
8 sell the product to, your customers, were
9 going to use the product in an off-label
10 fashion. You knew that, didn't you?
11 A. We were going to promote it
12 on-label, obviously. But with any market and
13 almost all products customers prescribe it
14 however they want.
15 Q. Sir, my question to you was,
16 you knew at the time of the primary care
17 physician launch, Viva Zyprexa, that you were
18 going to be promoting it to doctors who would
19 be prescribing the product in an off-label
20 fashion?

Jordan, Jack E. (October 26, 2006)
358:23-359:10
Issues: 01 Plaintiff's Trial Designation

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

358:23 Q. Isn't that true?
24 A. My response is we always, it
359: 1 was our company policy, to always promote
2 on-label. And with all products in all
3 markets, doctors promote or can prescribe
4 however they want.
5 And so it wasn't any
6 different in this market that they would,
7 probably, prescribe it sometimes off-label,
8 yes.
9 Q. You wanted the doctors to
10 prescribe it off-label.

Jordan, Jack E. (October 26, 2006)
359:12-14
Issues: 01 Plaintiff's Trial Designation

359:12 A. The reality is, again, with
13 any product in all markets doctors prescribe
14 off-label; they're allowed to do that.

Jordan, Jack E. (October 26, 2006)
360:6-16
Issues: 01 Plaintiff's Trial Designation

360: 6 Q. You, at Eli Lilly, and the
7 company knew at the time of the primary care
8 physician launch it was your intent that the
9 doctors prescribe the product and use it
10 off-label.
11 A. That's a different question.
12 No, it was not our intention.
13 (Whereupon, Deposition
14 Exhibit(s) 11 duly received,
15 marked and made a part of the
16 record.)

Jordan, Jack E. (October 26, 2006)
362:6-11
Issues: 01 Plaintiff's Trial Designation

362: 6 THE VIDEOGRAPHER: Off the
7 record.
8 (At this time, there
9 was a brief recess taken,
10 after which the following
11 proceedings were had:)

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

Jordan, Jack E. (October 26, 2006)
362:20-363:3
Issues: 01 Plaintiff's Trial Designation

362:20 You have read Exhibit No. 11,
21 is that true?
22 A. I have, yes.
23 Q. It's a document that was
24 represented came from your files. It's
363: 1 entitled Zyprexa Primary Care Strategy and
2 Implementation Overview; is that correct?
3 A. It is, yes.

Jordan, Jack E. (October 26, 2006)
363:16-367:23
Issues: 01 Plaintiff's Trial Designation

363:16 Q. I apologize. Maybe you could
17 help the jury, just help the jury and tell
18 the jury what a strategy and implementation
19 overview is?
20 A. In the context of this
21 document, it was a document that as I read it
22 Mike Bandick put it together, must have been
23 in the job for a month, maybe a little
24 longer, just kind of his thoughts about where
364: 1 things were going to go.
2 Q. Mike Bandick, in fact, is the
3 Brand Manager for Zyprexa in August of 2000,
4 was he not?
5 A. For primary care, yes, he
6 was.
7 Q. And Zyprexa was being
8 launched into primary care, right?
9 A. It was, yes.
10 Q. That's -- the Viva Zyprexa
11 launch is synonymous with the primary care
12 physician launch; one in the same, right?
13 A. Yeah. That was the theme at
14 the primary care launch was Viva Zyprexa,
15 yes.
16 Q. And it had a song surrounding
17 it, right?
18 A. It did, yes.
19 Q. Okay. And Mr. Bandick is the
20 Brand Manager for Zyprexa in primary care.
21 A. He was, yes.
22 Q. At the time that he wrote
23 this document.
24 A. Yeah. He'd just started the
365: 1 job not too long ago, yeah.
2 Q. The Strategy and
3 Implementation Overview has paragraphs on the

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

Background, on the Current situation, on the Opportunities, Challenges, Positioning, the Strategy, and Implementation, does it not?

A. It does have those things in here, yes.

Q. Yes, sir. I want to focus first on the Opportunities section of the Zyprexa Primary Care Strategy and Implementation Overview. Are you up there at the Opportunities section?

A. Yes, sir.

Q. "Opportunities: We believe there to be significant unmet medical need among office-based primary care physicians, PCPs. This customer group is huge. Greater than 250,000 prescribers, 59,000 are key targets, and its potential in this arena is virtually untapped. By targeting the top deciles, we can maximize return while building a strong clinical foundation. Zyprexa's profile is ideal for primary care: Safe, simple, well-tolerated, effective, and versatile. Zyprexa would enjoy first mover advantage in this segment, preempting Janssen, which is Risperdal, Abbott, which is Depakote, and Pfizer, which is Zeldox. Historically, Zyprexa has closed market share gaps in every segment in which we've actively competed."

Did I read that correctly?

A. You did.

Q. The opportunity in the primary care market as reflected here is to sell Zyprexa to a greater number of physicians, that being the primary care physicians which far outnumber psychiatrists, right?

A. There are more primary care physicians than psychiatrists, yes.

Q. Right. And Eli Lilly viewed the potential market for Zyprexa in the primary care market as a huge market, right?

A. No. It says this customer group is huge.

Q. Yes, sir. And then it says you would have first mover advantage. What is first mover advantage?

A. No other product that was approved for schizophrenia or bipolar mania had launched into that market with a sales force.

Q. Yes, sir. Was Depakote an antipsychotic medication?

A. No. It was a mood stabilizer.

Q. Right. And you said Zyprexa would enjoy first mover advantage in this

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

segment preempting, among others, Abbott and Depakote; is that correct?

A. Yes. Well, I didn't say that. That's what Mike wrote in this document.

Q. Right. And Mike was the Brand Manager in the primary care section. Now we see Challenges. There's some particular challenges that Eli Lilly faced in launching into the primary care market, weren't there?

Jordan, Jack E. (October 26, 2006)

368:2-370:8

Issues: 01 Plaintiff's Trial Designation

368:
A. These are Mike's thoughts early in the job that identified these challenges, yes.

Q. Right. Was one of the challenges listed for launching in the primary care physician market is it listed as follows: "Zyprexa's primary indications, schizophrenia and bipolar, are not viewed as PCP-treated conditions. So there's not a specific indication for Lilly representatives to promote in the PCP market."
Did I read that correctly?

A. You read that correctly.

Q. And the specific indications, sir, for the record, at the time of the PCP launch were bipolar mania and schizophrenia; is that correct?

A. Yes.

Q. And Mr. Bandick, who is then the primary care physician brand manager. Who is in charge and responsible, as you said, for the launch of Zyprexa into the primary care market, right?

369:
A. Yes, he was. Yeah.

Q. He said, quote/unquote, there's not a specific indication for Lilly representatives to promote in the PCP segment, didn't he, sir?

A. He was relatively new on the job. And consistent with what I said earlier is the patients, our research showed that the patients were in the primary care physician's office, they just weren't being identified and treated.

Q. My question to you was, sir, did Mr. Bandick, who was the Brand Manager in the primary care market, responsible for the Viva Zyprexa launch, state, quote, There's

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

not a specific indication for Lilly reps to promote in the PCP segment." Did he say that or not?

A. A few weeks in the job he was brainstorming, is how I read this document, and identified that the docs didn't think they had those patients and yet our research showed that those patients were in their offices.

Q. My question to you is, sir, did Mike Bandick, in the Strategy and Implementation Overview for Zyprexa in the Viva campaign launch state, quote, There's not a specific indication for Lilly reps to promote in the PCP segment, close quotes?

A. It's in this document but --

Q. Thank you, sir. Now, sir,

Jordan, Jack E. (October 26, 2006)
371:7-12
Issues: 01 Plaintiff's Trial Designation

Q. Sir, now, my question to you is we know this came from your files, this has been produced from your files. Did you ever respond to this document in any form that you know of and say "I disagree with you, Mr. Bandick?"

Jordan, Jack E. (October 26, 2006)
371:18-20
Issues: 01 Plaintiff's Trial Designation

A. Specifically to this document I don't remember what action I took but I know --

Jordan, Jack E. (October 26, 2006)
372:1-11
Issues: 01 Plaintiff's Trial Designation

A. -- in consistent conversations, the market research was very clear that up to a third of the patients on antidepressants had bipolar disorder that weren't being diagnosed by primary care physicians. So we knew we had an opportunity there on-label.

Q. My question to you was, sir, did you ever write a response to this

document, Exhibit No. 11, and tell
Mr. Bandick you disagreed with him?

Jordan, Jack E. (October 26, 2006)
372:14-375:21
Issues: 01 Plaintiff's Trial Designation

372:14 A. No, because we were in
15 alignment at the launch on what we were going
16 to do and how we were going to do it.
17 Q. Now, Mr. Bandick also has a
18 position for Zyprexa, does he not?
19 A. He does write down a position
20 here, yes.
21 Q. And is the position that
22 ended up being the actual position for
23 Zyprexa at the Viva Zyprexa launch, isn't it?
24 A. I'm not sure.
373: 1 Q. "The safe, proven solution in
2 mood, thought, and behavioral disorders," is
3 that what it says in this document?
4 A. It says that in this
5 document, yes.
6 Q. Do you remember the
7 three-by-three strategy for the Viva Zyprexa
8 primary care physician launch?
9 A. I do remember it, yes.
10 Q. And the three-by-three
11 strategy is this: One of the threes is mood,
12 thought, and behavioral disorders. That's
13 three on one side. And the other three sides
14 was broad spectrum efficacy, No. 1; No. 2,
15 safety; and No. 3, ease of use; isn't that
16 true?
17 A. I don't recall.
18 Q. Okay. I thought you told us
19 you recalled the three-by-three strategy?
20 A. I recall that phrase, I don't
21 recall the specifics.
22 Q. Okay, sir. Anyhow, the
23 position, tell the jury again if you haven't
24 already, can you explain to the jury what a
374: 1 position is with regard to a medical product
2 such as Zyprexa? What a position is?
3 A. A position is, ultimately,
4 how you want your customers to think about
5 your product.
6 Q. Right. And the position
7 listed in this document is "the safe, proven,
8 solution for mood, thought, and behavioral
9 disorders;" is that correct?
10 A. That's how Mike wrote it in
11 this document, yes.
12 Q. The very next sentence says,

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

begins, "We will emphasize safety to address the barriers to adoption." Did I read that correctly?

A. You did.

Q. And when you say "will emphasize safety," that means we, in positioning the product for our customers, including the doctors, will emphasize to them that this product is safe, right?

A. As written in this document, yes.

Q. Then going down under position it says, "quote, mental disorders, close quotes, is intentionally broad and vague providing latitude to frame the discussion around symptoms and behaviors rather than specific indications."

Did I read that correctly?

A. You did.

Q. And Mr. Bandick, the brand manager who was responsible for the primary care launch, stated that the position of mood, thought, and behavioral disorders was intentionally broad and vague, right?

A. In August of 2000, a few weeks on the job, he wrote this; however, in October of 2000, I was at the launch meeting, I saw the message, it was on-label, made it through our medical group, regulatory group.

Again, I want to make sure we position this as a brainstorming document early in his, early in his tenure in this responsibility.

Jordan, Jack E. (October 26, 2006)
376:2-377:15
Issues: 01 Plaintiff's Trial Designation

Q. My point here is, sir, you said "I want to make sure I position this document as a brainstorm." Is there anywhere in this document that says it's a brainstorm or does it, specifically, say it's a Strategy and Implementation Overview?

A. It, actually does. If you read the first sentence of the implementation it says "market research, message development, medical support, and the creation of a training calendar is in progress."

So you're talking about a document where market research, message development, medical support, and the calendar hadn't even been put in place. So

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

it's clearly a brainstorming document.
Q. And aren't mental disorders, excuse me, weren't mood, thought, and behavioral disorders the specific launch statement that was given for Viva Zyprexa -- mood, thought, and behavioral disorders?
A. Again, I don't recall the specifics.
Q. Okay. We'll look at that in a minute. But in this document Mr. Bandick specifically says, though, "mental disorders is intentionally broad and vague to frame the latitude around symptoms and behavior rather than the specific indications." Is that correct?
A. But this is a point where market research, message development, medical support, and the creation of training isn't even done yet so I don't know what to do with that phrase. I don't know what he meant by it. We still have a lot of work to do before the launch meeting.

Jordan, Jack E. (October 26, 2006)
377:18-22
Issues: 01 Plaintiff's Trial Designation

MR. ALLEN: Exhibit No. 12.
(Whereupon, Deposition Exhibit(s) 12 duly received, marked and made a part of the record.)

Jordan, Jack E. (October 26, 2006)
380:18-23
Issues: 01 Plaintiff's Trial Designation

Q. My question is: Do you recall seeing Zyprexa Launch Meeting Viva Zyprexa document, which I have marked as Jordan Exhibit No. 12?
A. I don't remember seeing this specific document, no.

Jordan, Jack E. (October 26, 2006)
381:22-22
Issues: 01 Plaintiff's Trial Designation

Q. Mr. Jordan, turn to Page 79.

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

Jordan, Jack E. (October 26, 2006)
382:18-383:8
Issues: 01 Plaintiff's Trial Designation

382:18 Q. What is the key elements
19 listed under Zyprexa Primary Care?
20 A. Broad efficacy, safety, and
21 ease of use.
22 Q. Doesn't it say, "Zyprexa
23 primary care, quote, three-by-three broad
24 efficacy, safety, ease of use, on one side
383: 1 and mood disturbances, thought disturbances,
2 and behavior disturbances on the other side?
3 A. It does, yes.
4 Q. Did the key message elements
5 in this document, Exhibit No. 12, mirror the
6 key message elements contained in Exhibit
7 No. 11, that is, the broad and vague term
8 mood, thought, and behavior disorders?

Jordan, Jack E. (October 26, 2006)
383:11-17
Issues: 01 Plaintiff's Trial Designation

383:11 A. Those terms are used, yes.
12 Q. Right. And those terms, at
13 least according to Mr. Bandick in Exhibit
14 No. 11, were intentionally vague so that the
15 sales representatives could frame the
16 discussion around symptoms and behavior and
17 not specific indications, isn't that true?

Jordan, Jack E. (October 26, 2006)
383:20-20
Issues: 01 Plaintiff's Trial Designation

383:20 A. No.

Jordan, Jack E. (October 26, 2006)
388:7-389:20
Issues: 01 Plaintiff's Trial Designation

388: 7 Q. Now after the launch of
8 Zyprexa into the primary care market, you, in
9 the marketing as the brand leader didn't just
10 leave things to chance, you wanted to see if
11 the proper message was getting out to the

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

doctors, didn't you?
A. We did do message recall, yes.
Q. And you wanted to see whether or not your campaign had been successful and doctors were responding to your message; isn't that true?
A. With all our segments we did do message recall, yes.
Q. Who is Zohar Porat?
A. She was a market research associate.
Q. For Eli Lilly?
A. For Lilly, yes.
(Whereupon, Deposition Exhibit(s) 13 duly received, marked and made a part of the record.)
MR. ALLEN: Sir, I'll hand you what's been marked as Jordan Exhibit No. 13.
MR. GOLD: Thank you, sir.
QUESTIONS BY MR. ALLEN:
Q. This is entitled Qualitative Telephone Focus Groups, Sales Rep and DM -- DM stands for district managers, doesn't it, sir?
A. It does, yes.
Q. Sales Rep and District Manager Topline Reaction to PCP Launch, December 2000, Zohar Porat, Lilly, Answers That Matter; is that correct?
A. Yes.

Jordan, Jack E. (October 26, 2006)
391:22-392:9
Issues: 01 Plaintiff's Trial Designation

391:22 what Exhibit 13 is. Exhibit 13 is where your company's surveying your sales representatives and your district managers to
392: 1 see how doctors are responding to messages on the PCP launch, right?
A. Yeah, part of it, yeah.
Q. Okay. Now let's go to the second page of this document under executive summary, third bullet point says, "SRs," that's sales representatives, right? Isn't that what it stands for?
A. I believe so, yes.

Jordan, Jack E. (October 26, 2006)
393:15-22

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

Issues: 01 Plaintiff's Trial Designation

393:15 Doesn't Ms. Porat in
16 Exhibit 13 in Bullet Point No. 3 of the
17 Executive Summary state, "Sales
18 representatives having most success when
19 their message centers on identifying patient
20 types and treating symptoms instead of
21 focusing on patient diagnosis?"
22 A. That's what it says --

Jordan, Jack E. (October 26, 2006)

396:3-397:8
Issues: 01 Plaintiff's Trial Designation

396: 3 Q. Okay, sir, are you on the
4 last page of Exhibit 13 which is also
5 Page 13?
6 A. I am.
7 Q. Of the Sales Rep and District
8 Manager Topline Reaction to the Primary Care
9 Physician Launch. Can you read for the jury
10 out loud the first bullet point under
11 Recommendations?
12 A. Now, I'm going to assume this
13 is a summary, given, you haven't given it to
14 me, of the first part of the detail piece
15 where they talk about symptoms and then go on
16 to diagnosis as part of the message which is
17 what I saw trained. So in that context:
18 "Continue focusing on patient symptomology
19 and having PCPs identify specific patients
20 rather than on patient diagnosis."
21 Q. Let's see if I can read this
22 a little slower for the jury. The first
23 bullet point under Recommendations on the
24 last page of Exhibit 13 reads as follows:
397: 1 "Continue focusing on patient symptomatology
2 and having primary care physicians identify
3 specific patients rather than on patient
4 diagnoses." Did I read that correctly?
5 A. You're reading's correct but
6 I don't know, I don't know that it's
7 represented correctly without seeing
8 everything.

Jordan, Jack E. (October 26, 2006)

397:23-398:6
Issues: 01 Plaintiff's Trial Designation

397:23 Q. Okay. Sir, do you recall

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

24 after the launch and periodically over the
398: 1 years, even before the PCP launch, you, at
2 Eli Lilly, would have district and
3 territorial sales meetings concerning the
4 products that you sold?
5 A. We did have district
6 meetings, yes.

Jordan, Jack E. (October 26, 2006)
398:21-24
Issues: 01 Plaintiff's Trial Designation

398:21 Q. You have previously testified
22 that Mr. Mike Bandick was the Brand Manager
23 in charge of the primary care physician
24 launch for Zyprexa, Viva Zyprexa launch in

Jordan, Jack E. (October 26, 2006)
399:1-19
Issues: 01 Plaintiff's Trial Designation

399: 1 October of 2000?
2 A. Yes.
3 Q. Okay. That's when I said
4 physician. And I'm going to hand you -- and
5 did you know or not know that Mr. Bandick --
6 and I think you attended -- let me ask this,
7 did you ever attend district or national
8 sales meetings with the sales force?
9 A. I did at various times, yes.
10 Q. Did you, in fact, attend the
11 national sales meeting of March the 13th,
12 2001, following the Zyprexa PCP launch?
13 A. I don't know if I did or not.
14 Q. Okay. But you know that
15 Mr. Bandick certainly when he attends such a
16 national sales meeting, what he says is
17 accurate and truthful, and he is giving the
18 sales representatives good and truthful
19 information, is he not?

Jordan, Jack E. (October 26, 2006)
399:23-402:19
Issues: 01 Plaintiff's Trial Designation

399:23 A. That would be my assumption,
24 yes.
400: 1 Q. Yes, sir.
2 (Whereupon, Deposition
3 Exhibit(s) 14 duly received,

Exhibit 8
Bruce Kinon, M.D.
Exhibit 16
Denice M. Torres

marked and made a part of the record.)

MR. ALLEN: Sir, I'll hand you what's been marked as Exhibit 14, which is portions of a transcript concerning Mr. Bandick's presentation at the Eli Lilly national sales meeting on March the 13th, 2001.

MR. GOLD: Thank you.

QUESTIONS BY MR. ALLEN:

Q. Do you recall being at this meeting or reading this transcript previously?

A. I do not, no.

Q. Sir, I ask you to turn simply to the second page of this transcript. I'm going to talk to you about Mr. Bandick's comments about money, okay? Just the second page.

Do you see where Mr. Bandick tells the sales representatives in March of 2001, "Just imagine the added impact that better sales messages, competitive differentiation and peer-to-peer activity will have on our future sales line. Don't get me wrong, unit share growth is good, and what we have accomplished in that area has not gone unnoticed. But dollars pay the bills and boost the stock price, so let's look at dollar growth."

Did I read that correctly?

A. You did.

Q. And then we, if you would turn to the next page, which is page four, Mr. Bandick discusses Year X, does he not?

A. Looks like he -- I see it in there.

Q. Yes. And he's talking to the sales representatives that are, actually, going out to sell the product, right?

A. I don't know where this came from.

Q. Sir, the document reflects it came from the national sales meeting. Who comes to the national sales meeting, sales representatives?

Assume with me it's at the national sales meeting. Who goes to the national sales meeting?

A. Most of them are sales people.

Q. Right. Let's see what Mr. Bandick says about Year X to the sales representatives. "This is Year X for Eli Lilly, and the conventional wisdom is that the companies just don't, quote, bounce back,

Exhibit 8
Bruce Kinon, M.D.
Exhibit 10
Denice M. Torres

close quotes, from losing patent protection from their biggest product." And then there's a section redacted by Lilly's lawyers, right?

A. I don't know who redacted it.

Q. We'll assume it's Eli Lilly's lawyers.

Jordan, Jack E. (October 26, 2006)

403:4-404:2

Issues: 01 Plaintiff's Trial Designation

Q. Mr. Bandick says, "And the conventional wisdom is that company's just don't bounce back from losing patent protection from their biggest product. We need to own this target, because the affiliate needs our help."

Did I read that correctly?

A. You did.

Q. When we refer to the affiliate we're talking about Eli Lilly U.S.A., are we not?

A. We are, yes.

Q. So Eli Lilly U.S.A. needed help from the Zyprexa primary care sales force to replace the lost sales that they were going to suffer and had suffered from Prozac, correct?

A. No. The forecast never was to make up for the lost sales of Prozac.

Q. Did Mr. Bandick tell the Zyprexa sales force that the affiliate needs our help, yes or no?

A. He did, yes.

Jordan, Jack E. (October 26, 2006)

404:23-408:19

Issues: 01 Plaintiff's Trial Designation

Q. You talked about Martha in this deposition, have you not, sir? Martha?

A. You've mentioned her and I've acknowledged her but I haven't talked about her, no.

Q. Okay. I'm sorry. I mentioned her and you acknowledged her.

Martha, in fact, was the patient profile that Eli Lilly used to try to get doctors to prescribe Zyprexa to the older folks who had dementia or Alzheimer's or had long-term care needs; isn't that right?

Isn't that who Martha is?
A. No.
Q. Okay. That's not who Martha is? Let's see what Mr. Bandick says on Page 13 which is the next page, it's the fourth page of Exhibit 14. I'll read what Mr. Bandick tells the sales force. "Let me call a time out and make one quick comment on Martha. What's the first thing you notice about Martha --
THE WITNESS: I'm sorry, I've lost which page you're on, I'm sorry.
MR. ALLEN: Yes, sir.
Page 13.
THE WITNESS: Okay, thank you.
QUESTIONS BY MR. ALLEN:
Q. Mr. Bandick tells the sales force, "Let me call a time out and make one quick comment on Martha. What's the first thing you notice about Martha? She's old exclamation point. That does two things. First, it reinforces Zyprexa as a nursing home drug. Our mission is to build a primary care franchise, and let our long-term care team drive the nursing home business. Second, it limits the perception of behavioral disturbance -- agitation, tension, anger, hostility all show up in primary care in a variety of packages. Young, old, male and female. When you describe Martha, make her symptoms more prominent than her age."
Did I read that correctly?
A. You did.
Q. That's off-label marketing, is it not, sir?
A. No, it's not.
Q. Thank you, sir.
So under your definition that you use at Eli Lilly those comments by Mr. Bandick are purely on-label promotion of Zyprexa?
A. Well, the process we used around the Martha profile was to have our medical department identify and help us describe an elder schizophrenia patient which is Martha. And so, you know, our physicians were competent in that endeavor, and did what we asked them to do.
Q. Did you see any description in Mr. Bandick's comments that he described Martha as being a schizophrenic?
Did he there in that transcript that I gave you in the national sales meeting describe Martha as a schizophrenic?

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

A. Well, we jumped so many pages I don't know if he does or doesn't because then -- we're missing so many pages he might have. I don't know. But all I know is it had to go through our medical department to help us identify a schizophrenia on-label patient.

Q. Let's see what Mr. Bandick said. Let me read it. He says it right here, "What's the first thing you notice about Martha? She's old." Doesn't it say that?

A. It does.

Q. Then it says "that does two things. And then he says "it reinforces Zyprexa as a nursing home drug." Does that sound like it's reinforcing Zyprexa as a drug for bipolar mania and schizophrenia to you?

A. I don't know what it says to you but --

Q. Thank you, sir.

A. -- all I know is it had to go through our medical department to identified that Martha had schizophrenia.

Jordan, Jack E. (October 26, 2006)

408:24-409:22

Issues: 01 Plaintiff's Trial Designation

A. Well, I mean, that's just the reality.

Q. So the reality is the medical department had to approve whatever the marketing department did to make sure it's medically proper and in accordance with the label?

A. The Martha profile had to go through the ELMR process which included medical, legal, our regulatory folks to make sure it's aligned with our label.

Q. Thank you, sir, that's a very good point. So the Martha profile, and, I guess, the Donna profile, and all the patients profiles, were not just a function of marketing but also of legal, the lawyers for Eli Lilly, the marketers for Eli Lilly, the regulatory people for Eli Lilly, and the medical team; is that right?

A. Yes.

Q. So Eli Lilly, when it markets to Martha, this is a company-wide agreement, right?

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

Jordan, Jack E. (October 26, 2006)
410:1-5
Issues: 01 Plaintiff's Trial Designation

410: 1 A. We never marketed to Martha.
2 We marketed to physicians.
3 Q. For Martha.
4 A. With a patient profile of
5 Martha.

Jordan, Jack E. (October 26, 2006)
410:12-411:11
Issues: 01 Plaintiff's Trial Designation

410:12 What's the next exhibit, sir?
13 (Whereupon, Deposition
14 Exhibit(s) 16 duly received,
15 marked and made a part of the
16 record.)
17 MR. ALLEN: I'll hand you
18 Exhibit No. 16. This is an
19 advertisement that has been produced
20 to us.
21 Exhibit 16, sir. We're
22 moving off of 15. Let me have 15,
23 please.
24 That was 14. We skipped one
411: 1 right now we'll come back to.
2 Exhibit 16, this is an
3 advertisement. I'll hold it up.
4 (Document displayed to
5 the jury)
6 Do you recall this
7 advertisement, Antipsychotic Power for
8 Routine Use?
9 A. I do not, no.
10 Q. Was Zyprexa an everyday
11 routine drug?

Jordan, Jack E. (October 26, 2006)
411:14-21
Issues: 01 Plaintiff's Trial Designation

411:14 A. Yeah. It was used in over
15 4 million patients at that point, yes.
16 Q. Was Zyprexa intended as a
17 routine drug? It says Antipsychotic Power
18 For Routine Use. Was antipsychotic power in
19 Zyprexa intended for routine use?
20 A. In schizophrenia, later in
21 bipolar mania, it was used routinely, yes.

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

Jordan, Jack E. (October 26, 2006)
412:17-413:2
Issues: 01 Plaintiff's Trial Designation

412:17 Q. Doesn't the second page of
18 this exhibit, the advertisement Antipsychotic
19 Power For Routine Use, have a nice picture of
20 an elderly woman?
21 A. Yes, it does.
22 Q. Is that Martha?
23 A. I don't know who she is.
24 Q. Isn't this attempt to market
413: 1 to Martha an Antipsychotic Power For Routine
2 Use promotion of Zyprexa off-label?

Jordan, Jack E. (October 26, 2006)
413:5-8
Issues: 01 Plaintiff's Trial Designation

413: 5 A. No.
6 Q. Donna. You remember Donna,
7 do you not, sir?
8 A. I do, yes.

Jordan, Jack E. (October 26, 2006)
415:1-7
Issues: 01 Plaintiff's Trial Designation

415: 1 (Whereupon, Deposition
2 Exhibit(s) 15 duly received,
3 marked and made a part of the
4 record.)
5 QUESTIONS BY MR. ALLEN:
6 Q. Would you look at Exhibit 15,
7 sir.

Jordan, Jack E. (October 26, 2006)
415:24-416:14
Issues: 01 Plaintiff's Trial Designation

415:24 Q. Sir, do you recognize
416: 1 Exhibit No. 15?
2 A. No, I don't, because the copy
3 is -- I mean, there's words in there that I
4 can't read.
5 Q. Yes, sir. That's just the

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

best I can do. This is a color document that you're familiar with that has a purple Z with a doctor reaching across to help his patients.

You're familiar with this marketing piece that was given to doctors, aren't you?

A. I'm going to have to read it because I can't tell by the picture.

Jordan, Jack E. (October 26, 2006)
417:3-9
Issues: 01 Plaintiff's Trial Designation

417: Q. Sir, you certainly recognize the cover of this document, don't you, sir?
A. I do not, no.
Q. Okay. This document is, in fact, a detail piece that is provided to physicians, isn't it, sir?
A. I don't know yet.

Jordan, Jack E. (October 26, 2006)
417:23-418:13
Issues: 01 Plaintiff's Trial Designation

417:23 Q. This is a Primary Care Resource Guide, isn't it, sir?
418: A. No. I think it's a --
Q. Excuse me, go ahead. You're correcting me properly. There's a primary care resource guide that trains the sales force how to utilize Exhibit No. 15, isn't there?
A. Yeah. I think -- it looks like a detail piece, yes.
Q. Yes, sir. It's a detail piece that is taken by the sales representatives to the doctors in their offices?
A. I believe this is, yes.

Jordan, Jack E. (October 26, 2006)
419:4-420:4
Issues: 01 Plaintiff's Trial Designation

419: let's go on with Exhibit 15.
By the way, these detail pieces that are given to doctors are not, the sales reps are trained how to talk to the

doctors about the detail piece, are they not?
A. They are, yes.
Q. Yes. And, in fact, the sales representatives are given things like the primary care resource guide training to tell them how to present detail pieces such as Exhibit 15 to the doctors, right?
A. There are resource guides and additional training that goes on, yes.
Q. Yes. And, sir, that wasn't my question. That was part of my question. The resource guides that you're talking about that is part of the sales rep's training teaches the sales reps how to present things like Exhibit 15 to the doctors.
A. They do, yes.
Q. Yes, sir, that's my point. All right, sir. Does this detail piece identify Donna?
A. Yes, it does, on the fourth page.

Jordan, Jack E. (October 26, 2006)
421:5-13
Issues: 01 Plaintiff's Trial Designation

Q. Now, sir, let's go to Exhibit 15. Are you there with Donna?
A. On Page 4, yes.
Q. Yes, sir. We have a circle next to Donna that says "anxiety, irritability, mood swings, and disrupted sleep," right?
A. Yes. Those are what's identified.

Jordan, Jack E. (October 26, 2006)
422:16-423:6
Issues: 01 Plaintiff's Trial Designation

Q. And now we go to the page on Donna. It says, "Donna. Single mom in her mid-30s, presents in drab clothing and seems ill at ease. Quote, I feel so anxious and irritable lately, close quotes. Her history is: Reports she has been sleeping more than usual, has trouble concentrating at work and at home. Several appointments earlier she was talkative, elated, and reported little need for sleep."
Next bullet point: "You have treated her with various medications

including antidepressants."
Did I read that correctly?
A. You did.

Jordan, Jack E. (October 26, 2006)

423:20-424:20
Issues: 01 Plaintiff's Trial Designation

Q. My only question to you is, sir, do you see a diagnosis of schizophrenia or bipolar mania in the Donna profile?
A. Now you're asking a question that -- the words, no, but the symptoms, the cluster of symptoms, actually, might be. I mean, that's part of the reason to have that discussion and have the MDQ so they can screen for bipolar mania.
Q. You said MDQ?
A. MDQ, yes.
Q. Yeah. The MDQ is the mood disorder questionnaire that was only released, I believe, in 2003, and the sales representatives were instructed to only use it with their high prescribers; isn't that right?
A. I don't know if that's the case or not.
Q. And you're not suggesting that in order to prescribe Zyprexa that the physicians needed to get an MDQ filed out, are you?
A. No. But we provided various tools to help them diagnose bipolar mania.

Jordan, Jack E. (October 26, 2006)

425:14-18
Issues: 01 Plaintiff's Trial Designation

I always admit when I make mistakes. I forgot to ask you a question about the Viva Zyprexa document, and I'd like to you to return to the Viva Zyprexa document, if you don't mind?

Jordan, Jack E. (October 26, 2006)

427:8-10
Issues: 01 Plaintiff's Trial Designation

Q. Yes, sir. And if you will go to Exhibit 12, the Zyprexa launch meeting

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

10 Viva Zyprexa document, look at the page 69,

Jordan, Jack E. (October 26, 2006)
435:23-436:2
Issues: 01 Plaintiff's Trial Designation

435:23 to give me any different answer. Can you
24 turn to Page 71 of this about your vision and
436: 1 strategy for primary care at the time of the
2 launch.

Jordan, Jack E. (October 26, 2006)
436:14-437:11
Issues: 01 Plaintiff's Trial Designation

436:14 Q. Are you at the page Zyprexa
15 Primary Care Vision and Strategy?
16 A. I am. 71?
17 Q. Yes. And the vision for the
18 PCP launch was "expand Zyprexa's market by
19 redefining how primary care physicians treat
20 mood, thought, and behavioral disturbances."
21 Did I read that correctly?
22 A. You did.
23 Q. Does it say expand Zyprexa's
24 market by having primary care physicians
437: 1 treat schizophrenia and bipolar mania?
2 A. Again, a vision is what you
3 want in the long-term. And mood is a part of
4 bipolar mania. Thought is what schizophrenia
5 and behavior disturbances are.
6 We had an active program in
7 the psychosis associated with Alzheimer's.
8 Q. Wasn't it your strategic
9 intent at the time of the primary care launch
10 to make Zyprexa an everyday agent in primary
11 care?

Jordan, Jack E. (October 26, 2006)
437:14-438:7
Issues: 01 Plaintiff's Trial Designation

437:14 A. Given that our data showed
15 that up to 30 percent of patients who were
16 treated with antidepressants were potentially
17 bipolar patients, that would make it an
18 everyday agent in the bipolar -- I mean in
19 the primary care physician's office.
20 Q. And, in fact, Zyprexa,
21 Page 72, Strategic Intent says: "Zyprexa can

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

and will become an everyday agent in primary care," correct?

A. Given that antidepressants are one of the most frequently used products by primary care physicians, and if you think about potentially up to a third actually have bipolar disorder, there was the opportunity that doctors would write it every day. Primary care physicians would write it every day, yes.

Jordan, Jack E. (October 26, 2006)
444:15-20
Issues: 01 Plaintiff's Trial Designation

Q. Sir, we're on the topic of diabetes. Let me just ask you generally, by the fall of 2002, if not before, were you aware as Brand Leader and Marketing Director for Eli Lilly that Zyprexa had a problem in the marketplace concerning diabetes?

Jordan, Jack E. (October 26, 2006)
444:23-445:7
Issues: 01 Plaintiff's Trial Designation

A. There were -- we were getting feedback that there was confusion in the marketplace around the whole diabetes issue in general.

Q. And didn't you in the marketing department take on a campaign or several campaigns to get your message out on what you wanted doctors to think about diabetes?

Jordan, Jack E. (October 26, 2006)
445:10-14
Issues: 01 Plaintiff's Trial Designation

A. Again, there was a lot of confusion in the marketplace around this issue. And so, yes, we did want to disseminate information to help customers understand what the data said.

Jordan, Jack E. (October 26, 2006)
447:15-18

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

Issues: 01 Plaintiff's Trial Designation

447:15 (Whereupon, Deposition
16 Exhibit(s) 17 duly received,
17 marked and made a part of the
18 record.)

Jordan, Jack E. (October 26, 2006)
448:15-20
Issues: 01 Plaintiff's Trial Designation

448:15 Q. Right. The message as
16 reflected on Exhibit 17 is under "Issues,
17 Diabetes and Hyperglycemia: It occurs with
18 all agents at comparable rates. Depend on
19 Lilly for diabetes care leadership." Did I
20 read that correctly?

Jordan, Jack E. (October 26, 2006)
449:6-18
Issues: 01 Plaintiff's Trial Designation

449: 6 A. You did, yes.
7 Q. And that is exactly what your
8 positioning statement was for diabetes in
9 relation to Zyprexa, that it occurred with
10 all agents at comparable rates and you could
11 depend on Lilly for diabetes care leadership,
12 correct?
13 A. The consistent message was
14 that diabetes occurred two to four times the
15 rate in people that struggle with
16 schizophrenia and bipolar disorder and that
17 diabetes occurred at comparable rates among
18 the atypical antipsychotics.

Jordan, Jack E. (October 26, 2006)
452:12-15
Issues: 01 Plaintiff's Trial Designation

452:12 (Whereupon, Deposition
13 Exhibit(s) 20 duly received,
14 marked and made a part of the
15 record.)

Jordan, Jack E. (October 26, 2006)
453:11-454:8

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

Issues: 01 Plaintiff's Trial Designation

453:11 Q. And my question is, as
12 reflected in Exhibit 20, it is the marketing
13 department and Zyprexa Brand Team's desire to
14 get the comparable rates message out across
15 the marketing mix?
16 A. That was not the totality of
17 the message we were trying to get out.
18 Q. Does this document reflect
19 that you -- Kathy Armington in Marketplace
20 Management's responsibilities included
21 getting the diabetes comparable rates message
22 out across the marketing mix?
23 A. The document reflects that;
24 however, if you notice these are bullet point
454: 1 form, so it certainly wasn't the complete,
2 completely what we communicated to customers.
3 Q. Right. What you
4 communicated, what you did in regard to
5 diabetes, as you did in regard to weight
6 gain, was attempt to minimize, eliminate, and
7 neutralize diabetes as an issue regarding
8 your product, correct?

Jordan, Jack E. (October 26, 2006)
454:11-13
Issues: 01 Plaintiff's Trial Designation

454:11 A. No. Our goal was to
12 eliminate confusion in the marketplace around
13 the issue.

Jordan, Jack E. (October 26, 2006)
455:1-13
Issues: 01 Plaintiff's Trial Designation

455: 1 Q. Sir, my question to you was
2 as the marketing, Director of Marketing, as
3 Brand Leader, were you responsible for
4 developing and approving the 2001 marketing
5 plan?
6 A. My team would have been
7 responsible to put it together and I,
8 ultimately, would have been responsible for
9 it, yes.
10 (Whereupon, Deposition
11 Exhibit(s) 23 duly received,
12 marked and made a part of the
13 record.)

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

Jordan, Jack E. (October 26, 2006)
455:20-23
Issues: 01 Plaintiff's Trial Designation

455:20 Q. And I've marked as Exhibit 23
21 portions of that marketing plan, including
22 your letter on the marketing plan. You
23 signed this letter, did you not?

Jordan, Jack E. (October 26, 2006)
456:6-460:11
Issues: 01 Plaintiff's Trial Designation

456: 6 Q. You're familiar with the 2001
7 marketing plan, aren't you?
8 A. I am, yes.
9 Q. Okay. You signed the letter
10 attached to the 2001 marketing plan, did you
11 not?
12 A. I did, yes.
13 Q. I will read your letter,
14 portions into the record. Turn to your
15 letter.
16 "Dear Zyprexa Teammates, Last
17 year, you often heard me say "2000 is the
18 critical year." Now that 2000 is complete,
19 we can be proud that we delivered outstanding
20 results in the critical year -- all caps the,
21 exclamation points. We had many successes,
22 not the least of which was that we fulfilled
23 our promise by selling $1.7 billion of
24 Zyprexa. We launched into new markets,
457: 1 launched a new indication, launched new
2 formulations, forged new relationships with a
3 broader range of customers, improved our
4 internal alignment, and re-established the
5 Zyprexa Team as truly incredible. Thanks for
6 the outstanding performance in 2000.
7 Exclamation point.
8 The "blank" patent
9 expiration" -- that would be the Prozac
10 expiration, wouldn't it?
11 A. I'm assuming.
12 Q. "The Prozac patent expiration
13 presents Lilly with even greater challenges
14 than anticipated and provides new
15 opportunities for the Zyprexa team. Oddly
16 enough, 2000 may be, all caps, the critical
17 year. But 2001 is different -- it's not just
18 critical -- it's a chance to do the
19 extraordinary. Yes, we face challenges. We
20 have to deliver over $400 million of
21 incremental net sales in the same year that

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

Zeldox is launching, and our current competitors will continue to challenge us." Did I read that correctly?

A. You did, yes.

Q. The title of the or the theme of the 2001 marketing plan was Limitless, isn't that true? Limitless?

A. It was, yes.

Q. That's how you positioned your marketing plan for the year 2001?

A. It was the position for what I would hope that people would have a year of top level performance, yeah.

Q. This is Exhibit 23 we're on, is that right, sir?

MR. GOLD: Yes, sir.

THE WITNESS: Twenty-three.

QUESTIONS BY MR. ALLEN:

Q. If you turn to the last page of this exhibit it contains -- The last page of the exhibit contains a page that says "Brand, the first step. The brand identity defines key meanings we want to have associated with this brand, including the positioning, essence, and product function." Did I read that correctly?

A. You did, yes.

Q. And then you have the positions for the various issues. And one of them is weight gain and one of them is diabetes; is that correct?

A. Yes.

Q. So this is the position that Eli Lilly wanted to have associated with its brand on diabetes; is that correct?

MR. FAHEY: Objection to the form.

A. It would have been what the product team and U.S. organization agreed would be the high level position, yes.

Q. Yes. And the high level position of the position on diabetes is at follows, I'm reading: Quote, "Diabetes may occur in patients taking antipsychotics and/or mood stabilizers. Zyprexa and other agents have a comparable rate of diabetes." Did I read that correctly?

A. You did, yes.

Q. And that's, as you call, the high level position on diabetes in the 2001 marketing plan, right?

A. Yes.

Q. Now, the reason that you established this position, this high level position of diabetes may occur in patients taking antipsychotics and/or mood stabilizers, Zyprexa and other agents have a

Exhibit 8
Bruce Kinon, M.D.
Exhibit 10
Denice M. Torres

comparable rate of diabetes, is because you wanted to reduce the perception that diabetes is linked to Zyprexa and help eliminate this risk from the risk/benefit equation; isn't that true, sir?

Jordan, Jack E. (October 26, 2006)
460:14-462:10
Issues: 01 Plaintiff's Trial Designation

460:14 A. No. The reason was it's because our scientists and medical groups analyzed all the data that we had and that was in the marketplace and communicated to us and to me that the data supported the high level of diabetes in this patient population, as well as that diabetes occurred at comparable rates among these patients.
Q. Yes. Wasn't diabetes an issue with your company and Zyprexa?
A. There was a lot of confusion in the marketplace, yes.
461: 1 Q. And didn't you have an Issues Management team dealing with the diabetes issue?
A. They were responsible for the competition and any issues in the marketplace.
(Whereupon, Deposition Exhibit(s) 22 duly received, marked and made a part of the record.)
Q. Right. I've handed you Exhibit 22. It's Issues Management Planning Diabetes.
You've seen this document before, have you not, sir?
A. I don't know.
Q. Do you see on the second page "Diabetes. Our Position?" The second page, "Diabetes. Our Position?"
A. Yes.
Q. And doesn't it say just like the 2001 marketing plan, "our position is stated as "Diabetes slash hyperglycemia may occur in patients taking antipsychotics and/or mood stabilizers, including Zyprexa, at comparable rates with the possible exception of Clozapine." Doesn't it say that?
462: 1 A. It does.
Q. And isn't that consistent with the stated position on diabetes as contained in the 2001 marketing plan?

Exhibit 8 Bruce Kinon, M.D.
Exhibit 10 Denice M. Torres

A. Yes.

Jordan, Jack E. (October 26, 2006)
464:4-465:6
Issues: 01 Plaintiff's Trial Designation

Q. Sir, do you see the section entitled Rationale For Our Position?
A. I do.
Q. Okay. And your position was previously stated on that same page one bullet point up, two bullet points up, Our Position.
A. Yes.
Q. And your position was "Diabetes may occur in patients taking antipsychotics and/or mood stabilizers including Zyprexa at comparable rates with the possible exception of Clozapine," right?
A. It does say that, yes.
Q. And the rationale for the position as stated in Exhibit 22 is "showing that diabetes is a common occurrence for all antipsychotics and not just Zyprexa will help reduce the perception that diabetes is linked, specifically, to Zyprexa, and in turn, will help to eliminate this risk from the risk/benefit equation." Isn't that what it says?
A. It does say that, yes.
Q. Yes. And so wasn't Eli Lilly trying to reduce the perception that diabetes is, specifically, linked to Zyprexa?

Jordan, Jack E. (October 26, 2006)
465:8-19
Issues: 01 Plaintiff's Trial Designation

A. Again, as our medical folks did extensive analysis, we saw diabetes as an issue in this patient population because of its incidence. And as they reviewed the data it was comparable across products.
The concern was if the confusion in the marketplace made choosing a product just on one specific attribute and not see the entire, all the data for all the molecules, we were concerned that physicians might make an inappropriate choice for that specific patient.

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

Jordan, Jack E. (October 26, 2006)
467:20-468:3
Issues: 01 Plaintiff's Trial Designation

467:20 Q. Sir, under Rationale For Your
21 Position on diabetes, right, it's the
22 rationale?
23 A. Yes.
24 Q. Doesn't your own document
468: 1 state that "the rationale is to help reduce
2 the perception that diabetes is linked,
3 specifically, to diabetes?"

Jordan, Jack E. (October 26, 2006)
468:9-21
Issues: 01 Plaintiff's Trial Designation

468: 9 A. I've tried to be consistent
10 in my answer and be open with my answer is
11 the rationale was that the data showed that
12 it was comparable rates among all products.
13 And there was confusion in the marketplace
14 around that there wasn't, it wasn't
15 comparable rates. So that was our rationale.
16 Q. Yes, sir. I'm asking what
17 this document states. Doesn't this document
18 state, Exhibit 22, under Rationale, that your
19 position on diabetes was taken, in part, to
20 help reduce the perception that diabetes is
21 linked, specifically, to Zyprexa?

Jordan, Jack E. (October 26, 2006)
468:23-469:14
Issues: 01 Plaintiff's Trial Designation

468:23 Q. Yes or no?
24 A. The issue is I don't remember
469: 1 seeing this document. I don't know who wrote
2 it. I don't know. I just don't know. This
3 document says some things. I'm trying to
4 communicate what the rationale was.
5 Q. Yes, sir, but I'm entitled to
6 ask my question.
7 A. Okay.
8 Q. And my question to you is
9 doesn't the document state that your
10 rationale for your company's position on
11 diabetes and Zyprexa was, in part, to reduce
12 the perception that diabetes is linked,
13 specifically, to Zyprexa? Doesn't the
14 document state that?

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

Jordan, Jack E. (October 26, 2006)
469:17-470:4
Issues: 01 Plaintiff's Trial Designation

469:17 A. It does, but I don't agree
18 with the document.
19 Q. Okay. And doesn't this
20 document also state that your company's
21 position on diabetes was taken in order to
22 help eliminate this risk from the
23 risk/benefit equation?
24 A. We tried to eliminate the
470: 1 confusion in the marketplace. I would never
2 support, and you'll see in our detailing
3 pieces, they never support eliminating it
4 from the risk/benefit discussion.

Jordan, Jack E. (October 26, 2006)
491:1-10
Issues: 01 Plaintiff's Trial Designation

491: 1 Q. Wasn't the goal of Project
2 BAD to reduce the negative impact of the
3 diabetes issue on the Zyprexa business?
4 A. The D, as I recall, did stand
5 for diabetes --
6 Q. Yes, sir.
7 A. -- and to eliminate confusion
8 around that issue in the marketplace.
9 Q. What did Project BAD, B-A-D
10 stand for in its entirety - BAD?

Jordan, Jack E. (October 26, 2006)
491:18-492:4
Issues: 01 Plaintiff's Trial Designation

491:18 Q. My question is what did BAD
19 stand for, sir?
20 A. As I recall, the B was for
21 bipolar, one of the As was for appropriate
22 dose, and there was another A, I don't
23 recall, and then D was diabetes.
24 Q. Wasn't your company's, Eli
492: 1 Lilly's, goal during Project BAD in August of
2 2000, that they would define success if they
3 reduced the negative impact of diabetes issue
4 on the Zyprexa business?

Exhibit 8
Bruce Kinon, M.D.

Exhibit 10
Denice M. Torres

Jordan, Jack E. (October 26, 2006)
494:14-495:6
Issues: 01 Plaintiff's Trial Designation

494:14 A. Yeah, part of it, yeah, is
15 sales.
16 Q. So when it says: Defining
17 Success: "Reduce the negative impact of
18 diabetes issue on the Zyprexa business" in
19 regard to Project BAD, what you were trying
20 to do was to increase the sales of Zyprexa,
21 correct?
22 MR. GOLD: Objection as to
23 form.
24 A. The first step was to make
495: 1 sure that the perception was consistent with
2 the data that our medical folks told us
3 reflected the truth. And, yeah, we felt like
4 if we could get that data into the
5 marketplace and help our customers that it
6 would positively impact Zyprexa's business.

Jordan, Jack E. (October 26, 2006)
508:1-3
Issues: 01 Plaintiff's Trial Designation

508: 1 Yes or no, when you were at
2 Eli Lilly when somebody asked does Zyprexa
3 cause diabetes, what was the answer?

Jordan, Jack E. (October 26, 2006)
508:6-20
Issues: 01 Plaintiff's Trial Designation

508: 6 A. Without being redundant on --
7 well, it is being redundant with the answer,
8 it was that diabetes is an issue in this
9 patient population, very complex issue. That
10 it was comparable among products. And as I
11 asked our medical team, the data never proved
12 that Zyprexa caused diabetes.
13 Q. And wasn't the answer then
14 when people asked does Zyprexa cause
15 diabetes, wasn't the answer no?
16 A. Actually, it was -- this is a
17 very complex issue, there's no data that
18 proves we cause diabetes, Zyprexa causes
19 diabetes, and we'd share the prevalence, the
20 prevalence and the comparable rates.

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

Jordan, Jack E. (October 26, 2006)
521:10-17
Issues: 01 Plaintiff's Trial Designation

521:10 Q. Sir, as we've, as you've
11 testified earlier, sales of Zyprexa in the
12 United States while you were the Marketing
13 Director and Brand Leader from 1998 through
14 2002, continually increased; is that correct?
15 A. They grew every year, yes.
16 Q. It became a multibillion
17 dollar blockbuster for Eli Lilly?

Jordan, Jack E. (October 26, 2006)
522:1-17
Issues: 01 Plaintiff's Trial Designation

522: 1 Q. Right?
2 A. It was successful, yes.
3 Q. Sir, you know the term
4 blockbuster, you used it in your business
5 every single day, didn't you? Blockbuster.
6 A. Not every single day, no.
7 Q. Tell the jury what a
8 blockbuster drug is?
9 A. There are various
10 definitions. Most of the time, as I
11 understand it now, it's any product whose
12 sales is above a billion dollars.
13 Q. Yes. And my question to you
14 is was Zyprexa a multibillion dollar
15 blockbuster for Eli Lilly?
16 A. Its sales were above
17 $1 billion, yes.

Jordan, Jack E. (October 26, 2006)
523:1-2
Issues: 01 Plaintiff's Trial Designation

523: 1 Q. Was it a multibillion dollar
2 blockbuster?

Jordan, Jack E. (October 26, 2006)
523:5-12
Issues: 01 Plaintiff's Trial Designation

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

523: 5 Q. What's the answer, sir?
6 A. Yes. Worldwide it was.
7 Q. In the United States it was a
8 multibillion dollar blockbuster, wasn't it?
9 A. It was successful, yes.
10 Q. My question to you is: In
11 the United States Zyprexa was a multibillion
12 dollar blockbuster, wasn't it?

Jordan, Jack E. (October 26, 2006)
523:15-17
Issues: 01 Plaintiff's Trial Designation

523:15 A. It was successful, yeah.
16 Q. So was it a multibillion
17 dollar blockbuster in the United States?

Jordan, Jack E. (October 26, 2006)
523:20-524:11
Issues: 01 Plaintiff's Trial Designation

523:20 A. Yes, it was successful.
21 Q. Okay, sir. Now, your message
22 alignment and your activities as Brand Leader
23 suddenly came to a halt in 2003 and things
24 suddenly weren't going so well, was it?
524: 1 A. No.
2 Q. That's not true?
3 A. No.
4 Q. Isn't it true that your boss,
5 Glyn Parkin, informed you and the other
6 individuals on the Zyprexa Brand Team that
7 our business with Zyprexa, the heart and the
8 soul of this corporation, the engine room,
9 the best mental health product on this planet
10 is faltering, slowing, and the slowdown has
11 been a sudden one?

Jordan, Jack E. (October 26, 2006)
524:18-526:20
Issues: 01 Plaintiff's Trial Designation

524:18 A. I don't recall that, no.
19 Q. Right. Let me ask you this,
20 though. I asked you that question almost off
21 the top this morning as the evidence will
22 reflect. Isn't it true that Zyprexa was the
23 heart and soul of the corporation and Lilly's
24 engine room?
525: 1 A. I never heard it.

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

(Whereupon, Deposition Exhibit(s) 28 duly received, marked and made a part of the record.)

QUESTIONS BY MR. ALLEN:

Q. Sir, I'll hand you what's been marked Exhibit 28. You know Mr. Glyn Parkin, he was your superior and you've already identified him as such, right?

A. Yes. At various times. I don't know --

Q. In 2003, he was your superior, was he not?

A. For part of the year, yes.

Q. What part of the year?

A. The first five or six months of the year.

Q. Right. Glyn Parkin, your superior first five or six months of 2003 -- By the way this says: "Filed, JEJ Presentations," does it not?

A. It does, yes.

Q. That's you, isn't it?

526: A. Yes.

Q. This was contained within your files, wasn't it?

A. It might have been.

Q. Might have been. Whose handwriting is that?

A. That's my writing so I'm assuming it was.

Q. All right, sir. Do you see where Glyn Parkin says "Neuro Sales Operation" -- these are PowerPoints, are they not?

A. They are.

Q. Isn't this a presentation you gave at the request of Mr. Parkin?

A. I don't know what it -- I don't know.

Q. Well, doesn't your handwriting reflect in the top right-hand corner "File JEJ Presentation?"

Jordan, Jack E. (October 26, 2006)
527:24-529:22
Issues: 01 Plaintiff's Trial Designation

527:24 A. I never gave this as a
528: presentation, no.

Q. Well, does that, your handwriting reflect "File," colon, "JEJ Presentation?"

A. It does.

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

Q. Okay. Glyn Parkin -- Are these PowerPoint presentations?

A. I don't know if it was ever presented but it's a PowerPoint -- yeah, the format's PowerPoint, yes.

Q. Yes. And it says "Glyn Parkin: The Challenge. I need your leadership, the corporation needs your leadership, at this time your leadership is needed in a massive way and in a way that" -- will look back -- "that you will look back on as a defining moment in your leadership careers. All of you."

Doesn't it say that?

A. It does, yes.

Q. And doesn't he say, "Glyn Parkin: The Challenge. Our business with Zyprexa, the heart and soul of this corporation, the engine room, the best mental health product on this planet, is faltering, slowing, and the slowdown has been a sudden one."

Bullet point: "Zyprexa details have decreased."

Bullet point: "Zyprexa contacts as perceived by our customers have decreased."

Bullet point: "Zyprexa is losing a disproportionate amount of business to Abilify."

Bullet point: "Zyprexa is capturing new business more slowly."

Bullet point: "Zyprexa's share of the market is decreasing in both private practice and CMHC settings."

Doesn't it say that?

A. It does, yes.

Q. Wasn't a red alert sent out by the company concerning what happened to Zyprexa in 2003?

Jordan, Jack E. (October 26, 2006)
530:1-3
Issues: 01 Plaintiff's Trial Designation

A. I don't recall a red alert.

Q. You certainly recall a red alert, don't you, sir, you got the red alert?

Jordan, Jack E. (October 26, 2006)
530:6-14
Issues: 01 Plaintiff's Trial Designation

Exhibit 8
Bruce Kinon, M.D.

Exhibit 16
Denice M. Torres

530: 6 Q. Didn't you?
7 A. No, I don't recall.
8 (Whereupon, Deposition
9 Exhibit(s) 20 duly received,
10 marked and made a part of the
11 record.)
12 QUESTIONS BY MR. ALLEN:
13 Q. Sure. Well, here's
14 Exhibit 29.

Exhibit 8
Bruce Kinon, M.D.
Exhibit 16
Denice M. Torres

Kinon, Bruce M.D. (July 10, 2006)

27:18-20
Issues: 01 Plaintiff's Trial Designation

27:18 Q. Sir, would you please state
19 your full name for the record.
20 A. Bruce Jerome Kinon.

Kinon, Bruce M.D. (July 10, 2006)

27:23-28:5
Issues: 01 Plaintiff's Trial Designation

27:23 Q. And what's your occupation?
24 A. Physician.
28: 1 Q. And you're a physician
2 employed by Eli Lilly; is that correct?
3 A. That's correct.
4 Q. And what's your job title?
5 A. Medical Fellow II.

Kinon, Bruce M.D. (July 10, 2006)

31:11-13
Issues: 01 Plaintiff's Trial Designation

31:11 Q. You've been with Eli Lilly
12 ever since 1996; is that correct?
13 A. Yes, that's correct.

Kinon, Bruce M.D. (July 10, 2006)

34:6-24
Issues: 01 Plaintiff's Trial Designation

34: 6 Q. Is it fair to say that your
7 job function has stayed pretty much the same
8 at Eli Lilly since 1996?
9 A. Although I'm a clinical
10 research physician generically, as one
11 becomes, receives promotions and title on its
12 technical track that indicates you have more
13 and more positions of seniority, of
14 supervision, of leadership.
15 Q. Okay. And what is the job
16 description of the clinical research
17 physician?
18 A. A clinical research physician
19 is the medical component of the medical team.
20 The clinical research physician is one who's
21 involved with the medical management of Lilly
22 clinical trials, the interpretation of data
23 from a medical point of view, and interacting
24 with the medical community.

Exhibit 16
Denice M. Torres

Kinon, Bruce M.D. (July 10, 2006)
35:13-36:6
Issues: 01 Plaintiff's Trial Designation

35:13 Q. How much of your time has
14 been spent dealing with Zyprexa-related
15 matters since 1996?
16 A. The majority of my time is
17 involved with Zyprexa.
18 Q. More than 90 percent?
19 A. Approximately, 90 percent.
20 Q. Okay. And can you, please,
21 describe the responsibilities you had
22 regarding Zyprexa since joining the company?
23 A. Since joining the company,
24 I've been involved as a clinical research
36: 1 physician in the component of Eli Lilly known
2 as the U.S. Affiliate. The U.S. Affiliate
3 is, basically, the U.S. area of the company
4 that is involved with the sales, marketing,
5 and medical management of sites within the
6 United States.

Kinon, Bruce M.D. (July 10, 2006)
39:4-21
Issues: 01 Plaintiff's Trial Designation

39: 4 Q. During your time at the
5 company can you describe the activities that
6 you engage in in connection with marketing of
7 Zyprexa?
8 A. I served in the capacity of
9 being a medical consultant to marketing.
10 Q. And what did that entail?
11 A. It was the responsibility of
12 medical to present data to marketing, help
13 them with the understanding of the medical
14 data, as well as review the various medical
15 data that was used in promotional pieces, as
16 well as other activities.
17 Q. And did you draft portions of
18 the marketing pieces with respect to the
19 medical content?
20 A. At times I would. But
21 generally, that was not my responsibility.

Kinon, Bruce M.D. (July 10, 2006)
40:8-13
Issues: 01 Plaintiff's Trial Designation

40: 8 Q. If you didn't draft the
9 marketing pieces themselves, was it your
10 function to review what was drafted and
11 provide comments back to the marketing
12 people?

Exhibit 16
Denice M. Torres

13 A. That's correct.

Kinon, Bruce M.D. (July 10, 2006)

40:24-42:9
Issues: 01 Plaintiff's Trial Designation

40:24 Q. Did you give presentations to
41: 1 various outside audiences about the risks and
2 benefits of Zyprexa?
3 A. Yes, I did.
4 Q. And what types of outside
5 audiences would you give presentations to?
6 A. I would give presentations at
7 scientific congresses, to advisory boards.
8 That was, generally, what I would do.
9 Q. A scientific congress, what
10 is that?
11 A. There are many different
12 scientific congresses that meet on a regular
13 basis, such as the American College of
14 Neuropsychopharmacology or the American
15 Psychiatric Association. I would present my
16 data, data that we thought was new, relevant,
17 at those various congresses.
18 Q. And you also mentioned that
19 you gave presentations to advisory boards.
20 What are those?
21 A. Advisory boards would be
22 groups of physicians that Eli Lilly would
23 contract as consultants to help us with
24 better understanding of our products.
42: 1 Q. And did Eli Lilly have
2 advisory boards that they used in connection
3 with Zyprexa?
4 A. Yes, they did.
5 Q. And did any of these advisory
6 boards deal with the issue of diabetes or
7 hyperglycemia?
8 A. At various times that topic
9 certainly did come up.

Kinon, Bruce M.D. (July 10, 2006)

45:6-14
Issues: 01 Plaintiff's Trial Designation

45: 6 Q. Do you recall that you were a
7 member of what was referred to as the core
8 team on what was referred to as the
9 hyperglycemia/diabetes project?
10 A. I don't recall that,
11 specifically.
12 MR. SUGGS: Okay. Let me
13 show you what has been previously
14 marked as Exhibit 4517.

Exhibit 16
Denice M. Torres

Kinon, Bruce M.D. (July 10, 2006)
46:15-47:13
Issues: 01 Plaintiff's Trial Designation

46:15 Q. For the record, this
16 Exhibit 4517 is a six-page document. The
17 first page has the heading
18 Hyperglycemia/Diabetes Project. Do you see
19 that?
20 A. Yes.
21 Q. And it also makes reference
22 to a core team. Do you see that reference?
23 A. I'll need a minute to review
24 this document, please.
47: 1 Q. Okay. Sir, I'm only going to
2 be asking you questions about the first page.
3 So that should shorten things up.
4 For the record, I'll
5 represent that the database that was provided
6 to us by Lilly in connection with the
7 production of documents indicates this
8 document is dated August 31, 2000, rather
9 than the 9/1/2004 date that's in the lower
10 left-hand corner.
11 Do you recall being a member
12 of this core team of the
13 hyperglycemia/diabetes project back in 2000?

Kinon, Bruce M.D. (July 10, 2006)
47:20-22
Issues: 01 Plaintiff's Trial Designation

47:20 A. When this team was initially
21 developed, I was a member of the medical
22 component of this team.

Kinon, Bruce M.D. (July 10, 2006)
51:11-18
Issues: 01 Plaintiff's Trial Designation

51:11 Q. Dr. Kinon, the first page of
12 Exhibit 4517 states that -- a list of project
13 goals, does it not?
14 A. Yes, it does.
15 Q. And the number one goal there
16 was to stop hyperglycemia and diabetes from
17 becoming a top ten attribute. Isn't that
18 what's listed there?

Kinon, Bruce M.D. (July 10, 2006)
51:21-52:8
Issues: 01 Plaintiff's Trial Designation

Exhibit 16
Denice M. Torres

51:21 THE WITNESS: Repeat the
22 question, please.
23 QUESTIONS BY MR. SUGGS:
24 Q. The very first goal that's
52: 1 listed for this group was to stop
2 hyperglycemia/diabetes from becoming a top
3 ten attribute; isn't that correct?
4 A. As far as I understand that
5 was not the goal of this group. I didn't
6 write this document. This document was
7 apparently written by Suni Keeling, whose
8 name is on the bottom of it.

Kinon, Bruce M.D. (July 10, 2006)
53:3-5
Issues: 01 Plaintiff's Trial Designation

53: 3 Q. Suni Keeling was in the
4 marketing department, correct?
5 A. That's correct.

Kinon, Bruce M.D. (July 10, 2006)
53:6-10
Issues: 01 Plaintiff's Trial Designation

53: 6 Q. And at least, according to
7 this document, the number one goal of this
8 project was to stop hyperglycemia and
9 diabetes from becoming a top ten attribute;
10 isn't that correct?

Kinon, Bruce M.D. (July 10, 2006)
53:13-24
Issues: 01 Plaintiff's Trial Designation

53:13 A. I'm not able to answer that.
14 I did not write this document.
15 Q. You can look at the document
16 and that's what's listed there as the first
17 goal, isn't it?
18 A. If I'm to read the document
19 in front of me the title is
20 hyperglycemia/diabetes project. The second
21 line says: On the forefront of managing the
22 issue. The third line says: Project goals.
23 And the fourth line says: Stop H/D from
24 becoming a top ten attribute.

Kinon, Bruce M.D. (July 10, 2006)
60:11-19
Issues: 01 Plaintiff's Trial Designation

Exhibit 16
Denice M. Torres

60:11 Q. Sir, would you agree with me
12 that this goal of the hyperglycemia/diabetes
13 project of stopping hyperglycemia and
14 diabetes from becoming a top ten attribute
15 had nothing, whatsoever, to do with the
16 manipulation or change in the physical
17 properties of the drug itself but rather, had
18 to do with what the company wanted doctors to
19 think about the drug?

Kinon, Bruce M.D. (July 10, 2006)
60:22-61:8
Issues: 01 Plaintiff's Trial Designation

60:22 A. It's my understanding that
23 the point of this group was to better
24 understand the hyperglycemia issue from a
61: 1 medical point of view and to provide the
2 answers that doctors needed through the
3 marketing channel if need be.
4 Q. Sir, isn't it just a plain
5 fact that the company didn't want doctors to
6 think that hyperglycemia and diabetes were
7 linked with the use of Zyprexa?
8 A. No, not at all.

Kinon, Bruce M.D. (July 10, 2006)
61:9-11
Issues: 01 Plaintiff's Trial Designation

61: 9 MR. SUGGS: Let me hand you
10 what's been previously marked as
11 Exhibit 8905.

Kinon, Bruce M.D. (July 10, 2006)
61:17-22
Issues: 01 Plaintiff's Trial Designation

61:17 Q. For the record, this is a
18 two-page e-mail from Paula Trzepacz -- am I
19 pronouncing her name correctly?
20 A. Trzepacz.
21 Q. Trzepacz. To a number of
22 individuals.

Kinon, Bruce M.D. (July 10, 2006)
62:3-63:8
Issues: 01 Plaintiff's Trial Designation

62: 3 Q. Including Dr. Kinon; is that

Exhibit 16
Denice M. Torres

correct?
A. I'll have to review the document.
Q. You've reviewed the document, haven't you, sir?
A. Yes, I have.
Q. And this e-mail from Dr. Paula Trzepacz went to both people in the medical department and in the marketing department, correct?
A. That's correct.
Q. And Dr. Trzepacz was who you reported to, correct?
A. That's correct.
Q. And what was her job title again?
A. Medical director.
Q. Medical director. And in this e-mail she's talking about redistributing the medical workload that, in her words, involve important issues that affect more than one Zyprexa silo. Do you see that language?
A. Yes.
Q. And what's a Zyprexa silo?
A. What she's referring to is, for example, the schizophrenia group would be one silo, the bipolar group would be another silo.

Kinon, Bruce M.D. (July 10, 2006)
64:15-65:18
Issues: 01 Plaintiff's Trial Designation

Q. Okay. In any event, in her second paragraph in about the middle of it Dr. Trzepacz says, quote, "The primary person responsible will be held accountable to drive the medical marketing strategy from the medical side." Do you see that?
A. Yes, I do.
Q. Okay. And then her plan was to have you be the number one guy on the issue of weight gain with Dr. Baker and Dr. Hay being the No. 2s and No. 3s, correct?
A. Yes.
Q. And her plan also entailed you, pardon me, Dr. Baker being the No. 1 guy on glucose issues, with you being the number two man, and Dr. Kennedy being the number three man; is that correct?
A. That's correct.
Q. And was that plan, in fact, carried out?
A. Yes, it was.
Q. So you were the number one guy dealing about the issue of weight gain,

Exhibit 16
Denice M. Torres

14 correct?
15 A. I was the number one
16 physician in the U.S. Affiliate Zyprexa team.
17 Q. And you were the number two
18 guy dealing with issues of glucose, correct?

Kinon, Bruce M.D. (July 10, 2006)
65:19-19
Issues: 01 Plaintiff's Trial Designation

65:19 A. That's correct.

Kinon, Bruce M.D. (July 10, 2006)
66:8-11
Issues: 01 Plaintiff's Trial Designation

66: 8 Q. Okay. Is it fair to say,
9 though, that you were very actively involved
10 in both the weight gain and the glucose
11 issues with respect to Zyprexa?

Kinon, Bruce M.D. (July 10, 2006)
66:14-18
Issues: 01 Plaintiff's Trial Designation

66:14 A. My predominant effort was in
15 the weight gain area.
16 Q. Okay. But were you also
17 involved in the glucose area?
18 A. To some degree.

Kinon, Bruce M.D. (July 10, 2006)
69:16-18
Issues: 01 Plaintiff's Trial Designation

69:16 Q. Do you recall that one of
17 your key messages about weight gain was no
18 significant weight gain over the long-term?

Kinon, Bruce M.D. (July 10, 2006)
69:21-70:7
Issues: 01 Plaintiff's Trial Designation

69:21 A. No, I have no recollection of
22 that message at all.
23 Q. Do you recall that another of
24 your key messages was "no association between
70: 1 weight gain with olanzapine and hyperglycemia
2 and diabetes?"

Exhibit 16
Denice M. Torres

A. I don't, specifically, recall that at all.

MR. SUGGS: Let me show you what's been previously marked as Exhibit 1213.

Kinon, Bruce M.D. (July 10, 2006)
70:13-18
Issues: 01 Plaintiff's Trial Designation

Q. Sir, I'm going to represent that the database that was produced to us by Lilly in conjunction with the production of documents states that this particular document was produced from your files. Do you have any basis to dispute that?

Kinon, Bruce M.D. (July 10, 2006)
70:19-22
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: I have to review the document, please.
Q. Do you recall my question?
A. No, I don't.

Kinon, Bruce M.D. (July 10, 2006)
71:8-17
Issues: 01 Plaintiff's Trial Designation

Q. Okay. As I mentioned before, the database that was provided to us by Lilly states that this document was produced to us from your files. Do you have any basis to dispute that?
A. I've never seen this document before.
Q. Okay. So are you denying that this document came from your files as represented to us by Eli Lilly?

Kinon, Bruce M.D. (July 10, 2006)
71:20-72:12
Issues: 01 Plaintiff's Trial Designation

A. I have no basis to deny or not. I just have never seen this document before.
Q. Okay. The title of the document is: Olanzapine Issues Surrounding Weight Gain, Diabetes and Hyperglycemia. Key

Exhibit 16
Denice M. Torres

Messages. Is that correct?
A. That's correct.
Q. And then about midway through the page there's a heading that says: No Significant Weight Gain Over Long-term. Do you see that language?
A. I see that on this document before me.
Q. And that was, in fact, one of the key messages that you wanted doctors to believe about Zyprexa, correct?

Kinon, Bruce M.D. (July 10, 2006)
72:15-15
Issues: 01 Plaintiff's Trial Designation

72:15 A. That is certainly incorrect.

Kinon, Bruce M.D. (July 10, 2006)
72:21-24
Issues: 01 Plaintiff's Trial Designation

72:21 Q. So you're denying that one of your key messages for physicians was that there was no significant weight gain over the long-term?

Kinon, Bruce M.D. (July 10, 2006)
73:3-16
Issues: 01 Plaintiff's Trial Designation

73: 3 Q. Is that correct?
A. I deny that that was a statement.
Q. Okay. And then the one right below that says, quote, "No association between weight gain with olanzapine and hyperglycemia and diabetes." Do you see that language?
A. I do see that.
Q. And that was another key message that the company wanted doctors to believe; isn't that correct?
A. I have no idea whether these were key messages or not. As far as I could

Kinon, Bruce M.D. (July 10, 2006)
74:1-75:3
Issues: 01 Plaintiff's Trial Designation

74: 1 Q. Directing your attention to

the following page. There's a bolded heading about a third of the way down that says: Explain the Data Results and Reemphasize Its Importance. Do you see that?

A. Yes, I do.

Q. And then it says, "In this study, 70 percent of patients treated with olanzapine either lost weight, remained stable, or gained less than or equal to 22 pounds over the long-term." Do you see that language?

A. Yes.

Q. And do you know what study that's referring to?

A. I don't know, specifically. This may be, this may be referring to one of my studies. But I certainly did not write these conclusions.

Q. Did you do a study in which you found that 70 percent of patients treated with olanzapine either lost weight, remained stable, or gained less than or equal to 22 pounds over the long-term?

75: 1 A. We published on long-term
2 weight gain with Zyprexa. We never presented
3 the data this way at all in the article.

Kinon, Bruce M.D. (July 10, 2006)
75:7-17
Issues: 01 Plaintiff's Trial Designation

75: 7 Q. Well, did your study find
8 that 70 percent of the patients treated with
9 Zyprexa either lost weight, remained stable
10 or gained less than or equal to 22 pounds
11 over the long-term?
12 A. I'm not aware of that
13 calculation. How that was arrived at.
14 Q. So is that language
15 describing the results from the study false?
16 A. In my opinion that would be
17 false.

Kinon, Bruce M.D. (July 10, 2006)
76:24-78:16
Issues: 01 Plaintiff's Trial Designation

76:24 Q. Did the data that the company
77: 1 had show that 30 percent of the Zyprexa users
2 gained more than 22 pounds over the
3 long-term?
4 A. The data would be consistent
5 with that.
6 Q. Okay. And if, in fact,
7 70 percent of -- and by the way, there were

reports of people gaining like 80, 90 pounds of weight while they were using the drug; is that correct?
A. There were some reports, yes.
Q. Okay. And about 30 percent of them gained more than 22 pounds, correct, over the long-term?
A. It might have been that.
Q. And 22 pounds of weight gain is a lot of weight gain, isn't it?
MR. WASSON: Objection to the form.
A. That would be considered a significant amount of weight.
Q. Clinically significant, correct?
A. Depends upon the amount of
78: 1 time.
Q. Well, it also depends on the weight of the individual, right?
A. That's correct.
Q. Because don't doctors, typically think if you have weight gain more than 7 percent of your body weight that is clinically significant?
A. That's correct.
Q. So if you had people gaining more than 22 pounds on the drug, for anybody who weighed less than 300 pounds that would be clinically significant, correct?
A. Seven percent or greater increase in body weight would be clinically significant.

Kinon, Bruce M.D. (July 10, 2006)
79:8-19
Issues: 01 Plaintiff's Trial Designation

79: 8 Q. Okay. When it says here that 70 percent of patients treated with olanzapine either lost weight, remained stable, or gained less than or equal to 22 pounds, do you recall from your studies how many people gained, say, 15 to 20 pounds of weight while on the drug?
A. The long-term weight gain on olanzapine that we published on over a period of one to three years, the mean weight gain is, approximately, 15 pounds or 6 to 7 kilograms.

Kinon, Bruce M.D. (July 10, 2006)
80:7-15
Issues: 01 Plaintiff's Trial Designation

Exhibit 16
Denice M. Torres

80: 7 Q. So what you're saying is that
8 the studies that were done by you showed that
9 if you looked at all the people who took the
10 Zyprexa in your study that the average weight
11 gain for the entire group was 15 pounds,
12 correct?
13 A. The average weight gain over
14 a long period of time, one to three years,
15 would be about 15 pounds, that's correct.

Kinon, Bruce M.D. (July 10, 2006)
81:22-82:3
Issues: 01 Plaintiff's Trial Designation

81:22 Q. Okay. So bottom line what
23 your studies were showing is that on average
24 people were going to have clinically
82: 1 significant weight gain with Zyprexa,
2 correct?
3 A. That's correct.

Kinon, Bruce M.D. (July 10, 2006)
82:19-83:1
Issues: 01 Plaintiff's Trial Designation

82:19 Q. Now if you could direct your
20 attention back to Exhibit 1213, the last
21 bolded item there says Summarize and
22 Disassociate Olanzapine and Weight Gain From
23 Diabetes and Hyperglycemia. Do you see that
24 on there, sir?
83: 1 A. Yes, I do.

Kinon, Bruce M.D. (July 10, 2006)
83:9-84:4
Issues: 01 Plaintiff's Trial Designation

83: 9 Q. The goal of disassociating
10 olanzapine and weight gain from diabetes and
11 hyperglycemia was a tough goal to accomplish,
12 wasn't it, sir?
13 A. I don't know, specifically,
14 what is meant by this statement in this
15 particular document. I did not write it and
16 I'm not aware of it.
17 Q. Sir, weight gain, trying to
18 say that weight gain is not linked with
19 diabetes is flying in the face of accepted
20 medical principles, is it not, sir?
21 MR. WASSON: Objection to the
22 form.
23 A. If one were, tried to remove
24 or distance weight gain from diabetes as a

Exhibit 16
Denice M. Torres

84: 1 risk factor, yes, that would be.
2 Q. Because it's generally
3 accepted that if you gain weight you're more
4 likely to develop diabetes, correct?

Kinon, Bruce M.D. (July 10, 2006)
84:7-15
Issues: 01 Plaintiff's Trial Designation

84: 7 A. Weight gain is known to be a
8 risk factor for the development of diabetes.
9 Q. And, in fact, in 1995, before
10 Zyprexa even went on the market, a group of
11 outside consultants warned Lilly that
12 clinically significant weight gain is a risk
13 factor for developing other medical
14 conditions including type two diabetes. Were
15 you aware of that, sir?

Kinon, Bruce M.D. (July 10, 2006)
84:18-18
Issues: 01 Plaintiff's Trial Designation

84:18 A. I was not aware of that.

Kinon, Bruce M.D. (July 10, 2006)
84:19-21
Issues: 01 Plaintiff's Trial Designation

84:19 MR. SUGGS: Okay. Let me
20 show you what's been previously
21 marked as Exhibit 1586.

Kinon, Bruce M.D. (July 10, 2006)
85:2-8
Issues: 01 Plaintiff's Trial Designation

85: 2 MR. SUGGS: For the record
3 this is a document entitled
4 Executive Summary, The Third United
5 States Schizophrenia Advisory Panel
6 Meeting dated December 10, 1995.
7 Apparently, the meeting was
8 held in San Juan, Puerto Rico.

Kinon, Bruce M.D. (July 10, 2006)
87:10-88:9
Issues: 01 Plaintiff's Trial Designation

Exhibit 16
Denice M. Torres

87:10 Q. Dr. Kinon, can I direct your
11 attention, please, sir, to Page 2. In the
12 second paragraph it starts off by saying,
13 "the meeting began with first-time
14 presentation of efficacy and safety results
15 from HGAJ, the pivotal phase 3 trial by
16 Charles Beasley Jr." Do you see that
17 language, sir?
18 A. Yes, I do.
19 Q. And are you familiar with a
20 study that was known within Lilly as HGAJ?
21 A. Yes.
22 Q. And what was that?
23 A. Study HGAJ was a randomized
24 double-blind clinical trial comparing
88: 1 Zyprexa, olanzapine, versus haloperidol.
2 Q. And haloperidol is another
3 antipsychotic drug; is that correct?
4 A. That's correct.
5 Q. Okay. And haloperidol was, I
6 believe, what was often referred to as a
7 first generation antipsychotic; is that
8 correct?
9 A. That's correct.

Kinon, Bruce M.D. (July 10, 2006)
89:20-90:4
Issues: 01 Plaintiff's Trial Designation

89:20 Q. Thank you. Now if I could
21 direct your attention to Page 8. At the end
22 of the first full paragraph on that page it
23 states that, "Patients who remained on
24 olanzapine for 12 months gained an average of
90: 1 24 pounds at the end of the 24-month" --
2 pardon me -- "at the end of the 12 months."
3 Did I read that correctly?
4 A. Yes.

Kinon, Bruce M.D. (July 10, 2006)
91:15-21
Issues: 01 Plaintiff's Trial Designation

91:15 Q. Okay. Were you -- do you
16 recall being informed that the studies that
17 had been done before Zyprexa went on the
18 market found that the average weight gain for
19 people who were on the drug for at least a
20 year was about 24 pounds on average?
21 A. No. We clearly state in our

Kinon, Bruce M.D. (July 10, 2006)
92:16-23
Issues: 01 Plaintiff's Trial Designation

92:16 Q. So is it your testimony as
17 you sit here today that up until now you were
18 not aware of this statement that patients who
19 remained on olanzapine for 12 months gained
20 an average of 24 pounds at the end of 12
21 months?
22 A. It's something that I'm not
23 familiar with now, no.

Kinon, Bruce M.D. (July 10, 2006)
98:3-99:2
Issues: 01 Plaintiff's Trial Designation

98: 3 Q. Dr. Kinon, would you agree
4 with me that the Zyprexa package labeling did
5 not state to doctors that if they had their
6 patients on Zyprexa for 12 months that on
7 average they could expect their patients to
8 gain 24 pounds of weight?
9 A. That specific language is not
10 in the label.
11 Q. Thank you.
12 If I could direct your
13 attention back to Page 8 of Exhibit 1586. In
14 the middle of the page there is some
15 italicized language. It states, quote,
16 Several advisors commented on the association
17 of olanzapine with weight gain and encouraged
18 Lilly to subject the data to a full analysis.
19 Clinically significant weight gain is a risk
20 factor for other conditions such as increased
21 blood pressure, increased cholesterol and
22 type two diabetes. The advisors also noted
23 that Lilly has an opportunity to develop
24 strategies to help manage the weight gain."
99: 1 Do you see that language?
2 A. Yes, I do.

Kinon, Bruce M.D. (July 10, 2006)
99:19-100:3
Issues: 01 Plaintiff's Trial Designation

99:19 company -- well, let's take it this way. At
20 least by 1996 were you, through the virtue of
21 your training and experience or your reading
22 in the field or whatever, were you aware that
23 clinically significant weight gain is a risk
24 factor for other conditions, such as
100: 1 increased blood pressure, increased
2 cholesterol, and type two diabetes?
3 A. Yes, I was aware of that.

Kinon, Bruce M.D. (July 10, 2006)

Exhibit 16
Denice M. Torres

101:23-102:9
Issues: 01 Plaintiff's Trial Designation

101:23 simple. Did anyone tell you back in 1995
24 analysis was done which showed a
102: 1 statistically significant increased incidence
2 of high glucose in Lilly's own clinical
3 trials? Yes or no?
4 A. I'm not aware that anyone,
5 specifically, told me of that analysis that
6 you're referring to.
7 MR. SUGGS: Okay. I'm going
8 to show you what's been previously
9 marked as Exhibit 1605.

Kinon, Bruce M.D. (July 10, 2006)

102:14-104:5
Issues: 01 Plaintiff's Trial Designation

102:14 MR. SUGGS: For the record
15 this is a computer printout dated
16 June 19, 1995 and it's entitled
17 Treatment Emergent Abnormal High or
18 Low Laboratory Values at Any Time
19 FID-MC-HGAJ Acute Phase.
20 Sir, do you recall that the
21 HGAJ study that we were referring to
22 before, I believe you said that was
23 the largest clinical study that was
24 done with respect to Zyprexa?
103: 1 A. Yes, I am.
2 Q. And do you recall that it had
3 an acute phase?
4 A. Yes.
5 Q. And do you recall, I think
6 you testified before that study involved a
7 comparison between the use of olanzapine or
8 Zyprexa and haloperidol; is that correct?
9 A. That's correct.
10 Q. Okay. If I could direct your
11 attention to Page 11. At about the middle of
12 the page are the results of nonfasting
13 glucose, do you see that?
14 A. Yes, I do.
15 Q. And can you explain to the
16 jury what nonfasting glucose testing is?
17 A. Nonfasting glucose is what we
18 call random glucose testing. The patient has
19 not fasted for eight hours prior to obtaining
20 a blood sample for the determination of
21 glucose or sugar.
22 Q. Okay. And in this particular
23 computer analysis the two categories there
24 are low and high, correct?
104: 1 A. That's correct.
2 Q. And for the high it shows
3 that there was a statically significant

Exhibit 16
Denice M. Torres

4 increased incidence of high glucose in the
5 olanzapine or Zyprexa users, correct?

Kinon, Bruce M.D. (July 10, 2006)
104:8-13
Issues: 01 Plaintiff's Trial Designation

104: 8 A. It would appear from this
9 analysis that there was a higher incidence of
10 the high glucose values versus the
11 haloperidol group.
12 Q. And that it was statistically
13 significant, correct?

Kinon, Bruce M.D. (July 10, 2006)
104:16-24
Issues: 01 Plaintiff's Trial Designation

104:16 A. That's correct.
17 Q. Okay. And what it found was
18 that the incidence of high glucose in Zyprexa
19 users was more than twice that in the
20 haloperidol group, correct?
21 A. Based upon this particular
22 analysis, which is looking at a random blood
23 value at any time over the course of many,
24 many, days. This is one value.

Kinon, Bruce M.D. (July 10, 2006)
110:22-111:4
Issues: 01 Plaintiff's Trial Designation

110:22 sir. All the -- is it fair to say, sir, that
23 all the clinical trials that your company did
24 with respect to Zyprexa to get it approved to
111: 1 market here in the United States, to the
2 extent it looked at glucose levels at all, it
3 did so in terms of random glucose testing?
4 A. That's correct.

Kinon, Bruce M.D. (July 10, 2006)
115:20-23
Issues: 01 Plaintiff's Trial Designation

115:20 Q. Sir, do you recall that when
21 Lilly brought Zyprexa to market in 1996 it
22 made false and misleading statements about
23 weight gain?

Kinon, Bruce M.D. (July 10, 2006)

Exhibit 16
Denice M. Torres

116:2-7
Issues: 01 Plaintiff's Trial Designation

116: 2 A. I'm not aware that Eli Lilly
3 ever made any false misleading statements
4 about weight gain.
5 MR. SUGGS: Let me show you
6 what's been previously marked as
7 Plaintiff's Exhibit No. 1169.

Kinon, Bruce M.D. (July 10, 2006)
116:12-20
Issues: 01 Plaintiff's Trial Designation

116:12 MR. SUGGS: For the record,
13 this is a letter from the FDA to
14 Charles R. Perry at Eli Lilly dated
15 November 14, 1996. And I'll
16 represent on the record that the
17 database that was provided to us by
18 Lilly with respect to this document
19 says that it was produced from the
20 files of Dr. Kinon.

Kinon, Bruce M.D. (July 10, 2006)
121:1-23
Issues: 01 Plaintiff's Trial Designation

121: 1 Q. Dr. Kinon, I'd like to direct
2 your attention to Exhibit 1169. The first
3 paragraph states quote, "This concerns a
4 number of labeling pieces for Zyprexa
5 identified as a multi-page detail aid,
6 OL-0026 Stat-Grams identified as OL-0077 and
7 OL-0078; a letter to the California
8 Department of Health Sciences assumed to be
9 an example of other letters to other states
10 with an attached backgrounder; and a John Q
11 Public letter, all submitted as required with
12 a form FDA 2253 and also found during normal
13 surveillance activities. This also concerns
14 other promotional activities such as, an
15 interactive teleconference held on or about
16 October 2, 1996. The Division of Drug
17 Marketing, Advertising and Communications,
18 DDMAC, considers these promotional labeling
19 pieces, and promotional activities to be
20 false or misleading, and in violation of the
21 Federal Food, Drug, and Cosmetic Act." Do
22 you see that language, sir?
23 A. Yes.

Kinon, Bruce M.D. (July 10, 2006)
122:23-123:14

Exhibit 16
Denice M. Torres

Issues: 01 Plaintiff's Trial Designation

122:23 Q. Now if I could direct your
24 attention to Page 4 at the top, there's a
123: 1 reference made to an interactive
2 teleconference held on or about October 2,
3 1996, by Gary D. Tollefson, Vice-President of
4 Lilly Research Laboratories. Do you see
5 that?
6 A. Yes, I do.
7 Q. And who is Dr. Gary D.
8 Tollefson? Did you report to him in any way
9 back in October 1996?
10 A. No, I did not.
11 Q. Was he a senior person there
12 in the company at that time?
13 A. Yes. He was a vice-president
14 for Lilly Research Laboratories.

Kinon, Bruce M.D. (July 10, 2006)
124:2-125:21
Issues: 01 Plaintiff's Trial Designation

124: 2 Q. His position in the company,
3 how high up in the company was he?
4 A. He would be considered senior
5 management.
6 Q. If I could direct your
7 attention to the following page it states
8 quote, "When asked a question about weight
9 gain, Dr. Tollefson's response misleadingly
10 turned an adverse event into a therapeutic
11 benefit. He states, so we went back and
12 analyzed the data and saw that the vast
13 majority of weight gain reported initially as
14 an adverse event, in fact, was weight gain
15 occurring in patients who had baseline,
16 before starting treatment, had been below
17 their ideal body weight."
18 And the following language is
19 bolded, it says, "So we really look at this,
20 with the majority of patients, as being part
21 of a therapeutic recovery rather than an
22 adverse event. And that data, I think is
23 fairly compelling, because it was included in
24 our label."
125: 1 Did I read that correctly?
2 Doctor?
3 A. I'm reading it.
4 Q. My question was: Did I read
5 that correctly?
6 A. Yes, you did.
7 Q. Okay. And then the FDA goes
8 on to state quote, "The information on weight
9 gain was indeed included in the approved
10 labeling, but as an adverse event, not a
11 therapeutic benefit. Since the product was

approved at the time of this teleconference, Dr. Tollefson knew or should have known what information the approved labeling contained and in what section it appeared. His statements were therefore, false and misleading.

Now, sir, does that refresh your recollection that when Lilly brought Zyprexa to market in 1996 it made false and misleading statements about weight gain?

Kinon, Bruce M.D. (July 10, 2006)
125:24-126:2
Issues: 01 Plaintiff's Trial Designation

125:24 A. I was not aware that Lilly
126: 1 ever made any false and misleading statements
2 about weight gain.

Kinon, Bruce M.D. (July 10, 2006)
127:4-17
Issues: 01 Plaintiff's Trial Designation

127: 4 Q. Sir, do you deny that,
5 thereafter, Lilly continued to make
6 statements that weight gain was beneficial in
7 some patients?
8 A. No. We had made those
9 statements.
10 Q. Okay. And according to the
11 FDA, to make statements like that with
12 reference to weight gain, that it was a
13 benefit, or a part of the therapeutic
14 recovery, was false and misleading according
15 to the FDA, correct?
16 A. According to the FDA in this
17 document, yes.

Kinon, Bruce M.D. (July 10, 2006)
129:18-20
Issues: 01 Plaintiff's Trial Designation

129:18 MR. SUGGS: Let me show you
19 what's been previously marked as
20 Exhibit 6890.

Kinon, Bruce M.D. (July 10, 2006)
130:2-6
Issues: 01 Plaintiff's Trial Designation

130: 2 MR. SUGGS: For the record,

this is a document dated December 9, 1998, and refers to a Zyprexa Medical Marketing Meeting Agenda for a meeting on December 9, 1998.

Kinon, Bruce M.D. (July 10, 2006)
131:21-132:23
Issues: 01 Plaintiff's Trial Designation

131:21 Q. Okay. And in about the middle of the page of this particular agenda from December of 1998 it says: Weight gain and link to diabetes question mark. What does the data say and what is our action plan, question mark.
Do you see that?
A. Yes, I see that.
Q. And was your team, your medical marketing team also engaged in this issue of whether or not there was a link between weight gain and diabetes with Zyprexa?
A. Yes, we were.
Q. Okay. And you see that there are handwritten notes on this document?
A. Yes, I do.
Q. Do you recognize the handwriting?
A. No, I don't.
Q. The very bottom handwritten note says: "Weight gain plus genetic vulnerability lead to hyperglycemia." Do you see that language?
A. Yes, I do.
Q. And that formula, if you will, is a generally-accepted scientific view

Kinon, Bruce M.D. (July 10, 2006)
132:24-24
Issues: 01 Plaintiff's Trial Designation

132:24 then; is that correct?

Kinon, Bruce M.D. (July 10, 2006)
133:3-10
Issues: 01 Plaintiff's Trial Designation

133: 3 A. As far as I understand it weight gain is believed to be a risk factor for hyperglycemia in patients with a genetic predisposition.
Q. So you would agree with that statement "weight gain plus genetic

vulnerability lead to hyperglycemia,"
correct?

Kinon, Bruce M.D. (July 10, 2006)
133:13-134:2
Issues: 01 Plaintiff's Trial Designation

A. I would agree to it in terms of general medical knowledge. I have no idea what this person is referring to, specifically.
Q. Would you say, sir, I realize this is calling for an opinion on your part, but based on the discussions you had with people back in Lilly at or around this time back in December of 1998, would it be your belief and understanding that it was well understood by the people that you dealt with in the medical marketing area, that weight gain and genetic vulnerability lead to hyperglycemia?

Kinon, Bruce M.D. (July 10, 2006)
134:5-15
Issues: 01 Plaintiff's Trial Designation

A. I don't know what other people believed. It's common medical knowledge that weight gain or excessive weight gain is a risk factor for diabetes. This could be a vulnerability based upon patient's family history and also many other factors.
Q. But, sir, you wanted to, you personally wanted to avoid linking weight gain and diabetes or hyperglycemia; isn't that correct?

Kinon, Bruce M.D. (July 10, 2006)
134:18-22
Issues: 01 Plaintiff's Trial Designation

A. That's definitely not the case at all.
MR. SUGGS: I'm going to show you what's been previously marked as Exhibit 1215.

Kinon, Bruce M.D. (July 10, 2006)
135:3-137:2
Issues: 01 Plaintiff's Trial Designation

Exhibit 16
Denice M. Torres

MR. SUGGS: For the record Exhibit 1215 is an e-mail chain starting off with an e-mail from Peter Clark on November 30, 1998, at 9:26 a.m. and ending up with an e-mail from Robert Schmid on December 1, 1998.

QUESTIONS BY MR. SUGGS:

Q. You've reviewed the document?

A. Yes, I have.

Q. Okay. Let's start off talking about the first e-mail, at least chronologically, which was Peter Clark's e-mail to Jack Jordan, yourself, John R. Richard, with copies to Jeffrey Ramsey, Robert Schmid regarding the Wishing/Goldstein articles.

A. Yes.

Q. Am I correct that Peter Clark was in the marketing department?

A. He was a marketing associate, I believe, on the product team.

Q. And Jack Jordan was also in marketing?

A. Yes, he was.

Q. And was John Richards in marketing?

A. Yes.

Q. And Jeffrey Ramsey, was he in marketing?

A. I believe he was in with statistics.

Q. And Robert Schmid, who is he with?

A. Marketing on the product team.

Q. Okay. So you're the only medical guy, apparently, who's being copied on this e-mail?

A. Apparently.

Q. Okay. And there are references to articles by Wishing and Goldstein. Do you see that reference, sir?

A. Yes.

Q. And apparently, there had been an article published by Wishing in the Society of Biological Psychiatry that linked hyperglycemia with Zyprexa use, correct?

Kinon, Bruce M.D. (July 10, 2006)
137:5-139:10
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: Specifically, what are you asking?

Q. Well, just read on to the e-mail it states, quote, "Rob has asked me to

Exhibit 16
Denice M. Torres

summarize the points we would raise in response to the recent reports of hyperglycemia linked with Zyprexa use raised in the Wishing, published in the Society of Biological Psychiatry, and Goldstein, soon to be published in Psychosomatics Journal, articles." Do you see that language, sir?

A. I see that language, yes.

Q. So the marketing department was aware that there were these articles this that were either published or about to be published that were linking hyperglycemia with the use of Zyprexa, correct? Isn't that what it indicates?

A. That's what -- these articles do not link Zyprexa with diabetes. They're based on case reports of a very small number of patients. This is the opinion of Peter Clark.

Q. Okay. Anyway, in any event, the marketing department was concerned about these reports that were being published and wanted to know what the response was going to be, correct?

A. As reflected by Peter Clark's e-mail I would say yes.

Q. Okay. And then in the rest of the text of the e-mail contains what they were planning on saying at that point in time, correct?

A. That's correct.

Q. Okay. And he's got that set out in various bullet points there, correct?

A. That's correct.

Q. And if you drop down to the bullet points, the second and third bullet points say: Use of antipsychotics may result in weight gain. And then the bullet point below that says: Patients who gain weight may develop insulin resistance which may lead to hyperglycemia and diabetes. Correct?

A. That's what the bullet points say, that's correct.

Q. And that chain of weight gain, developing insulin resistance which may lead to hyperglycemia, and which may then go on to diabetes, that chain that's being talked about there was the type of medical chain, if you will, that was generally accepted in the field?

Kinon, Bruce M.D. (July 10, 2006)
139:13-15
Issues: 01 Plaintiff's Trial Designation

Q. Correct? That if you gain weight that can lead to, ultimately,

Exhibit 16
Denice M. Torres

15 diabetes, correct?

Kinon, Bruce M.D. (July 10, 2006)
139:18-140:14
Issues: 01 Plaintiff's Trial Designation

139:18 A. I don't know, specifically,
19 what Peter Clark was referring to but in
20 general medical knowledge weight gain can
21 lead, in some patients, into insulin
22 resistance, which in some patients may
23 eventually go on to be diabetes.
24 Q. Okay. After you got this
140: 1 e-mail back from those guys you said, you
2 wrote back to Peter Clark and copied the
3 others and you said, quote, "Thank you for
4 advising me of the response to the
5 hyperglycemia issue. I do have concerns
6 regarding making any connections between
7 olanzapine-induced weight gain and
8 hyperglycemia. Therefore, in my opinion, I
9 would not include your following statement,
10 quote, Patients who gain weight may develop
11 insulin resistance which may lead to
12 hyperglycemia and diabetes, end quote,
13 correct?
14 A. That's correct.

Kinon, Bruce M.D. (July 10, 2006)
235:13-16
Issues: 01 Plaintiff's Trial Designation

235:13 Q. And, sir, in fact, Lilly had
14 been minimizing the weight gain problem in
15 its communications with physicians; isn't
16 that correct?

Kinon, Bruce M.D. (July 10, 2006)
235:19-236:3
Issues: 01 Plaintiff's Trial Designation

235:19 A. Lilly has never minimized the
20 weight gain. We have been very proactive in
21 sharing all of our weight gain data, both
22 prospective as well as retrospective, with
23 all clinicians through scientific
24 presentations, medical letters.
236: 1 MR. SUGGS: Sir, let me show
2 you what's been previously marked as
3 Exhibit 4532.

Kinon, Bruce M.D. (July 10, 2006)

Exhibit 16
Denice M. Torres

236:8-237:16
Issues: 01 Plaintiff's Trial Designation

MR. SUGGS: For the record it's a seven page document, appears to be a PowerPoint presentation with the first page having the title Weight Change Strategy and Tactics.
QUESTIONS BY MR. SUGGS:
Q. Do you recall seeing this document, sir?
A. I'll have to take a look at it and read it, please.
Q. Do you recall seeing this document before, sir?
A. No, I do not.
Q. Let me direct your attention to Page 3. There's a heading on Page 3 Zyprexa Market Research Weight Gain and Other Side Effects June 1999. And below that it says Key Results with several bulleted items; is that correct?
A. Yes, that's correct.
Q. And the second bulleted item is "Lilly perceived as minimizing weight gain problem," do you see that language?
A. Yes, I do.
Q. And were you informed that the market research showed that physicians believed that Lilly was minimizing the weight gain problem?
A. Yes, I've heard about that.
Q. And from whom did you hear that?
A. We've heard that through market research.

Kinon, Bruce M.D. (July 10, 2006)
238:3-240:1
Issues: 01 Plaintiff's Trial Designation

Q. Sir, my question was when did you first learn that Lilly was perceived as minimizing weight gain by physicians?
A. I don't know exactly but certainly around the time of 1999, perhaps, 2000.
Q. And did that perception continue?
A. I don't know.
Q. The third bullet point item on that page three is Need For More Data On Weight Gain?
A. That's correct.
Q. Do you see that?
A. I see that.
Q. And you, as we talked about

Exhibit 16
Denice M. Torres

at the beginning of your deposition, were designated by Dr. Trzepacz as the number one person responsible for driving the medical marketing strategy with respect to weight gain, correct?

A. I was certainly significantly involved in the weight gain analyses.

Q. And you were certainly significantly involved in reviewing and approving the messages that went out to physicians about that issue, correct?

A. In part.

Q. Okay. Let me direct your attention to the following page. There's a reference to marketing materials. And they make reference to a new visual aid adherence section which accomplished three things, and then they have three bullet point items there, correct?

A. Yes.

Q. And the second one states Added Additional Facts. And the word "facts" is in quotes, to show that it is common with psychotropics, most patients gain little if any weight and few discontinue if they do gain and weight change plateaus over time without intervention." Do you see that language, sir?

A. Yes, I see that language.

Q. Did you review and approve that material?

Kinon, Bruce M.D. (July 10, 2006)
240:5-241:1
Issues: 01 Plaintiff's Trial Designation

A. This material, as far as I understand, never left the company. This never went into any promotional pieces that I've had to review. I've never seen this type of language before.

Q. And is that language that "weight change plateaus over time without intervention," is that factually accurate?

A. No, that's not. The published data that we have is that weight plateaus over time.

Q. And the bottom line bullet point there as to, or it says "bottom line weight change is manageable." Did you review and approve that part of the message?

A. No, I did not.

Q. Sir, isn't it a fact that the company repeatedly told physicians that weight gain was manageable?

A. When you say it's a fact, I don't know what you're referring to.

Exhibit 16
Denice M. Torres

Kinon, Bruce M.D. (July 10, 2006)
242:3-17
Issues: 01 Plaintiff's Trial Designation

242: 3 Q. Sir, if you could direct your
4 attention back to Exhibit 7668. Again, this
5 is the strategic alignment committee meeting
6 minutes from July 28, 2003, that were
7 submitted by you and Vince Truax where there
8 was the presentation about Lilly's new
9 strategy for weight gain and diabetes.
10 A. Yes.
11 Q. And do you see that the first
12 bulleted item under there in the From section
13 is weight gain is manageable?
14 A. Yes.
15 Q. And do you deny that Lilly
16 had a position which it promoted to
17 physicians that weight gain is manageable?

Kinon, Bruce M.D. (July 10, 2006)
242:20-20
Issues: 01 Plaintiff's Trial Designation

242:20 A. There's no denial of that.

Kinon, Bruce M.D. (July 10, 2006)
244:16-19
Issues: 01 Plaintiff's Trial Designation

244:16 And the reason why you had
17 that position was because you wanted to
18 minimize the liability of weight gain,
19 correct?

Kinon, Bruce M.D. (July 10, 2006)
244:22-245:1
Issues: 01 Plaintiff's Trial Designation

244:22 A. That's not correct.
23 MR. SUGGS: Let me show you
24 what's been previously marked as
245: 1 Exhibit 1110.

Kinon, Bruce M.D. (July 10, 2006)
245:6-16
Issues: 01 Plaintiff's Trial Designation

Exhibit 16
Denice M. Torres

245: 6 MR. SUGGS: For the record,
7 this is a six-page document.
8 Appears to be a PowerPoint
9 presentation. Has the title page
10 stating Issues Management Planning
11 Weight Gain.
12 QUESTIONS BY MR. SUGGS:
13 Q. Have you seen this document
14 before?
15 A. I'll have to take a look and
16 read it, please.

Kinon, Bruce M.D. (July 10, 2006)
247:10-248:19
Issues: 01 Plaintiff's Trial Designation

247:10 Q. Dr. Kinon, my question was
11 have you seen this document before?
12 A. No, I have not.
13 Q. If I can direct your
14 attention to the second page. There's a
15 bolded heading entitled Issue, do you see
16 that section?
17 A. Yes.
18 Q. And the first point says
19 "weight gain remains the number one liability
20 of Zyprexa and is leading to many of the new
21 issues surrounding the drugs i.e. diabetes,
22 lipids, et cetera." Correct?
23 A. Yes.
24 Q. And you were aware of that,
248: 1 correct?
2 A. Yes, I was.
3 Q. And then below that it's
4 stated Our Position.
5 Is that right?
6 A. Yes.
7 Q. And the company's position as
8 reflected in this document is, quote, "Weight
9 gain can occur with Zyprexa as with other
10 antipsychotics and mood stabilizers. For
11 most patients, this can be managed allowing
12 them to receive the overwhelming benefits
13 Zyprexa offers." Do you see that language,
14 sir?
15 A. Yes, I do.
16 Q. And that was a position that
17 was developed in conjunction between the
18 medical department, your shop, and the
19 marketing department, correct?

Kinon, Bruce M.D. (July 10, 2006)
248:22-249:24
Issues: 01 Plaintiff's Trial Designation

Exhibit 16
Denice M. Torres

248:22 A. This is a marketing document.
23 This is, basically, a marketing position that
24 is reflected in this document.
249: 1 Q. And do you deny that this was
2 the message that went out to doctors?
3 A. I do not know if this was
4 used in sales calls or not. I'm not aware of
5 that information. As far as I see this is an
6 internal document.
7 Q. If I could direct your
8 attention down to the bottom. It states the
9 rationale for the position, correct?
10 A. Yes.
11 Q. And the rationale is quote:
12 "To minimize the liability of weight gain
13 while at the same time increasing focus on
14 Zyprexa's superior efficacy." Do you see
15 that language, sir?
16 A. I see that language, yes.
17 Q. And did anyone inform you
18 that the rationale for the position was to
19 minimize the liability of weight gain?
20 A. Again, I'm not aware of how
21 this language is used, whether this is an
22 internal document. I'm sure this type of
23 language was not used in direct sales calls
24 as far as I know.

Kinon, Bruce M.D. (July 10, 2006)
250:3-251:8
Issues: [redacted] 01 Plaintiff's Trial Designation

250: 3 Q. Well, I'm sure they didn't
4 tell the doctors that they were trying to
5 minimize the liability of weight gain.
6 My question to you, sir, is
7 did anyone tell you that the position of the
8 marketing department with respect to weight
9 gain was to minimize the liability of weight
10 gain?
11 A. That is consistent with
12 marketing's goals.
13 Q. And how did you learn of
14 that? Who told you that?
15 A. Some of the points on this
16 document were strategies that marketing was
17 trying to determine whether these would be
18 viable strategies or not.
19 Q. And from whom did you learn
20 that that's what they were doing?
21 A. I don't know, specifically,
22 whom.
23 Q. Is this because of meetings
24 you were sitting in with the marketing
251: 1 people?
2 A. That's correct.
3 Q. So you were at meetings with

Exhibit 16
Denice M. Torres

the marketing folks where they talked about what their position was or what the rationale was and so forth with respect to weight gain; is that correct?

A. That's correct.

Kinon, Bruce M.D. (July 10, 2006)

255:4-256:23

Issues: 01 Plaintiff's Trial Designation

Next direct your attention to Page 4, please. There's a section there entitled What We Know. Do you see that section?

A. Yes.

Q. The last four bullet items state quote "Weight gain begins to be linked to the possible cause of hyperglycemia. Weight gain and hyperglycemia are directly linked in MD's minds. Weight gain is now linked or in the process of being linked to hyperglycemia/diabetes, hyperlipidemia, cardiovascular disease and compliance."

Do you see that language, sir?

A. Yes, I do.

Q. Were you informed of all those things in your meetings with the marketing people?

A. I don't recall if I was informed of all of those things but I may have been aware of them, yes.

Q. And then there's another section down there that says What We Don't Know. And the last bullet point states "Knowing that weight loss programs only work approximately 5 percent of the time in normal volunteers, does Lilly want to provide a program where if it doesn't work it may be looked at as another laughable attempt?" Do you see that language, sir?

A. I see that language, yes.

Q. Was that your understanding, also, that weight loss programs only work, approximately, 5 percent of the time in normal volunteers?

A. Definitely not. We've done extensive research on behavioral programs and we've funded those independent investigators, and they clearly show that these type of programs do help patients lose weight or help prevent excessive weight gain on all psychotropic drugs. No, I do not agree with this statement at all.

Kinon, Bruce M.D. (July 10, 2006)

Exhibit 16
Denice M. Torres

257:12-17
Issues: 01 Plaintiff's Trial Designation

257:12 Q. Sir, the feedback that you
13 got from physicians finally got to the point
14 in the summer of 2003 that you had to make a
15 substantial change in the approach that you
16 were taking; isn't that correct?
17 A. I don't know --

Kinon, Bruce M.D. (July 10, 2006)
257:20-259:6
Issues: 01 Plaintiff's Trial Designation

257:20 A. I don't, specifically, know
21 what you're referring to.
22 Q. If you could refer again to
23 Exhibit 7668. This again is the meeting
24 minutes from July 28, 2003, that were
258: 1 submitted by you and Vince Truax, correct?
2 A. Yes, we've been over that,
3 that's correct.
4 Q. And who is Vince Truax?
5 A. Vince Truax is the Brand
6 Manager for schizophrenia in the U.S.
7 affiliate.
8 Q. Okay. And we've talked
9 several times about this presentation by Mike
10 Magdycz. Am I pronouncing his name
11 correctly?
12 A. I believe it's Magdycz.
13 Q. Magdycz, okay. Was he in the
14 marketing department?
15 A. Yes.
16 Q. And he talks about having a
17 new strategy for weight gain and diabetes,
18 correct?
19 A. That's correct.
20 Q. And the change was to go from
21 weight gain as manageable. Weight gain is
22 predictable. Weight gain is not the only
23 predictor of diabetes. Diabetes risk is a
24 class effect with comparable rates across all
259: 1 products. Diabetes is mainly a patient
2 population issue. And handling diabetes and
3 weight gain as an objection.
4 All those things are what the
5 company had been, the approach the company
6 had been taking before, correct?

Kinon, Bruce M.D. (July 10, 2006)
259:9-18
Issues: 01 Plaintiff's Trial Designation

259: 9 A. This is a summarization of

Exhibit 16
Denice M. Torres

Mike Magdycz's, and this is, basically, a very shorthand notation of what was a very extensively detailed program that we offered physicians.

Q. Basically, what, all the items, the bullet points under the from section, are shorthand descriptions, if you wish, of what had been their strategy up to that time, correct?

Kinon, Bruce M.D. (July 10, 2006)
259:21-260:1
Issues: 01 Plaintiff's Trial Designation

259:21 A. In part, yes.
Q. And then he lays out below there in the "to" section, or this memo later out below there in the "to" section, what you were going to switch to, correct?

Kinon, Bruce M.D. (July 10, 2006)
260:4-23
Issues: 01 Plaintiff's Trial Designation

260: 4 A. It wasn't a matter of switching to it was a matter of changing the emphasis to.
Q. However, the to items are then -- Lilly understands the challenges physicians face in treating this population.
Lilly acknowledges weight gain challenges and potential consequences.
Lilly is providing me with options to address weight gain in some of my patients.
I am armed with the facts regarding diabetes.
Lilly is providing help regarding how to assess, counsel, and refer patients at risk for diabetes.
Is that correct?
A. That's correct.
Q. And this was regarded as a major change in emphasis, correct?

Kinon, Bruce M.D. (July 10, 2006)
261:2-14
Issues: 01 Plaintiff's Trial Designation

261: 2 A. It's the same message. It's, basically, going from one of being adversarial to one of being an ally for the physician. The third bullet point clearly

Exhibit 16
Denice M. Torres

says that Lilly is providing me, the clinician, with options to address weight gain in some of my patients. That's the same message as weight gain is manageable but now we are partnering with the physician. That was the change in emphasis.

Q. Sir, wasn't this program referred to internally as the "sorry we lied" campaign?

Kinon, Bruce M.D. (July 10, 2006)
261:17-21
Issues: 01 Plaintiff's Trial Designation

261:17 A. I've never heard that
18 expression.
19 MR. SUGGS: Let me show you
20 what's been previously marked as
21 Exhibit 5522.

Kinon, Bruce M.D. (July 10, 2006)
262:14-24
Issues: 01 Plaintiff's Trial Designation

262:14 Q. I'll represent to you that
15 the database as provided to us by Lilly
16 states that this exhibit, 5522, is August 1,
17 2003, and that date is several days after
18 Exhibit 7668, correct?
19 A. Correct.
20 Q. Okay. And, sir, do you
21 recall that there was the endocrine advisory
22 board that was called upon to review the
23 change in the approach that you guys were
24 going to be taking?

Kinon, Bruce M.D. (July 10, 2006)
263:3-22
Issues: 01 Plaintiff's Trial Designation

263: 3 A. I don't recall that.
4 Q. Sir, if I could direct your
5 attention in Exhibit 5522 to the second page.
6 Let me back up for a second.
7 On the first page the title
8 at the top says Endocrine Advisory Board
9 Areas For Opportunities. And then below that
10 there are several items listed. One is
11 "weight gain, strawman on the table, right
12 message, tone and guidelines emerging, need
13 to provide something practical for
14 physicians."
15 Do you see that language,

Exhibit 16
Denice M. Torres

sir?
A. Yes, I do.
Q. And, sir, that would clearly indicate that the endocrine advisory board was commenting on the various messages that Lilly had with respect to weight gain, correct?

Kinon, Bruce M.D. (July 10, 2006)
264:1-265:10
Issues: 01 Plaintiff's Trial Designation

264:
A. I've never seen this document before. This is a spreadsheet. It has no introductory comments on it. I have no idea where these comments -- for all I know this is someone's, basically, notes that they took during some meeting. There's not even an idea of where this meeting took place. I have no idea what this is about.
I could read through this and, perhaps, I will be able to piece it together.
Q. Actually, I just want to draw your attention in particular to one item on Page 2.
In the bottom box in the left-hand margin there's a heading Response to Letter and Statements, do you see that?
A. Yes.
Q. And about the fourth, fifth, column down it says, quote, change, end quote, in weight to, quote, potential, end quote, weight gain. And then to the right of that it says "want to keep the, quote, sorry we lied message really clean. Do you see
265:
that language?
A. I see that. I've never seen this before. I have no idea what this is about.
Q. You know what the sorry we lied message was?
A. I've never heard sorry we lied, with due respect.
Q. I didn't write this someone in your company did.

Kinon, Bruce M.D. (July 10, 2006)
265:12-15
Issues: 01 Plaintiff's Trial Designation

265:
Q. Isn't that what the new message was about? Your new message in the approach in your marketing was the sorry we lied approach?

Kinon, Bruce M.D. (July 10, 2006)
265:18-266:2
Issues: 01 Plaintiff's Trial Designation

265:18 THE WITNESS: What is the
19 question, please?
20 Q. This new message, this new
21 approach you guys were taking where you were
22 going from various things, like, weight gain
23 is manageable, weight gain is predictable,
24 weight gain is not the only predictor of
266: 1 diabetes. Where you were moving away from
2 that is your sorry we lied message?

Kinon, Bruce M.D. (July 10, 2006)
266:5-6
Issues: 01 Plaintiff's Trial Designation

266: 5 A. As I've answered I've never
6 been aware of this term -- sorry we lied.

Exhibit 16
Denice M. Torres

Torres, Denice M. (December 15, 2006)

31:4-11
Issues: 01 Plaintiff's Trial Designation

31: 4 Q. Can you tell the jury your
5 name, please.
6 A. Denice Torres.
7 Q. Ms. Torres, can you tell the
8 jury where you work?
9 A. I work for a division of
10 Johnson & Johnson called Ortho-McNeil
11 Neurologics.

Torres, Denice M. (December 15, 2006)

42:5-11
Issues: 01 Plaintiff's Trial Designation

42: 5 Now, prior to coming to work
6 with Eli -- with Ortho-McNeil in January
7 of 2004, where were you employed?
8 A. Eli Lilly & Company.
9 Q. And you had worked at Eli
10 Lilly & Company since when?
11 A. 1990.

Torres, Denice M. (December 15, 2006)

46:20-47:16
Issues: 01 Plaintiff's Trial Designation

46:20 Q. Now, in preparing for the
21 deposition, I looked at some documents to
22 determine what your work history and
23 background was, and I'm going to go over
24 that in some more detail. But just for
47: 1 the record for the jury, what was your
2 title at the time you left Eli Lilly at
3 the end of December of 2004?
4 A. Executive director, global
5 marketing.
6 Q. Executive director of global
7 marketing for what product?
8 A. Zyprexa, and then for a very
9 short time period, Symbyax.
10 Q. Okay.
11 Symbyax is a combination
12 product of Zyprexa and what else?
13 A. Prozac.
14 Q. Prozac is also a Lilly
15 product, right?
16 A. That's correct.

Torres, Denice M. (December 15, 2006)

68:1-69:10

Issues: 01 Plaintiff's Trial Designation

68: 1 So, let me see. You
2 graduated from Ball State. Is that in
3 Muncie?
4 A. Yes.
5 Q. You graduated from there in
6 1981 with a degree in what?
7 A. Psychology and sociology.
8 Q. Okay.
9 After graduating from Ball
10 State, you went to Indiana University
11 School of Law?
12 A. That's correct.
13 Q. Did you go straight from
14 Ball State to that law school?
15 A. I did.
16 Q. I presume if you got out on
17 time, you got out of law school in 1984?
18 A. That's correct.
19 Q. You're a lawyer?
20 A. Yes.
21 Q. You, in fact, went to work
22 at a law firm after you graduated?
23 A. I sure did.
24 Q. What law firm did you go to
69: 1 work for?
2 A. A firm called Smith,
3 Haughey, Rice & Roegge.
4 Q. Where?
5 A. In Grand Rapids, Michigan.
6 Q. You did litigation work; is
7 that correct?
8 A. I did. As a first-year
9 lawyer, I pretty much did research for
10 workers' compensation.

Torres, Denice M. (December 15, 2006)
70:2-8
Issues: 01 Plaintiff's Trial Designation

70: 2 You're still a lawyer
3 though, aren't you?
4 A. I sure am.
5 Q. What states are you
6 currently licensed to practice law?
7 A. I keep my license up in
8 Michigan.

Torres, Denice M. (December 15, 2006)
71:17-72:10
Issues: 01 Plaintiff's Trial Designation

71:17 Q. So, after finishing your law
18 job at the insurance defense firm with

some interim jobs, you went to work for the advertising company?
A. Yes.
Q. In Grand Rapids. After concluding that job, you got your M.B.A. --
A. Yes.
Q. -- from the University of Michigan?
A. Yes.
Q. In Ann Arbor?
A. Yes.
Q. And then you went to work for Eli Lilly in 1990 where you worked until the end of December 2004?
A. That's correct.

Torres, Denice M. (December 15, 2006)
73:6-19
Issues: 01 Plaintiff's Trial Designation

At the time you left, you were marketing executive director for Zyprexa global brand?
A. That's correct.
Q. You had been the managing executive director of marketing for Zyprexa global brand at Eli Lilly from when to when?
A. I was promoted while I was in that role, so, it was basically 2000 -- I can't remember if I started in 2000 or 2001, but about eight months or a year after being in that role, I was promoted.

Torres, Denice M. (December 15, 2006)
79:8-17
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: It was a blockbuster.
BY MR. ALLEN:
Q. Yes. It was a multibillion dollar blockbuster?
A. I don't think it actually was. I know it sold over a billion. I don't know if it ever got above that. It was -- suffice it to say, it was a very, very successful product.

Torres, Denice M. (December 15, 2006)
79:23-80:1
Issues: 01 Plaintiff's Trial Designation

79:23 THE WITNESS: Zyprexa was a
24 blockbuster, and it was
80: 1 multibillion, yes.

Torres, Denice M. (December 15, 2006)
80:4-5
Issues: 01 Plaintiff's Trial Designation

80: 4 That's what made it the
5 engine room of the company.

Torres, Denice M. (December 15, 2006)
80:8-18
Issues: 01 Plaintiff's Trial Designation

80: 8 THE WITNESS: It wasn't
9 the -- I think I've stated this
10 several times. Zyprexa was very
11 important to Eli Lilly & Company
12 in terms -- by saying "engine
13 room," engine room is what makes,
14 you know, a train work, you know,
15 something like that, and it was
16 not the only -- was it in the
17 engine room? Sure. Was it the
18 engine room? No.

Torres, Denice M. (December 15, 2006)
82:12-14
Issues: 01 Plaintiff's Trial Designation

82:12 Q. The first exhibit I need to
13 you show you I'm going to put on the
14 screen and see if it helps.

Torres, Denice M. (December 15, 2006)
83:4-10
Issues: 01 Plaintiff's Trial Designation

83: 4 This is a document I marked
5 as Exhibit Number 3. The court
6 reporter will denote it as
7 Torres-3 at the conclusion. It's
8 a memoranda of February 25, 2003.
9 And it just -- it is internal to
10 Eli Lilly. It was produced to us.

Torres, Denice M. (December 15, 2006)

84:19-85:6
Issues: 01 Plaintiff's Trial Designation

84:19 Q. By 2003, what were Zyprexa
20 sales worldwide?
21 A. I don't remember for sure,
22 but according to this document, it says
23 it's approaching $4 billion globally.
24 Q. $4 billion. Wasn't Zyprexa
85: 1 by early 2003 not only a $4 billion
2 worldwide sales drug, but one of the
3 "fastest growing" drugs in terms of
4 percentage sales in the world?
5 A. That's what it says here,
6 yes.

Torres, Denice M. (December 15, 2006)

85:8-19
Issues: 01 Plaintiff's Trial Designation

85: 8 I think by 2003, I don't
9 know if it's reflected in that document,
10 but you can probably recall from your
11 long experience involved in marketing, in
12 global marketing for Eli Lilly, wasn't by
13 2003 Zyprexa either the third or fourth
14 largest selling drug product in the
15 world?
16 A. Yes.
17 Q. So, it just goes without
18 saying, Zyprexa was a very important
19 financial product to Eli Lilly?

Torres, Denice M. (December 15, 2006)

85:22-22
Issues: 01 Plaintiff's Trial Designation

85:22 THE WITNESS: Yes.

Torres, Denice M. (December 15, 2006)

86:1-8
Issues: 01 Plaintiff's Trial Designation

86: 1 I handed you prior to the
2 start of the deposition, I think you have
3 it in front of you as Exhibit Number 1, a
4 document entitled, that we got from your
5 files, "Restructuring of the Marketing
6 Component" of the "Zyprexa Product Team."
7 You've looked at that, have you not?
8 A. Yes, I have, sir.

Torres, Denice M. (December 15, 2006)

87:5-7
Issues: 01 Plaintiff's Trial Designation

87: 5 Q. -- and let me get down here
6 to the nitty-gritty. "Restructuring the
7 Marketing Component" --

Torres, Denice M. (December 15, 2006)

87:21-24
Issues: 01 Plaintiff's Trial Designation

87:21 "We are pleased to announce
22 the restructuring of the Marketing
23 component of the Zyprexa Product Team.
24 In July of this year the Zyprexa Product

Torres, Denice M. (December 15, 2006)

88:1-89:2
Issues: 01 Plaintiff's Trial Designation

88: 1 Team, led by the efforts of Denice
2 Torres, Global Marketing Director for
3 Zyprexa, embarked upon an important
4 initiative, Project Open Door. The
5 purpose of this initiative was to
6 identify action steps to: (1) achieve our
7 goal of reaching $6 billion by 2006."
8 Did I read that correctly?
9 A. That's correct.
10 Q. It goes on, and I'm skipping
11 down to the last sentence of this first
12 paragraph. "The U.S. Affiliate -- with
13 significant leadership from Glyn Parkin
14 and Jack Jordan -- was instrumental in
15 the development of the new team." Did I
16 read that correctly?
17 A. That's correct.
18 Q. Now, as I went through this
19 document, it described the members of
20 this new restructured global marketing
21 team who had as one of its goals $6
22 billion in annual sales, right?
23 A. That was one of the goals,
24 yes.
89: 1 Q. It was the number one goal.
2 It's listed number one, isn't it?

Torres, Denice M. (December 15, 2006)

89:5-6
Issues: 01 Plaintiff's Trial Designation

89: 5 THE WITNESS: It's listed in

6 a sequence of several.

Torres, Denice M. (December 15, 2006)

89:8-90:7
Issues: 01 Plaintiff's Trial Designation

89: 8 Q. Well, it has a number by it,
9 doesn't it?
10 A. Just as you would list
11 apples, oranges, pears, et cetera, it's
12 one of the goals. It wasn't meant to say
13 that was the primary goal and everything
14 else supported that.
15 Q. Well, it says the purpose --
16 it's misspelled "the purposed," but I
17 would assume that means purpose, "of this
18 initiative was to identify action steps:
19 (1) achieve our goal of reaching $6
20 billion by 2006." Did I read that
21 correctly?
22 A. You read that correctly in
23 terms of that is listed as number 1 in
24 the sequence of three different items.
90: 1 Q. Let's look at number 2 then.
2 Number 2: "identify drivers that produce
3 the greatest customer and affiliate
4 value." So, the number one goal, $6
5 billion in sales; and the number two goal
6 is "identify drivers that
7 produce...affiliate value."

Torres, Denice M. (December 15, 2006)

90:11-91:9
Issues: 01 Plaintiff's Trial Designation

90:11 Q. Is that correct?
12 A. You missed out on an
13 important word, "Customer."
14 Q. Okay.
15 Number 3 is "insure world
16 class global marketing for Zyprexa."
17 A. Yes.
18 Q. Are there any other goals
19 listed?
20 A. No. Those were the three
21 goals.
22 Q. The three goals -- all
23 right.
24 Now, I'm back to my
91: 1 question. When I looked at this
2 document, when the -- did you prepare
3 this document, by any chance?
4 A. I think I prepared a good
5 part of it, yes.
6 Q. That's what I figured,

because this is kind of your team, isn't it?

A. Yes.

Torres, Denice M. (December 15, 2006)

93:21-94:22
Issues: 01 Plaintiff's Trial Designation

Exhibit Number 1 concerning the "Restructuring of the Global Marketing for Zyprexa," this restructuring took place in what year, ma'am?

A. Like I said, I can't remember exactly when it was. We started working on it pretty quickly after I joined the team. And so I think -- I'm sure it happened within -- well, I'm not sure. But it seems to me like it happened within eight or nine months of me coming on the team.

Q. You came on the team when?

A. Again, I can't remember if it was 2000, 2001. I really don't remember.

Q. Now, after this team was formed --

A. It was 2001. My daughter was born in 2000. Okay.

Q. After this team was formed, you still remained in charge of global marketing for Zyprexa until the time you left?

A. Yes.

Torres, Denice M. (December 15, 2006)

108:23-109:1
Issues: 01 Plaintiff's Trial Designation

Let me just hand you Exhibit 5. Just for the record, we'll spend one second on it.

Torres, Denice M. (December 15, 2006)

109:7-20
Issues: 01 Plaintiff's Trial Designation

Q. Zyprexa marketing, August '02, Denice Torres, Director of Global Marketing. Does that reflect that?

A. Yes.

Q. All the individuals below that worked for you?

A. That's correct.
Q. Including, but not limited to Mr. Michael Bandick, director of marketplace management, right?
A. That's correct.
Q. Marketplace management is the same as issues management, is it not?
A. No.

Torres, Denice M. (December 15, 2006)

110:5-7
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: Do you want me to explain marketplace management?
BY MR. ALLEN:

Torres, Denice M. (December 15, 2006)

110:8-112:9
Issues: 01 Plaintiff's Trial Designation

Q. Yes, ma'am, please, shortly, if you can.
A. Marketplace management entails all the groups that are listed here in terms of the reports, competition, issues management, access, thought leaders and -- access and basically, you know, thought leaders in the marketplace, meaning there are a number of different of these groups or categories that fit under one umbrella, and that's marketplace management. So, issues management is one aspect of that.
Q. One other aspect is thought leaders?
A. Yes.
Q. And I see under there, there's -- in this graph -- Mr. Fibich wins the bet, it's going to be a little longer than we thought -- Mike Bandick goes down here, and underneath him, the position is open, but it says "Access, TL," that's thought leader?
A. Thought leader, yes.
Q. And "Customer Meetings"? Is that right?
A. Yes.
Q. The people under marketplace managers include Matt Pike, who is the manager of issues management; is that correct?
A. That's correct.
Q. "Issues management" is what, ma'am?

A. Issues management can -- it primarily focused in on issues that affected the affiliates and where there needed to be some type of an answer. It could be clinically oriented, it could be on the basis of, there were payor -- some payor things where there was information that was required, you know, certainly dealing with competitive challenges around data, et cetera. So, that was what that group did. It was a pretty -- it's whatever came up. And so, you know, you have a core amount of responsibilities, but with any drug, things come up that require some answer or solution.

Torres, Denice M. (December 15, 2006)

121:21-24
Issues: 01 Plaintiff's Trial Designation

Q. You were in senior management, though, at Eli Lilly in regard to Zyprexa, were you not?
A. With regard to Zyprexa, yes.

Torres, Denice M. (December 15, 2006)

124:10-126:13
Issues: 01 Plaintiff's Trial Designation

Now, as a sales representative, did you have an important job?
A. Yes.
Q. Why was your job important?
A. My job was important because of the responsibilities, and so responsibility from a company standpoint to share the information about a disease state and customers in a therapeutic area, the responsibility to be well informed about customers, their challenges, about patient needs, et cetera, and ultimately to also share the role our drug would play in addressing some of those needs. And so that also was a very important aspect.
Q. Why does a company and why did Eli Lilly have sales representatives?
A. One of the -- you know, one big reason is that in many therapeutic areas, you know, whether Prozac or even Zyprexa, prescribers/physicians may not know about -- you know, they may not have learned as much in medical school about

certain conditions, et cetera, because they can't be experts in everything. So, what a sales representative can do is to help bring information about a therapeutic area, about treating customers -- treating patients or an actual drug, bringing that information to those customers.

Q. Right. And I think you are hitting the nail right on the head. And let me just see if I can even define this better so the jury can better understand it and the people that will listen to your testimony when they evaluate their decision in this case. As a sales representative, you said doctors that you would go see can't know everything about drug products, right?

A. That's correct.

Q. And, in fact, you said, I think, and I'm paraphrasing your answer, that in their medical school training, there's no way they can learn about the drugs and the development of drugs and how drugs work and particularly about all the drugs that are on the market; is that correct?

Torres, Denice M. (December 15, 2006)
126:16-127:4
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: I mean, there's certain things that they have a responsibility for, and there's certain things from a sales representative standpoint, say, they may not know the dose of a drug, they may not know interactions and ask an individual. And they get information from a lot of different sources, but the role of the sales force is to help them with that.

Torres, Denice M. (December 15, 2006)
127:6-22
Issues: 01 Plaintiff's Trial Designation

Q. And the role of the sales representative is to give doctors truthful and accurate information about the risk and benefits of the product; is that true?

A. That's true.
Q. Is to give doctors truthful and accurate information about the indications for the product?
A. Absolutely.
Q. It is the role of the sales representative not to promote a product for off-label uses?
A. That's correct.
Q. To do so would be a violation of law?
A. Yes.

Torres, Denice M. (December 15, 2006)
130:15-131:6
Issues: 01 Plaintiff's Trial Designation

130:15 Q. It's your job as a sales representative to assist the doctor or the physician who you are calling upon with information that they need to know that it's important for them to know with their patients?
A. That's correct.
Q. And the reason you're going to the doctors' offices on behalf of Eli Lilly is to market and sell your product?
131: 1 A. To be of service to the customer. And the reason that we go there is to be of service, and the outcome, to use the product for the appropriate patient for the appropriate reason, yes.

Torres, Denice M. (December 15, 2006)
134:17-135:13
Issues: 01 Plaintiff's Trial Designation

134:17 Q. Now, you said it would be improper, illegal for the sales rep to promote off-label use. Do you recall that?
A. To promote for use, yes.
Q. Off-label use?
A. Yes.
Q. Tell the jury -- define what
135: 1 off-label use is.
A. Off-label use is if a prescribing physician used a drug for something other than it was indicated or approved by the FDA, that would be referred to as off-label use.
Q. Wasn't the majority of the use of Zyprexa in the United States off label?

A. I don't -- I don't know if it was the majority, but a good portion of use of all antipsychotics are used off label.

Torres, Denice M. (December 15, 2006)

135:17-136:15
Issues: 01 Plaintiff's Trial Designation

135:17 Q. Listen to my question. I'm not here to talk -- I'll let you know when I want to talk about Risperdal, Seroquel, Geodon, Abilify. I'll let you know that. You're here for Eli Lilly on behalf of the marketing of Zyprexa, right?
A. Yes.
136: 1 Q. Okay.
So, I'm going to limit my questions to Zyprexa unless I tell you otherwise. All right?
A. Okay.
Q. Wasn't the majority of the use of Zyprexa in the United States off label?
A. There was a good portion. I don't -- I don't remember the exact numbers. I don't remember it being the majority.
Q. Can you give the jury your best estimate, please.
A. Maybe 30 to 40 percent.

Torres, Denice M. (December 15, 2006)

137:4-139:7
Issues: 01 Plaintiff's Trial Designation

137: 4 As you became involved in global marketing for Zyprexa, you certainly knew that a substantial portion of Zyprexa sales both in the United States and around the world was related to off-label prescriptions?
A. When I joined the team?
Yes.
Q. Yes, ma'am.
And, in fact, did you not and weren't you one of the individuals at Eli Lilly along with others that used different channels and methods to promote and facilitate off-label prescriptions of Zyprexa?
A. Absolutely not, no.
Q. You never would do that?
A. No.

Q. Didn't John Lechleiter do that?
A. I'm not familiar with John Lechleiter doing --
Q. How about Alan Breier, Dr. Breier?
A. I'm not familiar with --
Q. If they did that, it'd be wrong?
A. Yes, it would be wrong.
Q. It'd be illegal?
A. If they were advising physicians to use the drug for indications other than what was approved, it would be wrong, yes.
Q. It would be wrong for them to assist and train sales representatives to promote the use of Zyprexa off label, would it not?
A. Yes, for the purposes of getting prescribers to use a drug off label, that would be wrong.
Q. Right.
So, if they -- if Dr. Breier or Jack Jordan or John Lechleiter tried to train or inform sales representatives to assist them in getting doctors to use the drug off label, that would be wrong?
A. If the goal were to get physicians/prescribers to use the drug off label, that would be wrong. If the goal were to inform or educate about other uses of Zyprexa, that would not be wrong.

Torres, Denice M. (December 15, 2006)
143:6-24
Issues: 01 Plaintiff's Trial Designation

Q. So, when you told us earlier that there was no indication for Alzheimer's, Alzheimer's dementia or Alzheimer's psychosis, you would agree that there are no double blind, placebo-controlled clinical trials submitted to the FDA supporting the safety and efficacy of Zyprexa for those conditions; is that correct?
A. I can't remember what was submitted to the FDA, but what I can say is, no, there was no approved use for those indications.
Q. Similarly, there was no double blind, placebo-controlled trials submitted to the FDA supporting the safety and efficacy of Zyprexa for use in long-term nursing home or resident care,

24 true?

Torres, Denice M. (December 15, 2006)
144:3-16
Issues: 01 Plaintiff's Trial Designation

144: 3 THE WITNESS: I guess if you
4 could preface or if you could
5 restate your question, because in
6 general, you know, writing a -- so
7 no one would write a prescription
8 for long-term nursing care. So,
9 I'm not sure what you're referring
10 to in terms of -- you know, could
11 you have individuals with, you
12 know, schizophrenia in a nursing
13 home? Absolutely. They're in
14 every -- that's part of the
15 population. For bipolar disorder,
16 absolutely.

Torres, Denice M. (December 15, 2006)
144:20-145:10
Issues: 01 Plaintiff's Trial Designation

144:20 Q. Long-term care. I've seen
21 it summarized in your documents, LTC.
22 You've seen that in your marketing
23 documents, haven't you?
24 A. Yes.
145: 1 Q. Wasn't --
2 Just for the record, your
3 company and you in marketing concentrated
4 part of your efforts in marketing Zyprexa
5 for LTC, did you not?
6 A. The U.S. affiliate, yes.
7 Q. In fact, the U.S. affiliate
8 of Zyprexa had an LTC sales force, did
9 they not?
10 A. Yes, they did.

Torres, Denice M. (December 15, 2006)
145:19-146:5
Issues: 01 Plaintiff's Trial Designation

145:19 Q. You said they had a
20 long-term care sales force. What was
21 their job?
22 A. To promote an indication in
23 those settings.
24 Q. So, the long-term care sales
146: 1 force was only to promote Zyprexa for
2 indicated uses, and the only indicated

uses were what, ma'am?
A. Schizophrenia and bipolar mania.

Torres, Denice M. (December 15, 2006)

146:13-149:1
Issues: 01 Plaintiff's Trial Designation

Just for the record, Zyprexa never had an approved indication by the FDA for bipolar depression, did it?
A. That's correct.
Q. Okay.
Zyprexa never, ever, not ever as we sit here to this day, has ever had an indication for depression at all, has it?
A. That's correct.
Q. Bipolar or otherwise, correct?
A. Correct.
Q. Okay.
So, if anybody ever was prescribing Zyprexa for depression or bipolar depression, that was an off-label prescription, wasn't it?
A. Yes.
Q. Okay.
Didn't Eli Lilly go out and try to get doctors to prescribe Zyprexa for depression and bipolar depression?
A. No.
Q. They never did that?
A. Not that I'm aware of.
Q. Let me get this clear on the record. Just so there's no doubt, Zyprexa never had an indication at any time for anxiety, did it?
A. No.
Q. So, it would be wrong to try to promote Zyprexa for anxiety?
A. Yes.
Q. It never had an indication for hallucinations, did it, unrelated to schizophrenia?
A. No. Unrelated to schizophrenia or bipolar.
Q. Right. Let me just get out the list here. I have a list.
Zyprexa never had an indication for complicated mood disorder, did it?
A. I don't think you can get an indication for complicated mood disorder.
Q. Therefore, you didn't have an indication for that, did you?
A. No.

Q. It didn't ever have an indication for attention deficit disorder, did it?
A. No.
Q. Therefore, it would be illegal to promote sales of and use of Zyprexa for attention deficit disorder, wouldn't it?
A. Correct.
Q. It never had an indication for hyperactivity disorder, did it?
149: 1 A. No.

Torres, Denice M. (December 15, 2006)

149:10-18
Issues: 01 Plaintiff's Trial Designation

149:10 Q. Just for the record, it would have been illegal to promote Zyprexa for hyperactivity.
A. Hyperactivity associated with -- I mean, if it was part of a clustering of symptoms, if you're saying that the only thing that the person exhibited was hyperactivity, yes, that would be wrong.

Torres, Denice M. (December 15, 2006)

152:12-20
Issues: 01 Plaintiff's Trial Designation

152:12 Q. It would be wrong to suggest in the sales and marketing of Zyprexa to physicians when you make sales calls to tell them Zyprexa is indicated for the cluster of symptoms of agitation and depression? That would be wrong, wouldn't it?
A. If those were the only two symptoms, yes.

Torres, Denice M. (December 15, 2006)

154:18-23
Issues: 01 Plaintiff's Trial Designation

154:18 Zyprexa had limited indications, did it not?
A. Zyprexa had an indication for schizophrenia and bipolar mania.
Q. That's it.
A. Yes.

Torres, Denice M. (December 15, 2006)
159:18-160:5
Issues: 01 Plaintiff's Trial Designation

159:18 Q. Ma'am, as you're looking
19 through there, we're going to put Exhibit
20 Number 2 up for the jury to see this
21 document. "Zyprexa Product Team Off-Site,
22 July 25, 2001." "Lilly. Answers that
23 matter."
24 I will flip through the
160: 1 document along with you.
2 I feel relatively certain,
3 ma'am, that you have read through this
4 document now enough to tell the jury what
5 this document is.

Torres, Denice M. (December 15, 2006)
160:11-12
Issues: 01 Plaintiff's Trial Designation

160:11 Q. Tell the jury what this
12 document is, Exhibit Number 2, ma'am.

Torres, Denice M. (December 15, 2006)
160:15-17
Issues: 01 Plaintiff's Trial Designation

160:15 THE WITNESS: I'm finished
16 looking at it. I don't remember
17 this document.

Torres, Denice M. (December 15, 2006)
161:2-162:2
Issues: 01 Plaintiff's Trial Designation

161: 2 This is a document that came
3 from Lilly's files and has been produced
4 in this case. And by the way, right down
5 here, the jury will have seen this before
6 by the time we go to trial, but there's
7 a, what do we call that, a slogan at Eli
8 Lilly, is there not?
9 A. "Answers that matter"?
10 Q. Yes.
11 A. Yes.
12 Q. What's that mean?
13 A. I can tell you what it means
14 to me. It's providing people with
15 information that in the customers, take
16 holder, et cetera, that -- providing
17 information that's pertinent to them,
18 meaningful to them.

Q. It means that Lilly, when they give you the answer, they know the answers matter, that the answer is going to be truthful, it's going to be accurate, the information and data is not going to be spun, but it's going to be direct and to the point and truthful, right?

Torres, Denice M. (December 15, 2006)
162:5-6
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: I think that's fair, right. Absolutely.

Torres, Denice M. (December 15, 2006)
162:8-15
Issues: 01 Plaintiff's Trial Designation

Q. What I said is fair, isn't it?
A. Absolutely.
Q. It's fair of doctors and patients to expect that when Lilly gives them answers about their product, the data is not going to be spun, and the answers are going to be accurate, right?

Torres, Denice M. (December 15, 2006)
162:18-24
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: Yeah. I think it means that the company will be honest and --
BY MR. ALLEN:
Q. Truthful?
A. -- straightforward, truthful, thank you.

Torres, Denice M. (December 15, 2006)
164:2-166:6
Issues: 01 Plaintiff's Trial Designation

Design team on the Zyprexa product team under "Decision Makers," design team decision makers, team leaders, "Vin Rampey" and "Denice Torres." Did I read that correctly?
A. Yes.

Q. **What is the design team?**
A. I guess for this -- I somewhat remember this. It definitely was a project. I don't remember this document or a meeting. Basically you can see the group on the bottom, what it looks like from going through this --
Q. **This group on the bottom, the support group?**
A. I'm sorry. The support group, yes. I'm thinking that maybe they put together a good portion of the document to lead the team through a discussion around the work of -- you know, the vision, developed the vision for the team and what's the culture, next steps. Basically, what does the brand represent. I don't know if -- what I don't know is, did the meeting happen? I don't know that.
Q. **That's what the answer always is when we have PowerPoint presentations, but I'm just going to go with the document that I had.**
Did y'all have meetings there at Eli Lilly?
A. Oh, we had a lot of meetings, yes.
Q. **Did you have Zyprexa product team meetings?**
A. Yes.
Q. **Did you have Zyprexa product team meetings off site?**
A. Yes. At times I'm sure we did.
Q. **Yes.**
Did you have PowerPoint presentations at the meetings?
A. Sure.
Q. **And the PowerPoint presentations were prepared so the participants in the meeting could -- it would act as, I guess my word I'm choosing, as an anchor or focus on the next topic?**
A. Yes. Or we're providing information, sure.

Torres, Denice M. (December 15, 2006)
167:1-12
Issues: 01 Plaintiff's Trial Designation

Q. **Nevertheless, Exhibit Number 2 is a PowerPoint presentation of a Zyprexa product team off-site meeting July 25, 2001. You're listed as a member of the decision makers design team and a**

team leader; is that right?
A. Yes. The second one is right. The first one is -- I don't know if -- it looks like the document was prepared for that. I don't know if the meeting ever happened. I really don't remember the meeting.

Torres, Denice M. (December 15, 2006)
169:2-19
Issues: 01 Plaintiff's Trial Designation

169:2 Q. Let me ask this. In global marketing, you were the director of it, we've seen that. We're going to see where you were on some other teams. We know you were on the Zyprexa product team. Were you ever informed about any of Patricia Cavazzoni's findings in regard to blood sugar glucose levels and Zyprexa?
A. Yes.
Q. Who told you about them?
A. I think I was -- I'm sure I was in meetings where she made some presentations in a group or, you know, shared some of her findings. I wasn't on the medical team, but, sure, she shared some things broadly about the profile of Zyprexa, yes.

Torres, Denice M. (December 15, 2006)
170:14-172:9
Issues: 01 Plaintiff's Trial Designation

170:14 Q. Everybody had a responsibility to accurately and truthfully market this product, right?
A. That's correct.
Q. Did Patricia Cavazzoni -- do you recall being told about her data concerning continuous analysis of blood sugar glucose levels?
A. I don't specifically recall that.
Q. Do you recall being told
171:1 about her analysis that indicated Zyprexa was statistically significantly related to -- Zyprexa administration was statistically significantly related to increases in blood sugar glucose in individuals who took Zyprexa?
A. I don't specifically remember that.
Q. Do you recall being told --

any presentations by Dr. Charles Beasley.
A. I was only in one meeting with Charles Beasley.
Q. Do you recall that meeting?
A. Only because he was swearing, and someone said that was his personality. But that's what I remember about it.
Q. Tell me what year that meeting took place.
A. It was right when -- pretty early on when I joined the team.
Q. What were you all talking about in that meeting?
A. I don't know. I just remember something he said. It was a little bit, you know --
Q. Inappropriate?
A. I think he used a couple of swear words, which typically did not happen at a Lilly meeting.
Q. Somebody told you that was just his personality?
A. Yes.

Torres, Denice M. (December 15, 2006)
173:18-174:8
Issues: 01 Plaintiff's Trial Designation

173:18 Did Dr. Beasley ever come to you as director of global marketing and tell you Zyprexa was the worst offender in regard to weight gain among the second generation antipsychotics other than clozapine?
A. No. I really never had a one-on-one conversation with Charles Beasley.
Q. Did anybody at Eli Lilly ever tell you as director of global marketing that Zyprexa was the worst offender in regard to weight gain among the second generation antipsychotics except for clozapine?

Torres, Denice M. (December 15, 2006)
173:18-174:8
Issues: 01 Plaintiff's Trial Designation

173:18 Did Dr. Beasley ever come to you as director of global marketing and tell you Zyprexa was the worst offender in regard to weight gain among the second generation antipsychotics other than clozapine?

A. No. I really never had a one-on-one conversation with Charles Beasley.

Q. Did anybody at Eli Lilly ever tell you as director of global marketing that Zyprexa was the worst offender in regard to weight gain among the second generation antipsychotics except for clozapine?

Torres, Denice M. (December 15, 2006)
174:15-21
Issues: 01 Plaintiff's Trial Designation

A. I don't remember the terminology.

Q. Did anybody ever tell you at Eli Lilly that Zyprexa's weight gain profile, the average weight gain profile was double that of Risperdal?

A. I don't believe so.

Torres, Denice M. (December 15, 2006)
175:19-178:23
Issues: 01 Plaintiff's Trial Designation

Q. So, in order to be an effective, truthful director of global marketing and provide answers that matter, you must be provided with the accurate facts about the risk profile of the drug?

A. Yes.

Q. Assume with me that it was known at Eli Lilly that the average weight gain on Zyprexa was at least double or approximately double that of Risperdal. You should have been informed of that?

A. With reference to Risperdal, I knew about the weight gain. I mean, with reference to Risperdal, I don't specifically remember that. Maybe someone said it, I don't remember. But am I familiar with the weight gain profile of Zyprexa, yes.

Q. That wasn't my question. You know, you're talking about -- you talked about, for example, that one of the channels of the U.S. affiliate in marketing was the sales department, right?

A. Yes.

Q. You talked about the fact that in the sales department, we know we

have sales representatives, you were one back in the early 1990s, right?
A. Yes.
Q. You talked about the fact that you have to give accurate and truthful and, as you said, direct information, is that right?
A. That's correct.
Q. In order to give that type of information to doctors, the sales force must be told and the marketing department must be told the accurate information concerning the side effect profile of the product, right?
A. Yes.
Q. Were you ever told that there was animal model testing done on Zyprexa in regard to weight gain?
A. Yes. I believe I was part of conversations, yes.
Q. What were you told the animal model testing showed, if you recall?
A. I don't think I specifically recall.
Q. So, as you sit here today, December of 2006, it's Friday, December the 15th, I think we're in New Jersey, Windsor Township, you cannot recall anything you were told about animal testing in regard to weight gain at Eli Lilly on Zyprexa?
A. Not specific to animal models. You know, in general what I was told, I could tell you that. That's not to say it didn't happen. I just don't remember any specifics.
Q. Do you recall that Dr. --
Do you recall anybody from the medical or clinical department at Eli Lilly telling you that the animal model testing indicated that Zyprexa, when administered on diet-restricted rats, that is, in other words, food intake did not increase, that those animals still gained weight on Zyprexa? Were you ever told about that?
A. No. I don't remember that.

Torres, Denice M. (December 15, 2006)
179:19-180:2
Issues: 01 Plaintiff's Trial Designation

Q. As director of global marketing, were you ever told that there was statistically significant findings of elevated blood glucose levels in the HGAJ

study for individuals who took Zyprexa?
A. I don't remember the name of the study, so, I wouldn't remember the specifics.

Torres, Denice M. (December 15, 2006)
180:17-22
Issues: 01 Plaintiff's Trial Designation

Q. Were you ever told that Eli Lilly had in their review of their epidemiologic information determined that there was an association between second generation antipsychotics including Zyprexa and diabetes?

Torres, Denice M. (December 15, 2006)
181:1-9
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: No. There was a lot of discussion about weight and about diabetes, but an association directly with the antipsychotics? No. I mean, there were case reports, et cetera, but did they refer to it as, you know, a direct association? No.

Torres, Denice M. (December 15, 2006)
181:11-18
Issues: 01 Plaintiff's Trial Designation

Q. So, as director of global marketing, you were not told of any epidemiologic information or data supporting an association between second generation antipsychotics including Zyprexa and diabetes?
A. I'm sorry. I don't remember that.

Torres, Denice M. (December 15, 2006)
181:21-185:5
Issues: 01 Plaintiff's Trial Designation

Let's go to Exhibit Number 2, the Zyprexa product team, "Answers That Matter." I'm going to skip to the page with the heading "The Chance to Make

History." Do you see that? "The Chance to Make History." All right? Are you there?

A. Yes.

Q. By the way, I think it would help the jury to tell the jury in direct language so they understand it because when they look at your testimony, what is the Zyprexa product team?

A. When I joined the team, the product team were a group of individuals with different functions that were responsible basically for clinical studies. It was the medical portion of the team, a regulatory portion of the team, I believe reporting in to the product team leader, which was Alan Breier. So, medical, regulatory, marketing and the whole clinical study function.

Q. Basically, as you said, I think this is a term of art you used, this was a cross-functional team?

A. Yes.

Q. When you used that term, so the jury understands it, you had individuals at Eli Lilly from the medical department, the regulatory department, the clinical trials department, the marketing department that all came together who had as their responsibility the successful marketing and sales of Zyprexa on behalf of Eli Lilly?

A. They had as their responsibility -- it was much broader than that.

Q. Tell the jury.

A. Their responsibility -- you know, you used the words "safety" and "efficacy." It was responsibility of the product team to ensure both the safety and understand the efficacy -- understand the safety and the efficacy of the product. And from a marketing standpoint, yes, it was also important to provide information to customers that, you know, would help with the usage of the product and, sure, the sales of the product.

Q. Right.

That's what you said, and it's back on that page, you don't need to turn to it, it's right there on the screen, the head of that whole team is Dr. Alan Breier? Do you see it?

A. Yes.

Q. The people on the team, as you said, included Dr. Breier, who's a medical doctor, medical department, but

you also had marketing and marketing research individuals, scientific communications, right? Right?

A. Yes.

Q. And you, who were in global marketing and head of global marketing?

A. In -- marketing, yes.

Q. Let's go back to the page I was on on the Zyprexa product team, "The Chance to Make History." "Olanzapine," that's Zyprexa, "the first team to dramatically speed time to registration...making history and setting the new... registration standard." You got this drug through your efforts -- or through your team's efforts before you got there, took this drug to FDA and got it approved on a new speed system, right?

Torres, Denice M. (December 15, 2006)
185:8-13
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: The -- what I remember from that time, I think there was some new way of submitting information to the FDA that would help facilitate them receiving the information.

Torres, Denice M. (December 15, 2006)
185:15-186:14
Issues: 01 Plaintiff's Trial Designation

Q. Now, this next -- this last one, I'm skipping down to number 3, it doesn't look like it's anything about science. It says, "Zyprexa: The first team with the opportunity to set the all industry commercialization standard for the most successful pharma brand in history." What does that mean?

A. The commercialization would be the product offering to the customer. So, in order to submit the -- in order to be a standard for commercialization, you'd have to be outstanding in understanding your customers, understanding your customer needs and delivering value to those customers. And doing all of those things right would be -- we would be incredibly successful financially, yes.

Q. Right. In fact, this commercialization and being successful

financially was very important to Eli Lilly because you were about to bet the farm on Zyprexa, right?

Torres, Denice M. (December 15, 2006)
186:18-187:15
Issues: 01 Plaintiff's Trial Designation

Q. Right?
A. You've asked me like two or three things in there. What's with the "bet the farm"?
Q. Well, let's go to the next page. Straight Talk - What's at Stake." Do you see that?
A. Yes, I do see that.
Q. Can you read that out loud for the jury, please.
A. "The company is betting the farm on Zyprexa...the ability of Eli Lilly to remain independent and emerge as the fastest growing pharma company of the decade depends solely on our ability to achieve world class commercialization of Zyprexa. If we succeed, Zyprexa will be the most successful product ever...we will have made history."
Q. Okay.
"Straight talk," that means no ambiguity, right? Correct?

Torres, Denice M. (December 15, 2006)
187:19-188:9
Issues: 01 Plaintiff's Trial Designation

Q. Correct?
A. Straight talk mean directly, yes.
Q. "What's at stake." What's that mean?
A. I don't know. Whoever wrote it, I don't know what they had in mind. "What's at stake" means here's the bottom line.
Q. Bottom line. "The company is betting the farm on Zyprexa." Did I read that right? Did I read that right?
A. That's what I see here.
Q. Does that offend you?
A. I wouldn't use those words.

Torres, Denice M. (December 15, 2006)
188:11-15
Issues: 01 Plaintiff's Trial Designation

188:11 Does it appear that the
12 company, being Eli Lilly, in order to
13 make history and to commercialize
14 Zyprexa, under the direction of Dr. Alan
15 Breier, was betting the farm on Zyprexa?

Torres, Denice M. (December 15, 2006)
188:18-189:3
Issues: 01 Plaintiff's Trial Designation

188:18 THE WITNESS: Was the
19 company betting the farm on
20 Zyprexa? I think I've answered
21 that before. In short term, it
22 was very successful, it was very
23 important to the company. But
24 betting the farm I don't think is
189: 1 accurate. It would mean that all
2 resources were going to Zyprexa,
3 and that was not the case.

Torres, Denice M. (December 15, 2006)
189:5-190:9
Issues: 01 Plaintiff's Trial Designation

189: 5 Q. "Straight talk," "Straight
6 talk." "The ability of Eli Lilly to
7 remain independent." What's that mean?
8 A. It means --
9 Q. To avoid a takeover?
10 A. Yes.
11 Q. "Straight talk - What's at
12 Stake. The company is betting the farm
13 on Zyprexa...the ability of Eli Lilly to
14 remain independent," i.e. avoid a
15 takeover, "and emerge as the fastest
16 growing pharma company of the decade
17 depends" -- what's that word "solely"?
18 A. That's what it says.
19 Q. "Solely," what's that mean?
20 A. Solely? It means primarily.
21 It means -- primarily.
22 Q. "Solely" actually means
23 only, doesn't it?
24 A. Yes.
190: 1 Q. The company's straight talk.
2 "What's a Stake, July 2001." Zyprexa
3 product team. "The company is betting
4 the farm on Zyprexa...the ability of Eli
5 Lilly to remain independent and emerge as
6 the fastest growing pharma company of the
7 decade depends solely on our ability to
8 achieve world class commercialization of
9 Zyprexa."

Torres, Denice M. (December 15, 2006)
190:13-14
Issues: 01 Plaintiff's Trial Designation

190:13 THE WITNESS: You read what
14 was on the page, yes.

Torres, Denice M. (December 15, 2006)
192:10-20
Issues: 01 Plaintiff's Trial Designation

192:10 And it would be
11 inappropriate if we found out later that
12 they hid information from doctors about
13 their product? That'd offend you,
14 wouldn't it?
15 A. Absolutely.
16 Q. It would be offensive if you
17 found out that some of the senior
18 executives in the company were aware of
19 off-label promotion activities and didn't
20 stop it? That offend you?

Torres, Denice M. (December 15, 2006)
193:1-12
Issues: 01 Plaintiff's Trial Designation

193: 1 Q. It would be wrong if Dr.
2 Lechleiter -- tell the jury who Dr.
3 Lechleiter is.
4 A. Right now he's second in
5 command at Lilly.
6 Q. Right. Sidney Taurel, who
7 is he?
8 A. CEO.
9 Q. Sidney Taurel and John
10 Lechleiter were fully familiar with the
11 fact that off-label promotion of Zyprexa
12 was taking place, weren't they?

Torres, Denice M. (December 15, 2006)
193:17-18
Issues: 01 Plaintiff's Trial Designation

193:17 Q. If they were, what should
18 they do?

Torres, Denice M. (December 15, 2006)
193:21-23

Issues: 01 Plaintiff's Trial Designation

193:21 THE WITNESS: If they were
22 aware that there was off-label
23 promotion by the company?

Torres, Denice M. (December 15, 2006)

194:6-195:16
Issues: 01 Plaintiff's Trial Designation

194: 6 If they were aware of
7 off-label promotion activities or
8 attempts to get doctors to prescribe
9 their product Zyprexa off label, what
10 should those men do?
11 A. Anyone in the company would
12 have responsibility to --
13 Q. To what?
14 A. It would be inappropriate.
15 Inappropriate behavior, you know, would
16 need to be addressed.
17 Q. Right. We're going on to
18 your PowerPoint, "Describing our Culture,
19 current and future" from a
20 "consensus-driven" model to a "single
21 point of accountability." What's that
22 mean, if you know?
23 A. I believe what that would
24 mean is that we spend a lot of time in
195: 1 meetings trying to gain consensus and
2 move to a single point of accountability
3 so we can make decisions and not spend as
4 much time in meetings.
5 Q. Right. I think the last
6 point I want to make is. I think the
7 next to last page of this -- or three
8 back, "deliverables." We see that all
9 the time in your documents. The jury
10 will see it when I try the case,
11 "deliverables." Just tell the jury what
12 deliverables are.
13 A. Deliverables would be
14 outcomes.
15 Q. Outcomes?
16 A. (Witness nods.)

Torres, Denice M. (December 15, 2006)

195:22-196:2
Issues: 01 Plaintiff's Trial Designation

195:22 Q. Tell the jury. Your lawyer
23 keeps on objecting. Tell the jury what
24 it means, outcomes. What does it mean by
196: 1 that?
2 A. Responsibilities.

Torres, Denice M. (December 15, 2006)
196:17-197:13
Issues: 01 Plaintiff's Trial Designation

196:17 "Expected Deliverables,"
18 what's that mean?
19 A. It means outcomes that
20 should happen as a result of this
21 meeting, yes.
22 Q. Things that should happen,
23 right?
24 A. Yes.
197: 1 Q. And that's the
2 responsibility of the members of the
3 Zyprexa product team, correct?
4 A. Yes.
5 Q. Okay. And I'm going to get
6 in here. We'll talk about one,
7 "Regulatory and label reviews." Do you
8 see that?
9 A. Yes.
10 Q. You were involved in label
11 reviews, were you not, and voting on what
12 you considered appropriate labels in
13 marketing?

Torres, Denice M. (December 15, 2006)
197:16-198:7
Issues: 01 Plaintiff's Trial Designation

197:16 THE WITNESS: I don't
17 remember any voting. I mean, we
18 had a regulatory group. The
19 regulatory and clinical group were
20 very much -- worked together.
21 Would they share information with
22 me if they were going to propose
23 verbiage to the FDA, et cetera or
24 to other things? Yes, they would.
198: 1 BY MR. ALLEN:
2 Q. The reason you wanted to be
3 kept apprised -- in fact, you got to vote
4 in the key decision maker team on labels,
5 give your vote. The reason you did is
6 you knew labels could affect the sales of
7 the product, right?

Torres, Denice M. (December 15, 2006)
198:10-200:22
Issues: 01 Plaintiff's Trial Designation

198:10 THE WITNESS: I don't
11 remember any voting. I don't know

what form you're talking about.
BY MR. ALLEN:
Q. Then let me rephrase my question. I will show you a document clearly on that point, but let me rephrase my question.
You knew in marketing that what the label said on the product could affect the sales of the product, right?
A. Sure. Could a label affect the sales? Yes.
Q. Tell the jury how the labels can affect the sales.
A. Well, if the label said, do not take with -- you know, while nursing, okay, that would exclude anyone that's nursing. If the label said don't -- I mean, there's a whole do not, those indications.
Q. Contraindications?
A. Absolutely.
Q. So, contraindications in the label can affect the sales, right?
A. Yes.
Q. That's what you're trying to say; is that right?
A. Basically anything that, you know, would exclude a group of people or -- yeah. I mean, that would definitely affect the sales.
Q. How long have you known that?
A. How long have I known the label --
Q. Could affect the sales.
A. Gosh, 15 years.
Q. Ever since you were at Eli Lilly?
A. Yes.
Q. Is that just basic core concept knowledge in the marketing department of Eli Lilly?
A. Yes.
Q. Is it just basic core concept knowledge on the Zyprexa product team in this cross-functional team?
A. Yes.
Q. So there's no secret, so there's no doubt, so there's no -- so you can be clear and give this jury straight talk, what you say in a label can affect your product sales, right?
A. Yes.
Q. No doubt about it, right?
A. That's correct.
Q. In fact, you, personally, viewed potential label changes that would enhance the warning on Zyprexa as a threat to Zyprexa sales, did you not?

Torres, Denice M. (December 15, 2006)

201:1-202:4
Issues: 01 Plaintiff's Trial Designation

201: 1 THE WITNESS: Were potential
2 label changes a threat?
3 BY MR. ALLEN:
4 Q. Yes, ma'am. You personally
5 know that?
6 A. Yes. Could they be a
7 threat? Sure. But the point is, you do
8 the right thing.
9 Q. Right.
10 You personally wrote down in
11 memoranda that label changes on Zyprexa
12 could threaten Zyprexa sales; is that
13 right?
14 A. Yes.
15 Q. Now, you said -- one thing
16 you indicated, if it says nursing mothers
17 should not take the product, that, as you
18 said, would exclude an entire segment or
19 category, right?
20 A. Well, a physician may decide
21 to -- well, from a company's standpoint,
22 you know, I can give a lot of other
23 examples, but from a company standpoint,
24 we would not be able to promote for
202: 1 nursing mothers. Now, may a physician
2 decide that the risk is worth it? Sure.
3 But that would not be the company's
4 responsibility.

Torres, Denice M. (December 15, 2006)

234:16-22
Issues: 01 Plaintiff's Trial Designation

234:16 Q. Thank you. Ma'am, I'm going
17 to hand you what's been marked as Exhibit
18 7, and we're not going to read the whole
19 thing. This is just -- I want to verify.
20 This is a Zyprexa Global Brand Plan
21 written or what you were responsible for
22 for 2005 to 2007.

Torres, Denice M. (December 15, 2006)

235:7-8
Issues: 01 Plaintiff's Trial Designation

235: 7 Q. You recognize this document,
8 don't you, ma'am?

Torres, Denice M. (December 15, 2006)
235:11-19
Issues: 01 Plaintiff's Trial Designation

235:11 Yes.
12 Q. Back to the first page.
13 Really, I'm going to focus on your title.
14 It says, "Marketing Executive Director."
15 Is that -- I think you tried to tell me
16 this earlier when I didn't understand.
17 That's just a title increase, I guess,
18 over global marketing director?
19 A. Yes. Same job.

Torres, Denice M. (December 15, 2006)
241:2-5
Issues: 01 Plaintiff's Trial Designation

241: 2 First thing that struck me
3 is 2005/2007 you're gone, so obviously
4 these plans were prepared well in advance
5 of your leaving; is that correct?

Torres, Denice M. (December 15, 2006)
241:8-244:10
Issues: 01 Plaintiff's Trial Designation

241: 8 Q. They had to be prepared
9 before you left?
10 A. I believe that this was --
11 if it was done in 2004, this would have
12 been called a longer range plan.
13 Q. Well, ma'am, I'm not -- I
14 can only use the words y'all used.
15 "Zyprexa Global Brand Plan." Right?
16 What's that mean? What is that?
17 A. The brand plan would be a
18 forward-looking outlook on the brand.
19 Q. And you were in charge of
20 preparing this sometime in 2004?
21 A. Yeah. It would have been
22 2004.
23 Q. Before you left. So, you
24 prepared these in advance, obviously, of
242: 1 the year indicated, right?
2 A. That's correct.
3 Q. Now, it says "Prelude to
4 Zyprexa Marketing Plan." I'm not going
5 to read the whole thing. I'd like to go
6 to -- "Prelude to Zyprexa Marketing Plan.
7 The atypical market is defined by product
8 usage and not by indications." What does
9 that mean? "The atypical market is
10 defined by product usage and not by

indications."
A. In terms of the atypical market, meaning antipsychotics, because there's so much grayness between -- the size of the market, I mean, basically what this is meaning is that the size of the market is the sum total of the sales for all antipsychotics.
Q. Well, it says "Prelude to Zyprexa Marketing Plan. The atypical market is defined by product usage and not by indications." Did I read that correctly?
A. You did read that correctly, yes.
Q. But isn't it true that the marketing of the product is supposed to be defined by the indications?
A. Sir, the word there is "market" and not marketing in the atypical -- with atypicals. Basically what this is saying is that, as we talked about earlier, you could have 30 something percent off-label usage. That still is the atypical, the drug, the basket of uses for the drug. That all equates to a total number of sales. Nowhere does it say that that is -- that this plan is meant to capitalize on the sum total of what is used for the drug. All it is saying is that the market for or, excuse me, atypicals, if you took the basket of them, by and large is defined by the total usage of those drugs.
Q. You're not supposed to try to capitalize on the off-label uses, are you?
A. That's correct.
Q. It would be wrong for Eli Lilly to try to capitalize through their marketing on off-label usage. That would be wrong, right?
A. Yes, sir.
Q. It would be a violation of law?
A. Yes.
Q. Violation of regulations?
A. That's correct.

Torres, Denice M. (December 15, 2006)
246:16-250:20
Issues: 01 Plaintiff's Trial Designation

Q. Ma'am, my only question to you was, and the record will reflect it and I can almost do it verbatim, it would be wrong in the marketing of Zyprexa, in

the marketing plan and activities for Eli Lilly to attempt to capitalize on the off-label usage?

A. That's correct.

Q. And just so -- you talked about --

You wanted to read the sentence, and you talked about diagnoses and medical diagnoses. This is under the heading of "Zyprexa Global Brand Plan." It's a marketing document. And it says, "Prelude to Zyprexa Marketing Plan." Isn't that what the heading is?

A. Yes. That's what the heading is.

Q. I was going to read the next sentence. "Off-label usage is commonplace with atypicals due to the medical necessity of addressing complicated symptomatology." Did I read that correctly?

A. Yes. And "It is important to note what while prescriptions are generated for these off-label uses, we have no intention or planned efforts to influence off-label usage."

Q. Ma'am, my only question was, did I read that question -- read that sentence correctly?

A. I believe you did read the sentence correctly.

Q. And I'm going to go down. Does this discussion -- let me ask. Does this discussion of off-label marketing make you nervous?

A. Sir, it doesn't. It's a characterization of the market.

Q. Now, the second paragraph: "Zyprexa, like all medicines used to treat mental illness, is prescribed to address a host of symptoms and disorders. These uses extend beyond schizophrenia and bipolar disorder, into areas such as depression." Did I read that correctly?

A. Yes.

Q. First of all, was Zyprexa -- we've already established was not indicated for depression, right?

A. That's correct.

Q. It could not be marketed for depression?

A. That's correct.

Q. It could not be promoted for depression?

A. That's correct.

Q. It would be wrong for you to do so, you, at Eli Lilly?

A. That's correct.

Q. "Into areas such as

depression, borderline personality." Did I read that correctly?
A. That's correct.
Q. Zyprexa was not indicated for borderline personality?
A. Correct.
Q. It could not be promoted for borderline personality?
A. Correct.
Q. It could not be marketed for borderline personality?
A. Correct.
Q. "Dementia," we've already established it's not indicated for dementia, right?
A. That's correct.
Q. It cannot be marketed for dementia?
A. That's correct.
Q. Cannot be promoted for dementia?
A. Correct.
Q. "Post traumatic stress disorder, stuttering and anxiety." Those last three, again, not in the indications for Zyprexa, right?
A. Correct.
Q. Could not be marketed for that purpose.
A. That's correct.
Q. Could not be promoted for that purpose?
A. Correct:
Q. "Consequently, a very large part of the market is not our target business given uses extend beyond our label." Did I read that correctly?
A. That's correct.

Torres, Denice M. (December 15, 2006)
251:9-252:8
Issues: 01 Plaintiff's Trial Designation

Q. Yes. It would be wrong for Eli Lilly in their marketing plans or in their promotional activities to attempt to capitalize on these off-label uses?
A. That's correct.
Q. Now, in "The 'Something Special' about Zyprexa," I'm just going to the last sentence of the first paragraph. I think we kind of established this earlier, just to put this in context. "In 2003, Zyprexa was the Number Three selling brand in the world," and it says "(IMS)." Right?
A. Yes.

Q. IMS is a private company that keeps track of numbers of prescriptions that are written on various pharmaceutical products?
A. Basically they're a very large data collection group, and so that would be --
Q. They can tell you --
A. -- one aspect of data about the marketplace.

Torres, Denice M. (December 15, 2006)
253:10-17
Issues: 01 Plaintiff's Trial Designation

Let me give you some of your competitors, and tell me if you agree. We're talking about the sentence "Like any market leader, we are the focus of every competitor." Did those competitors include Risperdal, Seroquel, Abilify, Geodon?
A. Yes.

Torres, Denice M. (December 15, 2006)
254:16-255:5
Issues: 01 Plaintiff's Trial Designation

Let me go on here to what I want to read. "Additionally, we face other marketplace pressures such as new competitive entrants, access challenges, litigation, increasing concerns around the impact of weight, and difficulties in maintaining premier share of voice." Share of voice, it's often seen in the documents as SOV, right?
A. That's correct.
Q. Share of voice means are you getting what you consider at Eli Lilly your fair share of talk in the marketplace, right?

Torres, Denice M. (December 15, 2006)
255:7-9
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: No. Share of voice is basically the amount of presence in a marketplace.

Torres, Denice M. (December 15, 2006)

255:11-256:24
Issues: [redacted] 01 Plaintiff's Trial Designation

255:11 Q. Thank you.
12 And you at Eli Lilly and
13 Zyprexa had the premier share of the
14 voice, and that's what you wanted to
15 maintain, right?
16 A. Yes.
17 Q. Thank you.
18 "Another factor that may
19 heavily influence the marketplace is the
20 results of the United States NIMH,"
21 that's the National Institutes of Mental
22 Health, "CATIE Trial," CATIE is an
23 acronym for Clinical Antipsychotic Trials
24 of Intervention Effectiveness, "a
256: 1 research project to evaluate the clinical
2 effectiveness of atypical antipsychotics
3 in the treatment of schizophrenia. The
4 results represent a significant upside or
5 downside for Zyprexa, depending on the
6 outcome."
7 Did I read that correctly?
8 A. Yes, you did.
9 Q. Now, tell the jury why --
10 what is the CATIE study?
11 A. The CATIE study was the --
12 you know, one of the largest studies that
13 was initiated and I believe sponsored by
14 all the different pharmaceutical
15 companies to look at efficacy rates of
16 new -- the newer antipsychotics and I
17 think versus the older antipsychotics.
18 Q. And you said, and I'm
19 paraphrasing, it was up on the board a
20 minute ago, we're going to go to another
21 page in a second.
22 The CATIE study results
23 could affect Zyprexa sales either
24 positively or negatively, right?

Torres, Denice M. (December 15, 2006)
257:3-4
Issues: [redacted] 01 Plaintiff's Trial Designation

257: 3 THE WITNESS: That's
4 correct.

Torres, Denice M. (December 15, 2006)
357:23-358:18
Issues: 01 Plaintiff's Trial Designation

357:23 Q. Didn't you at Eli Lilly know
24 if you truly warned about diabetes and

358: 1 hyperglycemia, it would affect your
2 sales? Didn't you know that?
3 A. Did we know that if there
4 was a warning for diabetes that that
5 could impact sales? Is that the
6 question?
7 Q. Yes, ma'am.
8 A. Sure, yes.
9 Q. Why would a warning about
10 diabetes impact sales?
11 A. A warning about anything
12 could impact sales because, again,
13 looking at the patients and the
14 characteristics of those patients,
15 everyone comes with their own set of
16 medical considerations that a warning can
17 have implications for certain individuals
18 with those medical conditions.

Torres, Denice M. (December 15, 2006)
359:15-360:18
Issues: 01 Plaintiff's Trial Designation

359:15 Q. You at Eli Lilly, you said
16 you knew -- you said in one of your
17 answers that Eli Lilly knew a warning
18 about diabetes would affect sales. When
19 did you learn that?
20 A. When did I learn that a
21 warning about diabetes could impact
22 sales? When did I learn that?
23 Q. Yes, ma'am.
24 A. Boy, it's something that I
360: 1 don't think anyone had to tell me that.
2 One could surmise a warning about
3 anything could impact sales. You
4 wouldn't even have to be an expert in the
5 area to know. If you know anything about
6 pharmaceuticals, a warning, information
7 in the warning could impact sales just
8 like information on efficacy would be a
9 positive -- it could be a positive
10 impact.
11 Q. So, what you're saying is
12 you wouldn't even have to be in the
13 industry, it was just good old common
14 sense that if there was a warning in the
15 package insert, you knew from your
16 experience and common sense that it would
17 impact sales? Is that what you're
18 telling me?

Torres, Denice M. (December 15, 2006)
360:20-361:1
Issues: 01 Plaintiff's Trial Designation

360:20 THE WITNESS: I said in
21 general terms that information in
22 a warning could have the potential
23 to impact sales and, again, a
24 number of factors would have to be
361: 1 taken into consideration.

Torres, Denice M. (December 15, 2006)
361:3-14
Issues: 01 Plaintiff's Trial Designation

361: 3 Q. Can you remember or tell
4 this jury when you knew that a warning
5 about diabetes or hyperglycemia, when you
6 knew that warning would impact sales in
7 regard to Zyprexa. Can you tell us an
8 approximate date or year?
9 A. I think as I mentioned
10 earlier, I -- no. A date or year?
11 Absolutely not. I could have said that
12 the first day I started work that, you
13 know, again, something in the warning has
14 the potential to impact sales.

Torres, Denice M. (December 15, 2006)
361:24-362:5
Issues: 01 Plaintiff's Trial Designation

361:24 Q. Yes, ma'am. Let me hand you
362: 1 Exhibit Number 11. A copy for your
2 lawyer. This is a document Mr. Fibich
3 provided me today. Is this 11? Is that
4 right?
5 A. It says 11, yes.

Torres, Denice M. (December 15, 2006)
362:8-18
Issues: 01 Plaintiff's Trial Designation

362: 8 "Scenario and Contingency
9 Planning Session, US Zyprexa Brand Team."
10 Were you on the U.S. Zyprexa
11 Brand Team?
12 A. No, I was not.
13 Q. You were on the global brand
14 team, right?
15 A. Global product team.
16 Q. I'm sorry. You know these
17 members, you dealt with these members all
18 the time?

Torres, Denice M. (December 15, 2006)

362:21-363:18
Issues: 01 Plaintiff's Trial Designation

Q. You know Jack Jordan, right?
A. Yes.
Q. You worked with him on a weekly basis, did you not?
A. No, I didn't, sir.
Q. Mike Bandick, we saw the organizational chart, he was right underneath you, right, in issues management? He was the director, correct?
A. He -- I'd have to go back and look at this data. At one point he was -- he reported to me, and he also had a portion of his job where he reported to Jack Jordan, that I was not involved with.
Q. Well, I guess my point is, you knew Mr. Bandick and he -- you worked with him and at times he reported to you, and at times he reported to other people, right?
A. Yes.

Torres, Denice M. (December 15, 2006)

364:1-366:6
Issues: 01 Plaintiff's Trial Designation

Q. I just want to go to this "Metabolic Side Effects," number 1, here on this document. "Scenario Clarification and Probabilities." "A 'Black Box' label for Zyprexa appears to be a very low probability. However, a differential label warning of metabolic side effects for either Zyprexa only or a subset of the atypical antipsychotics is a very real possibility."
Did I read that correctly?
A. Yes, you did.
Q. Were you aware in 2003 that a change of the label concerning a warning about metabolic side effects was a very real possibility?
A. I can't say yes.
Q. If you can't say yes --
When did you become aware that it was a possibility? If you don't know, just tell me you don't know.
A. Well, a lot of information was submitted to the FDA in ongoing discussions with the FDA. So, was it a possibility that with the data that Lilly submitted and the other companies with atypical antipsychotics, that that could

result in a label change, I can't tell you exactly when I would have become aware of that.

Q. You knew what the consequences would be if there was a label change, though, didn't you?

A. The consequences to whom?

Q. To the sales.

A. To the sales of atypical antipsychotics?

Q. Yes, in general, and Zyprexa in particular.

A. Well, if it were a class effect, there would be potentially no impact whatsoever. You're talking about a group of individuals that are very, very ill. And, again, the risk/benefit would have to be taken into consideration. So, if this were a class effect like with increased suicidality for antidepressants, then all those things are taken into consideration when treating a patient. But I'm sure there's instances, you know, there have been label changes and no impact on prescribing because there's such an unmet patient need.

Torres, Denice M. (December 15, 2006)
367:14-368:24
Issues: 01 Plaintiff's Trial Designation

Q. We're back to the issue of how a label affects sales. You said you knew that from the day you started. We're on Exhibit 11, "Scenario Clarification and Probabilities." "A 'Black Box' label for Zyprexa appears to be a very low probability. However, a differential label warning of metabolic side effects for either Zyprexa only or a subset of the atypical antipsychotics is a very real possibility." You were aware of that at some point, correct?

A. Yes.

Q. You just don't remember when you were aware of it; is that right?

A. That would be fair.

Q. Bullet point number two, says "There would be little practical difference between these two scenarios, because Zyprexa would still lose access" -- and access to what, ma'am?

A. It would be basically reimbursement, certain reimbursement levels.

Q. Right. If you had a warning

concerning Zyprexa, it may affect your access to formularies; is that correct?
A. Reimbursement likely.
Q. Right. "There would be little practical difference between these two scenarios, because Zyprexa would still lose access and become primarily a 2nd or 3rd line treatment." Did I read that correctly?
A. You read that correctly.

Torres, Denice M. (December 15, 2006)
394:20-395:21
Issues: 01 Plaintiff's Trial Designation

Q. Let me hand you what's been marked as Exhibit Number 14. This is Anthony Fiola from global marketing, 3/30/01. This is over a year prior to April of 2002, is it not? Just simple math. March --
A. Simple calendaring, yes.
Q. That's all I'm asking. "Dear Affiliates." You said that your role in global marketing was to work with the affiliates, right?
A. Yes, I did say that.
Q. You said your role in global marketing was to implement global marketing plans that the affiliates could utilize, right?
A. Yes.
Q. This says, "Dear Affiliates, This hyperglycemia/diabetes document contains new information on: Diabetes Speaker Slides." Did I read that right?
A. Yes, you did.
Q. Eli Lilly hired speakers, physicians to go out, and they provided them with slide shows so they could go out and talk to doctors, didn't they?

Torres, Denice M. (December 15, 2006)
395:24-397:5
Issues: 01 Plaintiff's Trial Designation

Q. Didn't they?
A. I'm sorry. Repeat your question.
Q. Eli Lilly provided doctors, speakers, with slide shows to go and talk to other doctors?
A. If those individuals chose to talk to other doctors, they could use the side kit.

Q. Let me just use the term. Ma'am, I'm not trying to be difficult. Let me see the word you used, "speaker." What did you think the word "Speaker" meant?
A. Speaker?
Q. Yes, ma'am.
A. It would be either someone from the company or an opinion leader or a prescriber that would give a talk, and it could be a whole variety of settings.
Q. Right. This is somebody Eli Lilly hoped got out their message, right?
A. The message? Would get out information.
Q. Yes.
A. Share information, sure.
Q. And Eli Lilly made their own slides for these speakers, right?
A. As it pertained to Zyprexa, yes.

Torres, Denice M. (December 15, 2006)

398:1-399:5
Issues: 01 Plaintiff's Trial Designation

My question was, you in global research, global marketing, in your job, while you were on the global marketing team, conducted market research on hyperglycemia, your department, did it not?
A. I would imagine that questions were answered certainly in our brand equity in terms of associations with what was associated with Zyprexa. We could determine things, especially weight, with something that was associated with Zyprexa. So, in terms of overarching research, characteristics of the profile would come up.
Q. Ma'am, just so the record is clear, I didn't prepare this document. People at Eli Lilly did. This isn't talking about weight. It's talking about hyperglycemia and diabetes, isn't it? Hyperglycemia and diabetes, correct?
A. That is what it says.
Q. And it goes on to say after it gives a list, "To maximize Zyprexa's success in the market, it is critical that we actively address the issue." Did I read that correctly?
A. You did read it correctly, yes.

Torres, Denice M. (December 15, 2006)
399:24-400:8
Issues: 01 Plaintiff's Trial Designation

399:24 Q. It's been represented to me,
400: 1 ma'am, this came from your files. Do you
2 recognize this document?
3 A. No.
4 Q. Okay.
5 But you would agree that you
6 were on this global marketing team at or
7 near this time of this report of March
8 30, 2001, right?

Torres, Denice M. (December 15, 2006)
400:10-10
Issues: 01 Plaintiff's Trial Designation

400:10 THE WITNESS: Sure.

Torres, Denice M. (December 15, 2006)
400:13-401:7
Issues: 01 Plaintiff's Trial Designation

400:13 So, the goals, unless they
14 change in a day, the overall goals of the
15 team were as follows:
16 What's the number one goal
17 of the global marketing team? Let's read
18 it together. "Stop
19 hyperglycemia/diabetes from becoming a
20 Top 10 Attribute influencing
21 prescribing." Did I read that correctly?
22 A. You did, sir.
23 Q. Right.
24 Now, the number one goal was
401: 1 not to warn physicians about the
2 potential of weight gain, hyperglycemia
3 and diabetes, was it?
4 A. Number one goal?
5 Q. Yes, ma'am. Was it to warn
6 physicians about diabetes? Yes or no?
7 A. No.

Torres, Denice M. (December 15, 2006)
403:24-405:6
Issues: 01 Plaintiff's Trial Designation

403:24 Q. You said "Stop
404: 1 hyperglycemia" and "diabetes from
2 becoming a top 10 attribute influencing
3 prescribing." Correct?
4 A. I think the key words are

"influencing prescribing," which means influencing the choice.

Q. And you wanted to stop diabetes and hyperglycemia from influencing that choice, correct?

A. From being the overarching things that they considered.

Q. It doesn't say overarching. It's from being even in the top ten things they consider, correct?

A. Sir, I can't tell you what the person meant. But I could tell you, you're asking my opinion, you've given me a document, I have stated my opinion. Why did he choose top 10 and not top 5? How about top 20? I think with the sentiment of the sentences, we need to make Zyprexa seen in the sum total of its attributes. Are some of those attributes negative? Yes. Are there a lot of attributes positive? Yes. But in the sum total, what are the top attributes physicians associate with Zyprexa, the goal was to ensure that those positive things about Zyprexa were known and communicated.

Torres, Denice M. (December 15, 2006)

411:20-413:11
Issues: 01 Plaintiff's Trial Designation

Q. Ma'am, I'm going to hand you Exhibit 15, which is an e-mail you sent. Look at the very top. You sent this e-mail from Denice Torres. Do you see, Denice Torres sent this e-mail? That's you, right? Ma'am?

A. Did I send the -- it looks like I forwarded an e-mail.

Q. Yes, ma'am.

In September of 2002 from Denice Torres, you sent it to people in global marketing and people in U.S. marketing at the other affiliates, did you not?

A. Yes.

Q. You also sent it to Dr. Alan Breier, the head of the Zyprexa product team, right?

A. Yes.

Q. And we won't read the entire e-mail. You were forwarding an e-mail from Anthony Fiola, which is who you told me worked in global marketing under you, correct?

A. Yes, he did work on my team.

Q. And the subject matter is

"Issues Update." And you talked about issues today, right?

A. Yes.

Q. In fact, you had a whole department that worked underneath you, as we saw in the organizational chart, on issues management, right?

A. It was called marketplace management.

Q. Right.

And then underneath that we have issues management. Do you recall that?

A. Yes.

Torres, Denice M. (December 15, 2006)

414:5-417:1
Issues: 01 Plaintiff's Trial Designation

Mr. Fiola is writing the affiliates, right?

A. Yes.

Q. And you, of course, take Mr. Fiola's e-mail, and you forward it along to people who were involved in Zyprexa sales and marketing, as well as the medicine side of the company, right?

A. Correct.

Q. Okay.

Including Mr. Pike, also, right here, who is involved in, as you said, issues management, right?

A. Yes.

Q. Okay.

Now, the subject line is "Issues Update." And I want to read this.

"I wanted to take this opportunity to give you a brief update on the current state of affairs with regards to the issues facing Zyprexa, focusing mainly on diabetes."

Did I read that correctly?

A. You did, sir.

Q. "There is increased intensity regarding Zyprexa and alleged links to diabetes and serious metabolic concerns. During the past six weeks."

Did I read that correctly?

A. Yes.

Q. And one of the things that happened during the last six weeks among others was, "Zyprexa-associated Diabetes Mellitus," an article by Dr. Koller was published in Pharmacotherapy in July; is that correct?

A. You read that correctly.

Q. And Dr. Koller had published an article in Pharmacotherapy looking at the FDA adverse events reporting database. Had she -- is it a she, I think?

A. I don't remember that.

Q. Well, Dr. Koller had published that article dealing with the FDA database, right?

A. I'd have to see the publication. I don't remember the specifics.

Q. And Dr. Koller's article had suggested that the incidence of diabetes associated with Zyprexa as a second generation antipsychotic, there was a statistical association, correct?

A. Again, sir, if you gave me the article, I could reference it, but I don't remember --

Q. You don't recall --

A. -- the specifics of it.

Q. You don't recall it now?

A. I don't.

Q. Another thing. Y'all had gotten legal correspondence from Johnson & Johnson who makes Risperdal, right?

A. Yes.

Q. "Regarding use of 'comparable rates,'" right?

A. That's what it says, yes.

Torres, Denice M. (December 15, 2006)

418:1-23

Issues: 01 Plaintiff's Trial Designation

I very much apologize.

You said that "comparable rates" is what you were telling doctors; is that right?

A. I told you it was one aspect of a communication.

Q. And what was the aspect? Just say it out loud for the jury so we can all hear it.

A. What was the aspect?

Q. Yes. This comparable rates in regard to diabetes, remember, we're talking about the subject of diabetes, and what did this "comparable rates" message to doctors, what was that?

A. If I remember correctly, it was that atypicals in general had comparable rates as it pertained to the incidence of diabetes, and that in accordance with good medical practice, prescribers should evaluate every patient

for their risks and take appropriate
actions as they deem appropriate.

Torres, Denice M. (December 15, 2006)
419:11-16
Issues: 01 Plaintiff's Trial Designation

Q. Weren't you telling doctors in this "comparable rates" message that the rates of or incidence of diabetes associated with Zyprexa was no different from that of other second generation antipsychotics?

Torres, Denice M. (December 15, 2006)
419:19-21
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: I think the word was "comparable." Comparable doesn't say no difference.

Torres, Denice M. (December 15, 2006)
419:24-423:22
Issues: 01 Plaintiff's Trial Designation

By the way, when you use "comparable," what does comparable mean to you?
A. By and large in the same category.
Q. That's the message you were giving doctors?
A. Comparable rates.
Q. Right.
In fact, if you look at Page 2, do you remember the tag line? I didn't come up with that myself. This is Mr. Fiola who worked in marketing. He says, "On the commercial front, our tag line has been 'comparable rates.'" Right? "Tag line." Is that the word he uses?
A. It's an inappropriate use of the word, but it is the word he used.
Q. Okay.
Well, you forwarded this e-mail along to Alan Breier, Jack Jordan, Matthew Pike and others, didn't you?
A. I would not have a memo rewritten on the basis of one word.
Q. Ma'am, that wasn't my question. You're anticipating another

question.

My question to you is, you forwarded this e-mail of Mr. Fiola in which he says, "On the commercial front, our tag line has been 'comparable rates.'"? You forwarded this very e-mail along, did you not?

A. Yes, I did.

Q. I assume before you forwarded it along, you read it?

A. I would not assume that.

Q. You wouldn't?

A. No.

Q. Okay. Well, let me ask this.

Since you brought it up, I don't see anywhere in this e-mail when you sent it out to Michael Bandick, who is in charge of marketplace management, to Alan Breier, who is head of the Zyprexa product team, to Matthew Pike, who is head of issues management, and to Jack Jordan, who is head of the U.S. affiliate marketing, that you made any corrections or criticisms of the e-mail, did you?

A. I wouldn't see that as material. It's just a person with one year marketing using a statement. I wouldn't see that as material. The use of the term "comparable rates" was used in the broader context.

Q. Right.

And so you also, obviously, didn't disagree with what was known in global marking as of the time this e-mail was sent that "Zyprexa does lead to increases in appetite, which can contribute to obesity, a major risk factor in developing diabetes"? Is that correct?

A. Yes.

Q. So, it was known that Zyprexa could lead to weight gain, which was a major risk factor in developing diabetes, correct?

A. Weight gain is a major risk factor in developing diabetes, yes.

Q. Let's read it together again.

"Zyprexa does lead to increase in appetite, which can contribute to obesity, a major risk factor in developing diabetes," correct?

A. That's correct.

Q. Right.

And that was known -- well, let's say at least at by -- we'll go back to some other ones even earlier.

But by September of 2002, in global marketing, Mr. Fiola and to all the affiliates to whom he sent it, and to all the people whom you sent it, including Dr. Breier, it was known that Zyprexa does lead to increase in appetite, it does contribute to obesity, and it is a major risk factor in developing diabetes, correct?

Torres, Denice M. (December 15, 2006)
423:24-424:1
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: There was a whole chain there.

Torres, Denice M. (December 15, 2006)
424:3-8
Issues: 01 Plaintiff's Trial Designation

Q. Yes, ma'am, there certainly is.
A. Yes. Zyprexa can potentially lead to weight gain, yes. Is weight gain a major risk factor for diabetes? Yes.

Torres, Denice M. (December 15, 2006)
474:17-475:4
Issues: 01 Plaintiff's Trial Designation

Q. You know who Mr. Glyn Parkin is?
A. Yes. Vice president of sales and marketing for the U.S. affiliate, Zyprexa.
Q. In fact, Exhibit Number 1, "Restructuring of the Marketing Component for Zyprexa Product Team," he was the one -- he wrote this document, he's one of the men that you thanked for his "significant leadership," along with Jack Jordan, right?

Torres, Denice M. (December 15, 2006)
475:7-17
Issues: 01 Plaintiff's Trial Designation

Q. "The U.S. Affiliate -- with significant leadership from Glyn Parkin

and Jack Jordan -- were instrumental in the development of the new team," right?

A. Yes.

Q. Okay.

Now, in 2003, when did Mr. Parkin tell you that the engine of the company, Zyprexa, the heart and soul of the corporation, was slowing and faltering?

Torres, Denice M. (December 15, 2006)

475:20-21
Issues: 01 Plaintiff's Trial Designation

475:20 THE WITNESS: I don't
21 remember that conversation.

Torres, Denice M. (December 15, 2006)

476:7-478:14
Issues: 01 Plaintiff's Trial Designation

476: 7 Ma'am, I'll hand you what's
8 been marked as Exhibit Number 20. It is
9 a "Neuro Sales Operations Neuroscience
10 Retail Action Plan." This one came from
11 Mr. Jordan's files. Glyn Parkin, who you
12 thank, says, "The Challenge. I need your
13 leadership, the corporation needs your
14 leadership, at this time your leadership
15 is needed in a massive way and in a way
16 that you will look back on as a defining
17 moment in your leadership careers. All
18 of you."
19 Going to the next page.
20 "The challenge. Our
21 business with Zyprexa, the heart and soul
22 of this corporation, the engine room, the
23 best mental health product on this
24 planet, is faltering, slowing, and the
477: 1 slowdown has been a sudden one."
2 Do you recall that occurring
3 in 2003, ma'am?
4 A. Do I recall --
5 Q. Zyprexa sales suddenly began
6 to slow and falter in 2003?
7 A. I don't recall the specifics
8 of the sales curve. There was a decline.
9 I don't remember when they started, what
10 the abruptness was.
11 Q. Well, you were involved in
12 efforts to correct that, weren't you?
13 A. Sales decline?
14 Q. Yes.
15 A. Or slowing?
16 Q. In 2003, you were

specifically involved in efforts to correct this sudden sales decline?
A. I don't remember the date, but sales decline in general, yes.
Q. What caused the sales decline, ma'am?
A. New competition and concerns about weight gain.
Q. What about concerns about diabetes?
A. Actually, I think it was more -- I think there were three things. The company launched our product for ADD, Strattera, so, sales representatives were taking off to promote for Strattera. And another reason was, I believe, competition. And third, it was concerns about weight.
Q. Do you remember the SWAT team being created, Zyprexa SWAT team? You remember that, don't you? You were at those meetings, weren't you?

Torres, Denice M. (December 15, 2006)
478:17-19
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: I remember the term. I don't remember what the focus was.

Torres, Denice M. (December 15, 2006)
479:13-484:24
Issues: 01 Plaintiff's Trial Designation

Q. Ma'am, I'm putting up before the jury Exhibit 21. It's an e-mail correspondence from Mike Magdycz. You know who Mike Magdycz is, don't you?
A. Yes, I know Mike.
Q. Tell the jury who Mike Magdycz is.
A. Mike is an individual that worked in the U.S. affiliate and, at one point, came to the Zyprexa global marketing team.
Q. This was also sent to you, was it not?
A. Yes. I'm on the cc list.
Q. Mr. Magdycz at this point was working both for the U.S. affiliate and the global marketing team, was he not?
A. I don't know if it was during this time period.

Q. Well, it looks like in June of 2003 the subject matter of his e-mail is "Zyprexa Issues SWAT Team Urgent Action Required Privileged and Confidential."

Do you recall that?

A. No, I don't, sir. I could read the document and talk to you about it.

Q. Don't you recall being at the SWAT team meetings?

A. If you let me take a look at this, I'll take a look and see what it is, but --

Q. Your name is on this document, and both on the e-mail --

A. Sir, I'm not denying that. I really do not recall specifics of 2003 or '2 or '1. Depending on the topic. You've shown me a lot of different documents. I'm doing my best to answer the question. And if you want me to go through this document, I'll do that.

Q. Well, just go to the page as "Who is going to deliver?" It's right over your right shoulder. You don't have to look in the dark, you can look over your right shoulder and you can see where we are.

A. I'd rather read on the paper.

Q. I know, ma'am. You can read on the paper, but I'm trying to help you. Right there. Look over your shoulder. "Who is going to deliver? The issues SWAT team."

A. (Reviewing document.)

Q. Are you on the page, ma'am? I'm on the page. "Who is going to deliver?" Are you there?

A. Yes, I am.

Q. It says at the top, "The issues SWAT team." It gives the members, including Dr. Richard Petty. You remember Dr. Petty, don't you?

A. No, I didn't know Dr. Petty. I've heard his name, but I didn't personally know him.

Q. It says we are going to "Need protection from outside influence while we get this done." The people assigned to that are Jordan, that's Jack Jordan, Denice Torres and Mike Bandick."

Do you recall this now?

A. Do I recall the specifics? No.

Q. Tell us what you do recall about this issue.

A. Well, the team was put

together. It looks like all individuals from the U.S. affiliate, Tom Hardy, U.S. affiliate, U.S. brand manager; U.S. affiliate, Vince Truax; Mike Yost, U.S. affiliate; Kelly Copes-Anderson, U.S. affiliate; Mike Magdycz, I don't know if he was U.S. or global at the time. Joe Welch was U.S. McKinsey was --

Q. Why was this team created is what I'm asking?

A. If I can go back to the document. Let me take a look at it and see.

Q. Well, there's a page called "What is the problem?" Do you see in this document, "What is the problem?" You were copied on this document. You were sent this e-mail. You were listed as somebody involved. Do you see where it says, "Sales" are "below" the "plan?"

A. If you're going to ask me questions, I would like to look at the document, please.

Q. I'm asking you about the page "What is the problem?" Do you see that? "What is the problem?" Right over your shoulder. You got it? Do you recall that in 2003 sales were below the plan?

A. Again, I told you from a year's standpoint, I don't remember when they declined, but at some point, sales were below plan.

Q. It says, "Equity indicators." Equity means what people were thinking about the product, right, brand equity?

A. Yes.

Q. Okay.

So, when we talk about equity and we look at the documents concerning Zyprexa and it says "equity" or "brand equity," it means people's perception of our product, correct?

A. Actually, it can mean one of two things. It could mean the perception or the relevance of that attribute to prescribers. So, you could have weight gain that was always associated, but the relevance -- in the case of Zyprexa, my recollection is the relevance to prescribers changed.

Q. Right.

Torres, Denice M. (December 15, 2006)
485:10-16
Issues: 01 Plaintiff's Trial Designation

485:10 Q. Straightforward and honest
11 and direct to a jury.
12 The problem in 2003 that was
13 causing the dropoff in sales is
14 physicians started to suspect and believe
15 that Zyprexa caused more weight gain and
16 was causing diabetes, correct?

Torres, Denice M. (December 15, 2006)

485:18-486:21
Issues: 01 Plaintiff's Trial Designation

485:18 THE WITNESS: Again, they
19 were the three things. You asked
20 me this question before, and the
21 three things that we looked at in
22 terms of decline in sales, new
23 competition, the launch of
24 Strattera, and the third were
486: 1 concerns about Zyprexa and weight
2 gain.
3 BY MR. ALLEN:
4 Q. And you were on the issues
5 focus team, weren't you?
6 A. Issues focus team. I'm not
7 familiar with that.
8 Q. You are not familiar with
9 that?
10 A. Issues focus team? No.
11 Q. Well, how about the Zyprexa
12 focus team, you were on that, weren't
13 you, in the summer of 2003?
14 A. Zyprexa focus team?
15 Q. Yes, ma'am. You don't
16 remember that now?
17 A. Zyprexa focus team? No, I
18 don't.
19 Q. Okay, sorry.
20 Well, you were. Let me show
21 you that document.

Torres, Denice M. (December 15, 2006)

487:9-489:8
Issues: 01 Plaintiff's Trial Designation

487: 9 Q. Exhibit 22. Do you recall
10 being an author of a report to Zyprexa
11 U.S. and global marketing, "Subject:
12 Diabetes update" in the summer of 2003?
13 "Diabetes Update," to the "Policy
14 Committee," from, among others, Denice
15 Torres in global marketing.
16 A. (Reviewing document.)
17 Q. Do you recall that?
18 A. Just give me a moment,

please.
Q. There's only a question on the table.
A. Do I recall the focus team?
Q. You being on the Zyprexa focus team.
A. I remember this memo. I'm not sure of the term "focus." There were other teams, but I'm not sure that, you know, it was a branded focus team and people referred to a focus team.
Q. The only reason I said it is because it says it right on --
A. It says it on the document.
Q. It says on the document you wrote, "New Zyprexa 'Focus' Team." Did I read that correctly?
A. It does say that, yes.
Q. Right.
Do you recall that the focus team was created in the summer of 2003 to create new messages to surround Zyprexa? Do you recall that? Do you recall that?
A. If you're going to ask me questions, I need to read the document. So, if you can just give me a moment, let me look through it, and then I can answer your questions.
Q. Ma'am, my only question is, regardless of the document, do you recall that a new Zyprexa focus team was created in the summer of 2003 to create new messages surrounding diabetes and Zyprexa? Yes, no, or you do not recall?
A. I vaguely recall. There were so many teams created, I'd have to go through and say specifically what was this team.

Torres, Denice M. (December 15, 2006)
489:14-490:2
Issues: 01 Plaintiff's Trial Designation

But do you recall, without review of the document, just in honest and direct fashion to the jury that new messages were created surrounding diabetes and weight gain in the summer of 2003?
A. I don't know that -- no, I don't recall new messages being created. That doesn't mean they weren't created. I just don't recall new messages being created.
Q. Do you recall new stories being created?

Torres, Denice M. (December 15, 2006)
490:4-5
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: No.
BY MR. ALLEN:

Torres, Denice M. (December 15, 2006)
490:6-491:5
Issues: 01 Plaintiff's Trial Designation

Q. There was a Dr. Rosenhac. Do you know Dr. Rosenhac or who he is?
A. No.
Q. Were you on the weight task force in January of 2004? Were you on the weight task force?
A. I don't believe so.
Q. Did you know a weight task force was created in January of 2004?
A. Do I remember?
Q. Yes, ma'am. That's all I asked.
A. No, no, I don't remember that. There were several -- as you can see from these documents, there were multiple task forces being formed. It doesn't surprise me. But I don't remember specifics of a weight task force being formed.
Q. The reason multiple task forces were being formed in 2003 and 2004 is because Zyprexa was losing sales all of a sudden due to the concerns about diabetes, correct?

Torres, Denice M. (December 15, 2006)
491:8-18
Issues: 01 Plaintiff's Trial Designation

Q. Ma'am?
A. The reason task forces were being created was that Zyprexa was losing sales. And you asked me why were they losing sales. And I gave you the three factors: One, new competitive entries; two, taking an eye off implementation with the Strattera launch; and three, concerns about Zyprexa and weight. And I'm sure there were other concerns around that.

Torres, Denice M. (December 15, 2006)
492:9-493:4
Issues: 01 Plaintiff's Trial Designation

Q. Ma'am, you actually prepared, as marketing director, the Zyprexa global brand plan for 2004 and 2005, did you not, Exhibit 23?
A. Yes.
Q. And I'm going to skip back to Page 19, "World Wide Zyprexa Brand Equity - 2002." You told us what brand equity is, right?
A. Yes.
Q. This was a document you were in charge of preparing, right?
A. Yes. My team, yes.
Q. And your team was looking at global plan on marketing Zyprexa for 2004 to 2005, right?
A. Yes.
Q. And you have a chart or graph or table -- what did you call it, lines and graphs?

Torres, Denice M. (December 15, 2006)
493:7-495:24
Issues: 01 Plaintiff's Trial Designation

Q. What is this? Is this a table on Page 19?
A. Yes.
Q. Okay.
And it's on brand equity; is that correct?
A. Yes.
Q. And what you -- and the brand equity, the brand is Zyprexa, right?
A. (Witness reviewing document.)
Q. Zyprexa is the brand we're talking about, correct?
A. We are talking about Zyprexa.
Q. All right.
This is hard to read, the best copy they gave me. Under "Concerned will increase." Let me go to the second page, on Page 20. Do you see this? "When prescribed - worry patients will develop hyperglycemia" and "diabetes." It is a "weakness-linked to overall metabolic side effect concerns."
Did I read that correctly?
A. (Reviewing document.)
Q. Ma'am, I'll tell you, you

understand this chart. You created it?
A. No, I do. I'm sorry. Did you say "when prescribed - worry patients will develop diabetic ketoacidosis"? Is that what you asked me?
Q. Ma'am, I'm under "Worry patients will develop hyperglycemia" and "diabetes."
A. Yes, I do see that.
Q. Under the association, "Z" stands for Zyprexa, right? "Z" stands for Zyprexa?
A. Yes, it does.
Q. Okay.
Under the category of "Worry patients will develop hyperglycemia" and "diabetes," that's Zyprexa; is that correct?
A. Yes.
Q. "Worry patients will gain too much weight." That's Zyprexa, am I correct about that?
A. As a high association, and then you have other associations, yes.
Q. Yes.
Another high association is worry they "will develop hyperglycemia" and "diabetes," correct?
A. Yes.
Q. Okay.
So, just for the record, you keep on telling us the concerns around Zyprexa in the summer of 2003 were weight gain, but the fact of the matter is, in a very document you created, the concerns surrounding Zyprexa in the summer of 2003, a high concern was diabetes, correct?

Torres, Denice M. (December 15, 2006)
496:2-16
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: The concern was, as I said, was weight gain, you know, concerns with weight gain and the implications of weight gain with other things, yes. It's not inconsistent.
BY MR. ALLEN:
Q. Ma'am, I didn't ask you about weight gain. So, you changed my question in your answer.
As reflected in the table in Exhibit 23, which you were in charge of preparing, another high concern, high concern was "hyperglycemia" and

16 "diabetes," Zyprexa, correct?

Torres, Denice M. (December 15, 2006)
496:21-497:4
Issues: 01 Plaintiff's Trial Designation

496:21 A. You asked me about what is
22 in the chart, and the chart said -- you
23 asked me about "worry patients will
24 develop hyperglycemia/diabetes," and you
497: 1 asked me about "worry patients will gain
2 too much weight," and you said are these
3 under the category of "High Association,"
4 and I said yes.

Torres, Denice M. (December 15, 2006)
497:21-21
Issues: 01 Plaintiff's Trial Designation

497:21 Did you know --

Torres, Denice M. (December 15, 2006)
498:7-15
Issues: 01 Plaintiff's Trial Designation

498: 7 Q. -- that as early as February
8 of 2000, and even predating that date,
9 that the U.S. marketing department was
10 "driving the depression story" on Zyprexa
11 to potential consumers? Did you know
12 that?
13 A. No.
14 Q. It'd be wrong if they did
15 that, wouldn't it?

Torres, Denice M. (December 15, 2006)
498:19-499:15
Issues: 01 Plaintiff's Trial Designation

498:19 A. Depression on its own? Yes.
20 Depressive symptoms associated with
21 schizophrenia? No.
22 Q. Just for the record, ma'am,
23 you testified I think within the first
24 hour this morning that Zyprexa was not
499: 1 indicated for depression, right?
2 A. I did.
3 Q. It was not indicated for
4 bipolar depression, right?
5 A. That's correct.
6 Q. And has never been indicated

for depression?
A. Correct.
Q. And to suggest that in any form, shape or manner that somehow Eli Lilly was entitled to promote or market Zyprexa for depression would be wrong? You're not entitled to do that, are you?
A. I did say that, yes, that is correct.

Torres, Denice M. (December 15, 2006)

500:11-24
Issues: 01 Plaintiff's Trial Designation

Q. Did you know that Eli Lilly was out promoting Zyprexa for depression?
A. Who said they were out promoting for depression?
Q. This document. Let's read it together. It is from John Richards. Who is John Richards?
A. He was on the U.S. brand team.
Q. Okay.
Then the answer to your question is, Mr. John Richards is the one that says you're out promoting Zyprexa for depression --

Torres, Denice M. (December 15, 2006)

501:4-503:18
Issues: 01 Plaintiff's Trial Designation

Q. -- and he was writing to Jack Jordan. You know who Jack Jordan is, don't you?
A. Yes. Head of the brand team.
Q. You were on the key decision team with him. Do you recall that?
A. Key decision team? No. You keep throwing these terms out of --
Q. All these terms came from your documents. You were on the --
A. They may be. What I'm saying is there was a lot of teams being formed. Did I work with Jack Jordan? Yes, absolutely.
Q. Who is Eric Prouty?
A. Eric Prouty was on Jack Jordan's team.
Q. Okay.
And Jack Jordan is one of the affiliates who you were responsible in global marketing as working with to

help market Zyprexa, right?
A. Jack Jordan?
Q. Yes.
A. Yes.
Q. Okay.
E-mail from Mr. Richards. "Jack, attached as we discussed. As you can see, we have been driving the depression story with Zyprexa in our DTP" --
What's that, "DTP"?
A. Direct to physician.
Q. -- "in our direct to physician program since Q3 1998. We were ahead to the curve in recognizing communicating the importance of this attribute and how we can utilize it to differentiate ourselves in the marketplace. Please let me know if you have questions or comments. Thanks, JR."
Did I read that correctly?
A. Yes, you read it correctly.
Q. Was Eli Lilly out driving the depression story?
A. I don't have knowledge of Lilly -- what this said here, "communicating the importance of this attribute." So, I don't know in what context, you know, if it was promotion of depression, I'm not familiar with it.
Q. One thing you do know if you were driving a depression story to prescribe to doctors in direct to physician campaigns -- DTP is direct to physicians, right?
A. That's correct.
Q. If you were driving the depression story and trying to get a doctor to prescribe Zyprexa for depression, that would be promoting it for an off-label use, correct?

Torres, Denice M. (December 15, 2006)
503:21-504:3
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: If the activity was around asking physicians or insinuating to physicians that Zyprexa should be used exclusively for the treatment of depression, that would be wrong.

Torres, Denice M. (December 15, 2006)
504:14-21

Issues: 01 Plaintiff's Trial Designation

504:14 Ma'am, you knew or did you
15 know that when Zyprexa was launched to
16 the primary care, this Viva Zyprexa
17 market, you knew that there was not a
18 specific indication for Lilly
19 representatives to promote in the primary
20 care physician market? You knew that,
21 didn't you?

Torres, Denice M. (December 15, 2006)

504:24-505:2
Issues: 01 Plaintiff's Trial Designation

504:24 THE WITNESS: I don't know
505: 1 when the primary care group was
2 launched.

Torres, Denice M. (December 15, 2006)

506:3-507:4
Issues: 01 Plaintiff's Trial Designation

506: 3 Q. A challenge, what's a
4 challenge, ma'am?
5 A. A challenge is something
6 that you have to deal with.
7 Q. Right.
8 Do you see the language
9 here, "Zyprexa's primary indications -
10 schizophrenia and bipolar." Let me stop
11 here. Those are the only two
12 indications, not the primary ones.
13 They're the only indications, right?
14 Schizophrenia and bipolar mania, correct?
15 A. Yes.
16 Q. "Zyprexa's primary
17 indications - schizophrenia and bipolar -
18 are not viewed as PCP," primary care
19 physician "treated conditions, so,
20 there's not a specific indication for
21 Lilly representatives to promote in the
22 primary care physician" market.
23 Did I read that correctly?
24 A. You read it correctly.
507: 1 Q. Nevertheless, that didn't
2 stop Eli Lilly, did it? They went ahead
3 and marketed off label anyway, didn't
4 they?

Torres, Denice M. (December 15, 2006)

507:8-16
Issues: 01 Plaintiff's Trial Designation

Q. Didn't they?
A. What was the question?
Q. The fact that there's no indication in the label didn't stop Eli Lilly, they went ahead and promoted off label anyway, didn't they?
MR. WASSON: Objection.
THE WITNESS: Off label for what?

Torres, Denice M. (December 15, 2006)
507:18-508:1
Issues: 01 Plaintiff's Trial Designation

Q. Off label for Zyprexa.
The fact that -- let me rephrase the question.
The fact that something is off label, the condition is off label from Zyprexa didn't stop Eli Lilly. They would still promote the product for an off-label use, wouldn't they?

Torres, Denice M. (December 15, 2006)
508:4-23
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: No, sir. I mean, I would compare this to when Lilly launched Prozac, primary care physicians did not treat a lot of patients with depression. And it was because of Lilly's efforts and then Pfizer's efforts and then other company's efforts in terms of education that today depression is readily treated by primary care physicians.
So, at the time, was there a lot of treatment of bipolar mania patients? No. But, unfortunately, these patients go seven years before diagnosis is made. So, I would consider efforts to educate primary care physicians about bipolar a good thing for everyone.

Torres, Denice M. (December 15, 2006)
509:5-10
Issues: 01 Plaintiff's Trial Designation

509: 5 Q. My question to you simply
6 was, it didn't stop Eli Lilly from
7 promoting if a use was off label, did it?
8 MR. WASSON: Object to form.
9 THE WITNESS: I'm not aware
10 of an off-label promotion.

Torres, Denice M. (December 15, 2006)

510:5-8
Issues: 01 Plaintiff's Trial Designation

510: 5 Q. Did Eli Lilly have an
6 off-label strategy workshop to promote
7 the product to elderly people with
8 psychosis? This is Exhibit Number 27.

Torres, Denice M. (December 15, 2006)

510:13-15
Issues: 01 Plaintiff's Trial Designation

510:13 Q. And you knew about the
14 off-label workshop because you're on the
15 e-mail?

Torres, Denice M. (December 15, 2006)

510:18-512:14
Issues: 01 Plaintiff's Trial Designation

510:18 Q. "Subject:
19 Off-Label...Workshop," "Strategy
20 Workshop." October 2002. Do you recall
21 that?
22 A. I actually do recall this,
23 yes.
24 Q. Okay.
511: 1 Now, you've told us already,
2 there's no indication for dementia, is
3 there?
4 A. That's correct.
5 Q. There's no indication for
6 Alzheimer's, is there?
7 A. That's correct.
8 Q. There's no indication for
9 Alzheimer's or dementia-related symptoms
10 or side effects, is there?
11 A. That's correct.
12 Q. And this is an "Off-Label
13 Strategy Workshop"?
14 A. Actually, the person that
15 sent this out, there was quite a
16 hullalabu about this, because Jill Welch
17 said, I don't like the off-label term.
18 And that would have been --

Q. She was Jill Welch?
A. She was head of strategy and working for Jack Jordan.
Q. Yeah, she says that. She says, I do not like the 'off-label' term" and let's change to "'Elderly and new domains' maybe."
A. Actually, I think several people responded to this e-mail, because of the off label --
Q. Hey, ma'am. She says -- I'll read it to you. "I do not like the 'off-label' term - 'Elderly and new domains' maybe," correct?
A. That's what she said, yes.
Q. Okay.
We won't call it off-label workshop. We should call it an elderly and new domains maybe workshop; is that right?

Torres, Denice M. (December 15, 2006)
512:16-514:15
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: That's not what she's saying. She's saying off label, and everyone knows off label, bad connotations. What he's talking about is work in the elderly. This was during a time period when -- 2002, you know, the studies, we're still looking at the studies around Alzheimer's dementia.
BY MR. ALLEN:
Q. Ma'am, in 2002, Zyprexa was not indicated --
A. It was not indicated.
Q. -- for Alzheimer's and Alzheimer's dementia?
A. That's correct.
Q. Never had been.
A. That's correct.
Q. Shouldn't be promoted for it?
A. Shouldn't be promoted for it.
Q. Right.
Here it says in the e-mail, "A couple weeks ago when we stopped the borderline registration program." What was the borderline registration program?
A. It was a -- there were studies, if I remember correctly, studies that we were proposing, I don't remember if they started, to get an indication in

borderline.
Q. "It was clear that the domain" -- what's a domain? The term is used here. "It was clear that the domain." What's that?
A. I don't know what that refers to.
Q. "It was clear that the domain was too important to be dropped completely. Furthermore, it is important that any activity on off-label use in general gets incorporated in the organization and planning of the global Zyprexa team."
Did I read that correctly?
A. You did.

Torres, Denice M. (December 15, 2006)
527:17-530:4
Issues: 01 Plaintiff's Trial Designation

Exhibit 26 is an e-mail chain from Dr. Lechleiter. He's the number two man in charge at Eli Lilly, is he not?
A. Yes.
Q. He writes this e-mail to many people, and then there's some other chains, but he writes it's to Sidney Taurel. Who is Sidney Taurel?
A. The CEO of Lilly.
Q. He's the head man at Eli Lilly, right?
A. Yes.
Q. Okay.
And he's actually forwarding an e-mail that he received from Alan Breier, right, in November of 2001, correct?
A. Yes.
Q. Okay.
And in this e-mail, which you were a recipient of, right?
A. From Alan, yes.
Q. It says, "Update on Zyprexa Dementia Program." Do you see that, "Dementia Program"?
A. Yes.
Q. Did y'all have a program to promote Zyprexa to dementia patients?
A. We had studies ongoing in the area of dementia.
Q. The studies didn't turn out so well, did they?
A. No, they didn't.
Q. The studies determined that there was no proven safety or efficacy

for the use of Zyprexa in the elderly patients with either Alzheimer's, psychosis or dementia; isn't that true?

A. It says there were "mixed results."

Q. Well, let's see what it says. It says, "John, Following is an update on our Alzheimer's psychosis program."

Did I read that correctly?

A. Yes.

Q. "Zyprexa Product Team" -- you were on that, weren't you?

A. Yes, I was.

Q. -- "conducted 4 clinical trials with mixed results to support an indication for Alzheimer's psychosis," right? Right?

A. Yes.

Q. Now, ma'am, we don't have time, but the end result of the studies that were done did not support an indication for Alzheimer's psychosis, did it?

Torres, Denice M. (December 15, 2006)
530:6-20
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: I mean, it says that on the second page. I mean, Dr. Breier summarizes his points here. "We recommend not pursuing a formal indication for Alzheimer's psychosis because of the mixed clinical results, the need to initiate another global trial, the high FDA threshold, concerning safety risks, and strategic focus on high dose segments. The recommended approach is to support this segment with a publication strategy."

Torres, Denice M. (December 15, 2006)
530:23-532:12
Issues: 01 Plaintiff's Trial Designation

Your testing showed that there was not a proven indication on the testing, right? You could not support an indication on the testing?

A. With the clinical studies?

Q. Yes, ma'am.

A. Correct. Correct.
Q. Right.
Nevertheless, Dr. Breier says, "Lilly's current business in the elderly segment is about $500 million," right? Right?
A. I don't see that in here.
Q. Second page. It's right on the screen.
A. Okay, yes, uh-huh.
Q. As you just -- so, you sped read there. The bottom line is, he says, after "Lilly's current business in the elderly segment is about $500 million," he says, "We recommend not pursuing a formal indication for Alzheimer's psychosis because of the mixed clinical results, the need to initiate another global trial, the high FDA threshold, concerning safety risks, and strategic focus on high dose segments. The recommended approach is to support this segment with a publication strategy."
Did I read that correctly?
A. You did, sir.
Q. So, you couldn't get an indication from the FDA, but Dr. Breier says, we're not going to give up on promoting Zyprexa to the elderly, our approach will be to get publications out supporting the promotion to the elderly, correct?

Torres, Denice M. (December 15, 2006)
532:15-533:21
Issues: 01 Plaintiff's Trial Designation

THE WITNESS: There's two ways to read this. One is to "support this segment." Okay. Support this segment. There's $500 million, there's use in there. So, support this segment is one thing. That would be entirely correct.
If what he was saying here was to support the promotion of Alzheimer's dementia with a publication strategy, that would be wrong. I don't know exactly what he meant by that. There's two interpretations. But I couldn't tell you what Dr. Breier meant.
BY MR. ALLEN:
Q. At least we know he says we're doing $500 million in the elderly

worth of business, right?
A. He did say that.
Q. And he's also saying we can't support an indication in the elderly because the studies are mixed in that regard, right?
A. He did say that.
Q. And he's saying here's what we're going to do. Our approach will be to support the elderly through the publication plan, right?

Torres, Denice M. (December 15, 2006)
534:8-8
Issues: 01 Plaintiff's Trial Designation

534: 8 A. That's what he said.

Torres, Denice M. (December 15, 2006)
534:12-20
Issues: 01 Plaintiff's Trial Designation

534:12 Q. All of this is not only reported by Dr. Breier, the head of the Zyprexa product team, it's reported up to John Lechleiter, the second in command of your company, who reports it to the CEO of the entire company, Sidney Taurel, right?
A. That's what the e-mail said, yes.

Torres, Denice M. (December 15, 2006)
535:17-538:15
Issues: 01 Plaintiff's Trial Designation

535:17 Q. Ma'am, is this Exhibit 29? I apologize.
A. Yes, it is, sir.
Q. This is an e-mail chain.
A. I remember this e-mail.
Q. How do you remember this e-mail?
A. I remember because when it
536: 1 came across my desk, there was a reference on Page 3 or 4 of --
Q. Of what?
A. It's bolded. "It appears to me that the fact we are now talking to child psychs and peds" -- I'm sorry. The bolded section. The fact about seizing "the opportunity to expand our work with Zyprexa in the same child-adolescent

population" was a statement that was not supported by regulatory, promotional law and is an inappropriate statement.

Q. Well, that's where we're heading. But this e-mail chain, you received this e-mail, right?

A. Absolutely. And took action on it. I had a discussion with Dr. Breier. Dr. Breier, I believe, sent an e-mail, but also had a discussion with John Lechleiter.

Q. And just for the record, John Lechleiter is the one that wrote this e-mail chain, right?

A. Yes, he did, sir.

Q. And Dr. -- is it Dr. Lechleiter?

A. Yes, it is.

Q. He's second in command at your entire company; isn't that right?

A. That's correct.

Q. And what he says in this e-mail is, "Attached are my notes from a recent visit to Cincinnati in late February, where I met with a group of our Neuroscience sales representatives and spent part of the next day in the field calling on psychiatrists. I have highlighted" -- this is what he says. "I have highlighted in bold the inputs that I consider to be most significant or that came up most often, and would appreciate if the global" -- that's you, right -- "and U.S. teams would follow up as appropriate," correct?

A. Yes.

Q. Now, Dr. Lechleiter is going in the field with the sales representatives, is what he's doing on this trip, right?

A. Yes.

Q. He says in bold that I want you, the global and U.S. teams, to follow up on what I found in out in the field, right?

A. Yes.

Q. Now, some of this is redacted. I'm going under Zyprexa on the next page. You said you remember this e-mail, right?

A. I do.

Q. This e-mail concerns off-label marketing and promotion, doesn't it?

Torres, Denice M. (December 15, 2006)
538:19-20
Issues: 01 Plaintiff's Trial Designation

538:19 A. The -- John's note was
20 inappropriate.

Torres, Denice M. (December 15, 2006)
538:22-539:3
Issues: 01 Plaintiff's Trial Designation

538:22 My question to you was,
23 John, which is Dr. Lechleiter, second in
24 command at Eli Lilly in 2003, is writing
539: 1 a memo concerning off-label promotion of
2 Zyprexa to pediatric and adolescent
3 patients, right?

Torres, Denice M. (December 15, 2006)
539:5-8
Issues: 01 Plaintiff's Trial Designation

539: 5 THE WITNESS: He doesn't say
6 that. He says, "we must seize the
7 opportunity to expand our work
8 with Zyprexa" --

Torres, Denice M. (December 15, 2006)
539:10-540:24
Issues: 01 Plaintiff's Trial Designation

539:10 THE WITNESS: He says, "we
11 must seize the opportunity to
12 expand our work with Zyprexa in
13 this same child-adolescent
14 population."
15 That's what he says. He
16 doesn't go on to talk about off
17 label. The fact is, John was new,
18 and when he went out to the field,
19 he was new in this marketing
20 capacity. Following this memo,
21 Dr. Breier talked to him and said
22 let's talk about, you know,
23 promotional regulation.
24 BY MR. ALLEN:
540: 1 Q. **How do you know? Were you**
2 **privy to the conversation between Dr.**
3 **Breier and Dr. Lechleiter?**
4 A. No. Dr. Breier told me he
5 had that conversation with him, and I
6 believed him.
7 Q. **When did Dr. Breier tell you**
8 **this?**
9 A. Well, the day the e-mail
10 came out, I went and talked to Alan and

said that's inappropriate.
Q. Why didn't you write an e-mail back and say this was inappropriate?
A. I thought Alan would address it with his boss. I can't remember. I may have written an e-mail to Alan. He was down the hall from me. I thought it was inappropriate.
Q. I don't see any e-mails from either you or Dr. Breier telling Dr. Lechleiter that his conduct was inappropriate. Are you familiar with such e-mails?

Torres, Denice M. (December 15, 2006)
541:3-6
Issues: 01 Plaintiff's Trial Designation

541: 3 THE WITNESS: I don't -- I
4 had the conversation. Dr. Breier
5 said he had talked -- was going to
6 and had talked to Dr. Lechleiter.

Torres, Denice M. (December 15, 2006)
541:13-24
Issues: 01 Plaintiff's Trial Designation

541:13 My question to you was, are
14 you familiar with any e-mails being
15 written by yourself, Dr. Breier or
16 anybody else saying Dr. Lechleiter's
17 conduct in regard to exhibit -- what's
18 the number -- 29 is inappropriate?
19 A. I thought I wrote an e-mail.
20 I honestly don't remember. I do remember
21 having a conversation.
22 Q. Dr. Lechleiter says, "we
23 need to seize the opportunity." Doesn't
24 he say that?

Torres, Denice M. (December 15, 2006)
542:1-2
Issues: 01 Plaintiff's Trial Designation

542: 1 A. I think you've read that
2 twice already, yes.

Torres, Denice M. (December 15, 2006)
544:20-22
Issues: 01 Plaintiff's Trial Designation

544:20 Ms. Torres, we're on Exhibit
21 29, Dr. Lechleiter's e-mail concerning
22 off-label promotion. Do you follow me?

Torres, Denice M. (December 15, 2006)
545:7-13
Issues: 01 Plaintiff's Trial Designation

545: 7 THE WITNESS: Nowhere does
8 it here say anything about
9 off-label promotion. It wasn't an
10 e-mail about off-label promotion.
11 It was an e-mail about his notes
12 from a day in the field with
13 neuroscience reps.

Torres, Denice M. (December 15, 2006)
545:15-546:5
Issues: 01 Plaintiff's Trial Designation

545:15 Q. Did it concern you?
16 A. This statement, I've said it
17 several times, did concern me, but I also
18 knew --
19 Q. What's the statement? Read
20 it out loud and slowly for the jury,
21 please.
22 A. "It appears to me that the
23 fact we are now talking to child psychs
24 and peds and others about Strattera means
546: 1 that we must seize the opportunity to
2 expand our work with Zyprexa in this same
3 child-adolescent population."
4 Q. That would be off-label
5 promotion, wouldn't it?

Torres, Denice M. (December 15, 2006)
546:7-23
Issues: 01 Plaintiff's Trial Designation

546: 7 THE WITNESS: If we were
8 talking to physicians about an
9 indication for child-adolescent
10 with Zyprexa, that would be
11 off-label promotion.
12 BY MR. ALLEN:
13 Q. Now, Dr. Lechleiter, when he
14 writes this e-mail and he says under
15 "Physician comments," "Comment made that
16 we are losing scripts to Risperdal for
17 treatment of disruptive kids because J &
18 J has the data and we don't." Did I read
19 that correctly?

A. Yes, you did.
Q. Was Zyprexa indicated for disruptive kids?
A. No.

Torres, Denice M. (December 15, 2006)
546:24-547:13
Issues: 01 Plaintiff's Trial Designation

546:24 Q. Was it indicated for
547: 1 children with attention deficit or
2 hyperactivity disorder?
3 A. No.
4 Q. Was it indicated for any
5 pediatric patients?
6 A. No.
7 Q. Was it indicated for any
8 pediatric patients for anything?
9 A. No.
10 Q. It would be wrong to even
11 consider having your sales reps seize the
12 opportunity and try to market Zyprexa to
13 pediatric patients, wouldn't it?

Torres, Denice M. (December 15, 2006)
547:15-17
Issues: 01 Plaintiff's Trial Designation

547:15 THE WITNESS: Under the
16 guise of an indication, yes, it
17 would.

Torres, Denice M. (December 15, 2006)
548:9-21
Issues: 01 Plaintiff's Trial Designation

548: 9 Remember he said whatever is
10 in bold is the most important thing.
11 Remember that? He said what I put in
12 bold is the most important or words to
13 that effect. "I have highlighted in
14 bold, the inputs that I consider to be
15 most significant." Right? Right?
16 A. That's what it says, yes.
17 Q. The next thing is in bold,
18 "With child psychs, Zyprexa is a distant
19 third across a range of disorders."
20 Did I read that correctly?
21 A. Yes.

Torres, Denice M. (December 15, 2006)
549:8-12

Issues: 01 Plaintiff's Trial Designation

549: 8 First of all, there was not
9 a range of disorders for which Zyprexa
10 was indicated, was it?
11 A. No. Just schizophrenia and
12 bipolar mania.

Torres, Denice M. (December 15, 2006)

550:19-551:3
Issues: 01 Plaintiff's Trial Designation

550:19 Q. So, when he says "Zyprexa is
20 a distant third across a range of
21 disorders" for pediatric patients, the
22 fact of the matter is, even in adult
23 patients there wasn't a range of
24 disorders other than bipolar mania,
551: 1 schizophrenia, and later bipolar
2 maintenance that could even be used in
3 adults; is that right?

Torres, Denice M. (December 15, 2006)

551:5-19
Issues: 01 Plaintiff's Trial Designation

551: 5 THE WITNESS: Yes. There
6 were three indications. I don't
7 know what he meant by this. I
8 don't know what he meant by this
9 statement. I could tell you there
10 were two indications and then
11 three -- how many indications are
12 there now? I don't know. I don't
13 know what he meant by this.
14 BY MR. ALLEN:
15 Q. He then has an "editorial
16 note." This is his words. "Editorial
17 Note: It appears to me" -- now, "me" is
18 the second highest person in the company,
19 right?

Torres, Denice M. (December 15, 2006)

552:1-19
Issues: 01 Plaintiff's Trial Designation

552: 1 A. Yes.
2 Q. What was his position back
3 at the time this was written?
4 A. He had just -- I remember
5 when he went out in the field, he was --
6 his doctor is a Ph.D. and he had just
7 been, I guess, promoted and assigned a

responsibility to take over marketing. So, I mean, I looked at this and said, I know John. John would not intentionally do something that was illegal. And I looked at this and said, you know what, I don't think he knows some of the promotional laws. That was the discussion I had with Alan.

Q. You have no notes about that discussion, you have no e-mails about that discussion, you have no documents about this alleged discussion, do you?

Torres, Denice M. (December 15, 2006)
552:21-22
Issues: 01 Plaintiff's Trial Designation

552:21 THE WITNESS: Why don't you
22 ask Dr. Breier.

Torres, Denice M. (December 15, 2006)
553:3-554:6
Issues: 01 Plaintiff's Trial Designation

553: 3 A. I thought I wrote an e-mail
4 to Alan. I don't remember for sure. I
5 remember seeing the e-mail. I remember
6 having a discussion with Alan. I don't
7 remember other specifics.
8 Q. But all you know --
9 A. That's all I remember.
10 Q. All you know is Dr.
11 Lechleiter took over, was in charge of
12 marketing at the time he wrote this
13 e-mail?
14 A. No. He was in charge of
15 U.S. affiliate.
16 Q. I got you.
17 A. So, U.S. affiliate having
18 all the different elements to it.
19 Q. Dr. Lechleiter, at the time
20 he wrote this e-mail, was in charge of
21 the U.S. affiliate marketing, was he not?
22 A. He was in charge of the U.S.
23 affiliate, marketing being part of that.
24 Q. Right.
554: 1 So, when we have this
2 e-mail, Exhibit 29, written by Dr.
3 Lechleiter, it's written by the person at
4 the entire drug company who is in charge
5 of marketing in the U.S. affiliate,
6 right?

554:9-19
Issues: 01 Plaintiff's Trial Designation

554: 9 THE WITNESS: He had just
10 taken over the job. Did anyone
11 look at this and go, oh, gosh,
12 look what John is asking us to do?
13 No, that did not happen.
14 BY MR. ALLEN:
15 Q. "Editorial note: It
16 appears to me that the fact we are now
17 talking to child psychiatrists." Now,
18 why would you want to even go detail a
19 child psychiatrist on Zyprexa?

Torres, Denice M. (December 15, 2006)

554:23-555:22
Issues: 01 Plaintiff's Trial Designation

554:23 Q. See, if it's not indicated,
24 why are you going to detail the child
555: 1 psychiatrist about Zyprexa when it's not
2 indicated?
3 A. I don't know why he was. He
4 was there for Strattera.
5 Q. And peds, P-E-D-S that's
6 pediatricians, right?
7 A. He says, "It appears to
8 me... talking to child psychs...and
9 others about Strattera."
10 Q. "About Strattera" means?
11 A. Strattera is indicated for
12 attention deficit disorder. They would
13 be talking to psychs and peds.
14 Q. "Means we must seize the
15 opportunity to expand our work with
16 Zyprexa in this same child-adolescent
17 population." Correct? Isn't that what
18 he wrote?
19 A. That's what he wrote.
20 Q. So, he's -- in his role, he
21 is advocating that we market off label,
22 correct?

Torres, Denice M. (December 15, 2006)

556:1-6
Issues: 01 Plaintiff's Trial Designation

556: 1 THE WITNESS: No. He wrote
2 a comment. Nobody took it
3 seriously. They thought, John is
4 coming in, he doesn't know all the
5 promotional regulations. That's
6 what we thought.

Torres, Denice M. (December 15, 2006)
556:16-557:4
Issues: 01 Plaintiff's Trial Designation

556:16 Q. You are a recipient of this
17 e-mail, are you not?
18 A. I am. I'm telling you what
19 I -- I read it, I read it back to you.
20 This is what I thought about it. I don't
21 know what John thought. I had a
22 conversation with Alan. That's all I
23 know.
24 Q. Well, Eli Lilly had
557: 1 supported through educational grants the
2 use of Zyprexa in antipsychotic therapy
3 in children and adolescents, hadn't it?
4 A. I have no idea.

Torres, Denice M. (December 15, 2006)
557:13-558:11
Issues: 01 Plaintiff's Trial Designation

557:13 Q. Let me ask you this. Have
14 you ever seen Exhibit 30?
15 A. No.
16 Q. "Antipsychotic Therapy in
17 Children and Adolescents."
18 A. No, I haven't.
19 Q. Let me go to the third page.
20 "We wish to acknowledge that the
21 continuing education materials were made
22 possible by an unrestricted educational
23 grant from Eli Lilly & Company of
24 Indianapolis, Indiana.
558: 1 "The presenter of this
2 activity has indicated that there is a
3 relationship which, in the context of
4 this presentation, could be perceived as
5 a real or apparent conflict of interest,"
6 for example, "(...honoraria), but does
7 not consider that it will influence the
8 presentation of this continuing education
9 activity." Did I read that correctly?
10 A. I'm sorry. What page is
11 that?

Torres, Denice M. (December 15, 2006)
558:15-16
Issues: 01 Plaintiff's Trial Designation

558:15 THE WITNESS: Yes. You read
16 that paragraph correctly.

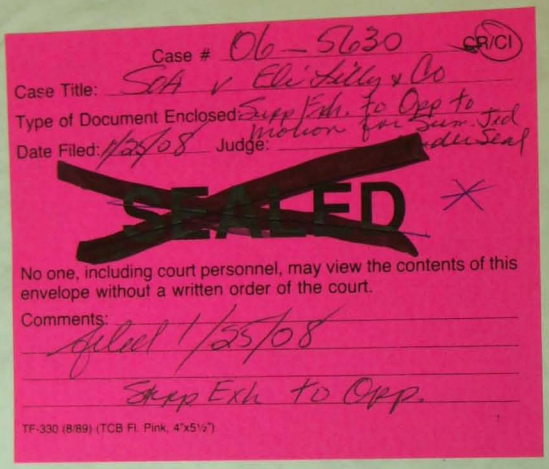
Torres, Denice M. (December 15, 2006)
558:19-559:9
Issues: 01 Plaintiff's Trial Designation

Eli Lilly, if you look on the very last page of this document entitled "Antipsychotic Therapy in Children and Adolescents," was supported by a educational grant from Eli Lilly & Company, right? Very last page?
A. "Made possible by an unrestricted educational grant."
Q. Here's what it says. I'll read it slowly. "The continuing educational materials" contained in this activity" were made possible by an unrestricted educational grant from Eli Lilly & Company." Did I read that right?
A. Yes, you did, sir.

Torres, Denice M. (December 15, 2006)
560:9-561:5
Issues: 01 Plaintiff's Trial Designation

Q. Ma'am, we were almost through, but we'll read exactly what it says. First it was supported by an "educational grant from Eli Lilly," right? On page 3, right?
A. Yes.
Q. Under there it says, "By completing this activity, participants will be able to: Discuss the prevalence and epidemiology of childhood onset schizophrenia." Does it say that?
A. Yes.
Q. And then it goes on, "Identify childhood psychiatric disorders that are effectively treated with antipsychotics." Do you see that?
A. I do see that.
Q. Now, this Zyprexa was not indicated for any childhood psychiatric disorder, was it?
A. Zyprexa? No.

06-5630 CA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Case Title: SEC v Eli Lilly & Co
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Dispositive #1

* See Judge Rindner's 6/13/08 order pages 25; 26, #1

documents unsealed per Judge 8/11/08

Pages 6930-6966

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, vs. ELI LILLY AND COMPANY, Defendant.	Case No. 3AN-06-5630 CIV

NOTICE OF FILING SUPPLEMENTAL PAGE 77 UNDER SEAL

On this date the State of Alaska is filing a pleading titled "Supplemental Page 77 to Plaintiff's Trial Deposition Designations." Because this page may be confidential under the Court's April 6, 2007 oral ruling, the State of Alaska is submitting this page under seal.

See Judge Rindner's 6/13/08 order
page 22, #20
Document unsealed Lwade 8/11/08

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006929A

Page 6929B

olanzapine-associated weight changes, parens,
OWC, close parens, period?"
A. Yes, I see that.
Q. Who's "John"?
A. I don't know yet.

Michael Bandick (June 9, 2006)

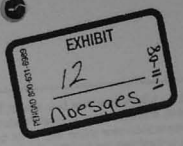
384: 5 Q. My question is: The only
6 John I see in there is John Lechleiter, is
7 that how you pronounce his name?

Michael Bandick (June 9, 2006)

384:11 Q. Assume with me the only John
12 referenced in this e-mail is John Lechleiter.
13 Who is John Lechleiter?
14 A. I can't assume that that's
15 the only John that could be referenced.
16 John Lechleiter, currently, I
17 believe, he's the President and Chief
18 Operating Officer of the company. He did not
19 have that role in 1999.
20 Q. Okay. Anyhow, the e-mail
21 says "John asked know the overview the topic
22 of olanzapine-associated weight changes,
23 parens, OWC, close presents, period.
24 I read that correctly, right?

Michael Bandick (June 9, 2006)

385: 8 Q. Did I read that sentence
9 correctly?
10 A. It appears that you did.
11 Q. Okay. Skipping down in this
12 paragraph to the third sentence says,
13 "Although," and I'll read it out loud.
14 "Although it is a significant issue for us,
15 perhaps our only/major clinical Achilles
16 heel, and our competitors have robustly
17 focused on it, parens, reminiscent of anxiety
18 and, redacted, close parens, the fact is
19 Zyprexa offers the best combination of
20 efficacy, safety, and ease of use of any
21 available treatment for psychosis and acute
22 mania. The most critical immediate issue is
23 to keep the focus where it belongs --
24 superior treatment and outcome -- an arena
386: 1 where we have no peer. What follows is a
2 high level review."
3 Did I read that portion of
4 the e-mail correctly?
5 A. Yes.
6 Q. And wasn't it always the
7 position of the Zyprexa marketing department
8 that Zyprexa provided superior treatment and
9 outcome and Zyprexa had no peer?



NAME = Williams, Margaret
CALLDATE = 05/17/2002
CALLID = 68130738
PRESCRIBERLN = Flores
PRESCRIBERFN = Kathryn
CITY = Soldotna
STATE = AK
ACTION : **********R**********Also got in a decent ZYP recap, reminded doc that ZYP is a great mood stabilizer, esp for pats whose symptoms were aggravated by an SSRI... Dr. Anderson just stabilized a bipolar pat earlier this week on 15 mg. Went over Lilly Answers Program with Anderson, Sheridan, and Flores and their nurses. Dr. Deede and Lori the PA were off, so no one was over on that side of the clinic. Still need to go over Lilly Answers Program w/them.
REACTION : Excellent, see above! Also visited personally with Sheridan and Flores.
FOLLOWUP : Review Hirschfeld Scales for ZYP recap*****R*****. Dr. Deede and Lori the PA were off, so no one was over on that side of the clinic. Still need to go over Lilly Answers Program w/them.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1500

NAME = Williams, Margaret
CALLDATE = 05/17/2002
CALLID = 68130741
PRESCRIBERLN = McIntosh
PRESCRIBERFN = Marguerite
CITY = Soldotna
STATE = AK
ACTION : **********R**********, ZYP mention only.
REACTION : Great with staff, good with doc.
FOLLOWUP : Really work ZYP via pat whose symptoms are aggravated by an SSRI, emphasize ZYP as a mood stabilizer.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1501

NAME = Williams, Margaret
CALLDATE = 06/06/2002
CALLID = 68698813
PRESCRIBERLN = Dahms
PRESCRIBERFN = Laurie
CITY = Palmer
STATE = AK
ACTION : Actually got in a decent ZYP detail for pats with unresolved symptoms, pats who fail on an SSRI, patients could be suffering from complicated mood disorder, perhaps bipolar, ZYP is an excellent mood stabilizer, very safe, easy to dose. Got in part of this with Moser too, and he was even agreeable, says he does treat bipolar patients... Just quick product mentions with Dr. Werner.
REACTION : Good, actually! Gee whiz, perhaps Moser is finally opening up to ZYP...
FOLLOWUP : Keep working ZYP, but softly...
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1565

NAME = Kristen Clouthier
CALLDATE = 06/27/2002
CALLID = 69271199
PRESCRIBERLN = Grant
PRESCRIBERFN = Madeleine
CITY = Anchorage
STATE = AK
ACTION : office luncheon, zyprexa dvd, cathy and donna, **********R**********
REACTION : **********R**********

**********R********** Zyprexa dvd was successful - it enerate many questions and conversation regarding the proper pt type. Julie Wilson, a new md there (was a resident at Prov) is interested to find out what the injectible zyprexa is used for. Pam engle was concerned about weight gain for those zyprexa pts but we discussed proper diet and the fact that if pts are feeling better perhaps they will be able to actually excercise. Also discussed the mechanism of zyprexa and that the drug does not cause weight gain, but it does increase the pts appetite. Suggested that when she prescribe zyprexa she discuss with her pts to let her know if they feel they are eating more. Dr. Hunt gave the example of using zyprexa most commonly for pts who have failed 2 ssri's and also for wont spanish ts in need that wont see psychs due to langueage barriers. He often manages those pts. Very important - anh is hiring two new psych nurse practicioners on staff within the next few months - so zyprexa pts may be handled in house in the future. One nurse on 10th and one on Mtn View.

FOLLOWUP : perhaps the two new nurses could pull charts of failing ssri pts and provide zyprexa opportunity. see what hunt thinks.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1632

NAME = Kristen Clouthier
CALLDATE = 06/27/2002
CALLID = 69271200
PRESCRIBERLN = Engle
PRESCRIBERFN = Pam
CITY = Anchorage
STATE = AK
ACTION : office luncheon, zyprexa dvd, cathy and donna. **********R**********
REACTION : **********R**********

**********R********** Zyprexa dvd was successful - it enerate many questions and conversation regarding the proper pt type. Julie Wilson, a new md there (was a resident at Prov) is interested to find out what the injectible zyprexa is used for. Pam engle was concerned about weight gain for those zyprexa pts but we discussed proper diet and the fact that if pts are feeling better perhaps they will be able to actually excercise. Also discussed the mechanism of zyprexa and that the drug does not cause weight gain, but it does increase the pts appetite. Suggested that when she prescribe zyprexa she discuss with her pts to let her know if they feel they are eating more. Dr. Hunt gave the example of using zyprexa most commonly for pts who have failed 2 ssri's and also for wont spanish ts in need that wont see psychs due to langueage barriers. He often manages those pts. Very important - anh is hiring two new psych nurse practicioners on staff within the next few months - so zyprexa pts may be handled in house in the future. One nurse on 10th and one on Mtn View.

FOLLOWUP : perhaps the two new nurses could pull charts of failing ssri pts and provide zyprexa opportunity. see what hunt thinks.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1633

NAME = Kristen Clouthier
CALLDATE = 06/27/2002
CALLID = 69271206
PRESCRIBERLN = Mackie
PRESCRIBERFN = Scott
CITY = Anchorage
STATE = AK
ACTION : office call - brought ****R*****zyprexa bag of goodies, chocolates, cherries, dried fruit. showed fishing pictures. Invite to both zyprexa ****R**** programs
REACTION : **********R********** dr. mackie graduated cum laude also and was in the top 10% of his medical class - very impressive - discussed zyprexa and ssri failure as his pt type but also alot of elderly. he is very aware of zyprexa and its uses. sharp man! He said he may attend the zyprexa program , give reminder.

FOLLOWUP : dvd, ***R*** zyprexa
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1635

NAME = Kristen Clouthier
CALLDATE = 07/10/2002
CALLID = 69529152

PRESCRIBERLN = Nolte
PRESCRIBERFN = Miriam
CITY = Anchorage
STATE = AK
ACTION : office call - reminders, zyp water bottles, digfast hascale, donna pt, **********R**********
REACTION : busy, quick reminders dosing and pt types **********R********** zyp donna and ssri failure dosing- invites to programs - are attending july 16th

FOLLOWUP : na
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1663

NAME = Kristen Clouthier
CALLDATE = 07/11/2002
CALLID = 69495263
PRESCRIBERLN = Flores
PRESCRIBERFN = Kathryn
CITY = Soldotna
STATE = AK
ACTION : **********R********** zyp desk reference and digfast - chocolate chip cookies of course for dr. anderson.
REACTION : he was leaving for a surgery in a minute so only reminders, but had some good time with kathy - discussed elderly and ssri failure pts , digfast tool and she was interested in the h questionaire - said it was good to have on hand for coding work and determining proper pt - reminded her about the program marvin.

FOLLOWUP : na
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1666

NAME = Kristen Clouthier
CALLDATE = 07/11/2002
CALLID = 69495268
PRESCRIBERLN = Davidhizar
PRESCRIBERFN = Lavern
CITY = Soldotna
STATE = AK
ACTION : intro of self and products again - left idc chart, **********R********** zyp desk ref and digfast
REACTION : was very nice, discussed marvin program - said he would be in town for it - would callif can make it - probably needs a reminder that morning so he will come. discussed zyp pt type - elderly and ssri pt, also angered or agitated, cant keep a job,marraige pt and dosing,- he said he has seen many people come through the door like that.

FOLLOWUP : reminder for program
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1667

NAME = Kristen Clouthier
CALLDATE = 07/11/2002
CALLID = 69495269
PRESCRIBERLN = Sanders
PRESCRIBERFN = Jim
CITY = Soldotna
STATE = AK
ACTION : *******R******** pens, pads, zyp desk reference, digfast, bag of goodies
REACTION : **********R**********quickly zyp digfast and proper dosing for elderly, ssri pt, donna t and the extreme mood disrder. invite to program.

FOLLOWUP : more on zyp
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1668

NAME = Kristen Clouthier
CALLDATE = 07/12/2002
CALLID = 69529146
PRESCRIBERLN = White, Jr.
PRESCRIBERFN = Roy Matison
CITY = Anchorage

STATE = AK
ACTION : lunch w/michele - **********R********** zyprexa h scale, digfast cards, preper pt focus - invites to programs
REACTION : complaints from lanza, jones, taylor, schultes, coalwell if cant bring wife wont come to programs anymore. **********R********** zyprexa pt type - elderly, multiple ssri, dosing digfast cheat sheet and key and h scale information - all found scale useful and discussed safety of zyp. vs other agents - scheultes asked about zyp and diabetes - was able to respond according and discuss moa of zyprexa- increase in appetitie which may lead to obesity but no causal relationship established between zyp and diabetes - also compared to other agents there is no increased incidence with zyp - high risk rate in this population anyway - he would like medical letter- but was satified with answer. **********R**********

FOLLOWUP : **********R**********
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1678

NAME = Kristen Clouthier
CALLDATE = 07/12/2002
CALLID = 69529148
PRESCRIBERLN = Coalwell
PRESCRIBERFN = Timothy
CITY = Anchorage
STATE = AK
ACTION : lunch w/michele - **********R********** zyprexa h scale, digfast cards, preper pt focus - invites to programs
REACTION : complaints from lanza, jones, taylor, schultes, coalwell if cant bring wife wont come to programs anymore. **********R********** zyprexa pt type - elderly, multiple ssri, dosing digfast cheat sheet and key and h scale information - all found scale useful and discussed safety of zyp. vs other agents - scheultes asked about zyp and diabetes - was able to respond according and discuss moa of zyprexa- increase in appetitie which may lead to obesity but no causal relationship established between zyp and diabetes - also compared to other agents there is no increased incidence with zyp - high risk rate in this population anyway - he would like medical letter- but was satified with answer. **********R**********

FOLLOWUP : **********R**********
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1679

NAME = Kristen Clouthier
CALLDATE = 07/15/2002
CALLID = 69571711
PRESCRIBERLN = Hagen
PRESCRIBERFN = Derek
CITY = Anchorage
STATE = AK
ACTION : office luncheon - **********R********** zyprexa reminder of ssri pt, elderly pt and thick chart donna pt, indications, dosing appropriate startting dose, digfast cards - h scale questionnaire.
REACTION : maples just started here, oberstad and maples covering out of town docs pts - alot of elderly from smith

whenever he is out - perfect zyp pt - they all took the digfast - found it useful and will use - especially foland - ********** R********** ***R********** zyp dvd again for different pt population

FOLLOWUP : **********R**********

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1687

NAME = Kristen Clouthier
CALLDATE = 09/11/2002
CALLID = 71297363
PRESCRIBERLN = Bosveld
PRESCRIBERFN = Robert
CITY = Anchorage
STATE = AK
ACTION : office call - **********R********** book for dr farr from marvan - cme for dr farr.

REACTION : dr little will be golfing this next weekend - in ak with steer - hasnt diagnose anyone for zyp yet but looking. bosveld said he looked up zyp in tthe drug manual and it was classified as a psychotic - i discussed the indication of zyp and that the original studies were done for schizo pts - and that fda changed our pi to be a novel psychotropic - which encompasses modd stabilization. he asked if can use it as an ssri - said no it is not indicated as an antideppressant or for mood depressant but it does have stabilization for both negative and positive symptoms - he was satisfied with that. *******R*******

FOLLOWUP : reminders reminders reminders - dr farr - cme?applebaum
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1950

NAME = Williams, Margaret
CALLDATE = 09/13/2002
CALLID = 71335378
PRESCRIBERLN = Bartling
PRESCRIBERFN = Victor
CITY = Fairbanks
STATE = AK
ACTION : Took in my usual muffins, got brief but decent detail time with each key doc, focused on Maguire recap, focused on bipolar patients and how ZYP is an efficacious, safe, and easy to dose mood stabilizer... The mood stabilizer light bulb seemed to finally "turn on" for Dr. Steiner, he did not remember that ZYP is a mood stabilizer, agreed that 1 of 3 pats depressed are bipolar depressed, has had patients get manic on an SSRI, so was all of a sudden rather interested in ZYP and was surprised ZYP is indicated for bipolar mania, his issue with ZYP is wt gain, send med letter on ZYP being used for bipolar disorder in general and strategies to manage potential weight gain. Dr. Judkins stated that he thinks primary care physicians will start to treat more and more bipolar pats since the medication (ZYP) is easy to dose, very safe, and actually works! Dr. Bartling declined being trained as a speaker (did really consider this and was complimented) as he has a very busy schedule at TVC, he's also the director of the Denali Nursing Home at the FBKS Memorial Hospital, and has several children. He and I discussed ZYP use in the elderly in more detail, but bipolar as well. Bartling wants more info on using ZYP in the elderly... All 4 docs just loved my Girdwood Forest Fair parade baby float photos, I knew they would! **********R**********

REACTION : Really friendly, actually. Even Dr. Steiner thanked me for kind of "interrupting" him and impressing upon him that ZYP IS indicated for bipolar mania and is a mood stabilizer...

FOLLOWUP : ZYP via handheld DVD...
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1960

NAME = Kristen Clouthier
CALLDATE = 09/13/2002
CALLID = 71468519
PRESCRIBERLN = Brock
PRESCRIBERFN = Heather
CITY = Anchorage
STATE = AK
ACTION : office call - samples, ****R***** pt education, goody bags, zyp pt education, cme opportunities- follow up with

hunt and heather for speaking times

REACTION : Heather - got the message about need ing dates- she is taking boards monday so very proccupied at the moment - will discuss wiht hunt mid next week and call. hunt - still interested yes - chld is sick so going home to work - will call me fter he and heather talk. grant - thank yous for the samples - ********** sharon smith - having ********** great success with zyp on her most dificult pts too - realizes weight can be managed but has a cuople pts ballooned up - she says she cant get these pts here to fill out any forms - discussed 5 minute sit down for behavioral and weight watchers... Jill johnson - always nice as can be - asked about using zyp as add on therapy to ssri - said not indicated there but third partied marvan and mcguire - it has been used in that instance - discusses quick efect. - **********

FOLLOWUP : follow up with spanish zyp pt education, spanish weight mgmt guides, water bottles for office and heather hunt talks.

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order

BATESNUMBER : ZYAKAG3 1963

NAME = Kristen Clouthier
CALLDATE = 09/13/2002
CALLID = 71468521
PRESCRIBERLN = Johnson
PRESCRIBERFN = Jill
CITY = Anchorage
STATE = AK
ACTION : office call - samples, *****R****** pt education, goody bags, zyp pt education, cme opportunities- follow up with hunt and heather for speaking times

REACTION : Heather - got the message about need ing dates- she is taking boards monday so very proccupied at the moment - will discuss wiht hunt mid next week and call. hunt - still interested yes - chld is sick so going home to work - will call me fter he and heather talk. grant - thank yous for the samples - ********** is interested in the cme - sharon smith - having ********** great success with zyp on her most dificult pts too - realizes weight can be managed but has a cuople pts ballooned up - she says she cant get these pts here to fill out any forms - discussed 5 minute sit down for behavioral and weight watchers... Jill johnson - always nice as can be - asked about using zyp as add on therapy to ssri - said not indicated there but third partied marvan and mcguire - it has been used in that instance - discusses quick efect. - **********

FOLLOWUP : follow up with spanish zyp pt education, spanish weight mgmt guides, water bottles for office and heather hunt talks.

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order

BATESNUMBER : ZYAKAG3 1964

NAME = Kristen Clouthier
CALLDATE = 10/22/2002
CALLID = 72417917
PRESCRIBERLN = Judkins
PRESCRIBERFN = Hunter
CITY = Fairbanks
STATE = AK
ACTION : office call - zyp slim jim, cme, digfast card

REACTION : he has tried zyp sucessfully- reminded him of the apa - he said he has used it for a couple of pts that have been previously treated with ssri and they became agitated or irritable. - no concerns at the moment - provided cme op to him - **********R********** also elaborate on how to diagnose more pts - broader pt profile - compared vs risperdol and indications

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order

BATESNUMBER : ZYAKAG3 2106

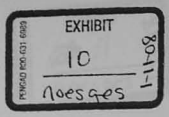
NAME = Warren, John K
CALLDATE = 08/18/2003
CALLID = 80158589
PRESCRIBERLN = Steer
PRESCRIBERFN = Paul
CITY = Anchorage
STATE = AK
ACTION : met Dr. S. but he was in a rush so only had a minute to talk. asked him what he uses seroquel for?

REACTION : for patients not responding to ssri. rep sold him on it.

FOLLOWUP : follow up and spend time of quality of Zyp. vs. Seroquel.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 2939

NAME = Warren, John K
CALLDATE = 10/14/2003
CALLID = 81807470
PRESCRIBERLN = Farr
PRESCRIBERFN = Ilona
CITY = Anchorage
STATE = AK
ACTION : quick visit to see Dr. Farr - also saw Dr Trujillo. briefiyasked about depression pts.and success with SSRI treatment. set up a lunch wirth office and also may need to take Dr. Farr out for lunch to avoid interruptions. Need to remember to hammmer Zyp. safety versus Risperdal.

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 3133

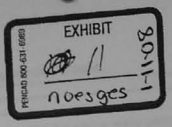


NAME = Williams, Margaret
CALLDATE = 04/08/2002
CALLID = 67188583
PRESCRIBERLN = Jones
PRESCRIBERFN = Leland
CITY = Anchorage
STATE = AK
ACTION : It was definitely MONDAY at this clinic today!!! Took in Reeses Peanut Butter Cups, so I got back okay... Gave Dr. Child a cupcake sized peanut butter cup, he was kind of tickled. Product mentions only with all docs EXCEPT I got some good ZYP detail time with Dr. Laufer - he asked about ZYP's use in the elderly, dosing, EPS. Covered all of this and overall safety profile, dose at night due to beneficial somnolence, addressed potential for weight gain. Then went over Donna patient and pat's with complicated mood symptoms, gave doc the Donna pat type leave-behind. Left this with all the docs with a personal note.
REACTION : Good, especially with Laufer, and in spite of the crazy day!
FOLLOWUP : **********R**********
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1377

NAME = Williams, Margaret
CALLDATE = 05/08/2002
CALLID = 67869189
PRESCRIBERLN = Case
PRESCRIBERFN = Kathleen
CITY = Anchorage
STATE = AK
ACTION : Got good ZYP detail time with Case and Cates, discussed Donna pat and her symptoms of complicated mood disorder, how she's often initially diagnosed as depressed, doesn't do well on AD's... Product mentions with Gerster. Reviewed Lilly Answers program with all 3 docs, their nurses, and front desk staff.
REACTION : Really good, actually.
FOLLOWUP : Have a lunch in June or July (the earliest I could get one!), so keep working the ZYP here. ***R***
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1472

NAME = Williams, Margaret
CALLDATE = 05/08/2002
CALLID = 67869191
PRESCRIBERLN = Cates
PRESCRIBERFN = John
CITY = Anchorage
STATE = AK
ACTION : Got good ZYP detail time with Case and Cates, discussed Donna pat and her symptoms of complicated mood disorder, how she's often initially diagnosed as depressed, doesn't do well on AD's... Product mentions with Gerster. Reviewed Lilly Answers program with all 3 docs, their nurses, and front desk staff.
REACTION : Very, very good!
FOLLOWUP : Have a lunch scheduled in June or July, couldn't get an earlier date, so keep working ZYP!
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1473

NAME = Jung, Thea S
CALLDATE = 07/15/2002
CALLID = 69576152
PRESCRIBERLN = Trombley Ii
PRESCRIBERFN = Dale
CITY = Anchorage
STATE = AK
ACTION : **********R**********
REACTION : **********R**********Did full Z detail w/both. Dr. T said to just keep reminding him about Z because it's not "stuck in" his head yet. Dr. B said she misunderstood and thought Z was just for bipolar or schizophrenia and was really excited to hear that it was applicable to her practice for "complicated mood". Said she's looking forward to trying it.
FOLLOWUP : Dr. T doesn't quite seem clear on the pt. type. Wants to know if he should lump Z in with the anti-anxiety drugs (he used Buspar as his example) or if he should lump Z in with the anti-depressants (he used Paxil as his example). I gave him the Donna pt. type and tried to explain that it's not in either.
**********R********** Ask Dr. B if she's tried Z now.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1688



NAME = Williams, Margaret
CALLDATE = 02/01/2001
CALLID = 58278674
PRESCRIBERLN = Blais
PRESCRIBERFN = Kendrick
CITY = FAIRBANKS
STATE = AK
ACTION : **********R********** ZYP detail*****R******. Doc initially said any pat's who needed ZYP were referred to a psych, but after detail realized he had pats who could benefit from ZYP and that ZYP wasn't just for schizophrenics. Was impressed with how safe ZYP is and how much ZYP has been used for elderly pats and how ZYP reduces hostility, agitation, improves cognition. Then went over ZYP and bipolar mania.
REACTION : Very good - doc was warm, friendly, receptive, actually engaged me in detail conversation, got interested in ZYP. Best interaction doc and I have ever had.
FOLLOWUP : Cover new info from Nat Meeting.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 607

NAME = Williams, Margaret
CALLDATE = 02/14/2001
CALLID = 58507860
PRESCRIBERLN = Brown
PRESCRIBERFN = Edward
CITY = Anchorage
STATE = AK
ACTION : **********R**********PZ/ZYP comparative detail, full ZYP recap with special emphasis on pat types. ********R********* Left doc a box of Valentine candy (staff too) **********R**********
REACTION : Very good, doc humored me and let me detail him, doc told me he has used ZYP quite a bit, esp for elderly pats...
FOLLOWUP : **********R**********follow up on any ZYP pats****R*****.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 635

NAME = Williams, Margaret
CALLDATE = 02/20/2001
CALLID = 58661137
PRESCRIBERLN = Heverling
PRESCRIBERFN = Susan
CITY = Anchorage
STATE = AK
ACTION : **********R********** ZYP full detail, emphasized the various pat types. *****R***** Took in giant goodie box, see below, left doc Tran reprint - introduced it, but didn't get to go over it as doc had several pats, assured me she would read, put it on her desk...
REACTION : Very good, actually. Doc and staff loved the Goodie Box I brought in, filled with useful items for their new clinic - **********R********** ZYP*****R*****pens and pads **********R**********
Doc told me she has used ZYP for the elderly who are starting to suffer from dementia/alzheimers, hadn't thought of using for bipolar... Doc up for an outing w/me and Dr. Glasgow, will call when I have arrangements made...
FOLLOWUP : **********R**********follow up on ZYP pats and Tran reprint****R*****.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 649

NAME = Williams, Margaret
CALLDATE = 08/28/2001
CALLID = 62516694
PRESCRIBERLN = Dunckel
PRESCRIBERFN = Phyllis
CITY = Anchorage
STATE = AK
ACTION : Great ZYP recap via different pat types, doc told me she's seeing lots of angry, hostile, irritated young adults this summer... Doc liked reclassification of ZYP as psychotropic instead of AP... Has used in elderly and

younger pat types, was interested in having some 10 mg samples around...

REACTION : Most excellent! Doc and I not only had a great professional visit, but also a really good personal visit about upcoming trip to Australia, my continuing blondness, hitting middle age, yoga (doc takes a yoga class during lunch on Tues & Thurs, over in Spenard).

FOLLOWUP : ZYP Shelton reprint review

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order

BATESNUMBER : ZYAKAG3 1018

NAME = Williams, Margaret
CALLDATE = 09/14/2001
CALLID = 62841690
PRESCRIBERLN = Forman
PRESCRIBERFN = Paul
CITY = Anchorage
STATE = AK
ACTION : Got brief detail time with Dr. Schwartz, just a quick wave from Dr. Forman as he was all dressed up in a suit and giving some visiting administrator a tour of the Family Practice Residency Clinic... With Dr. Schwartz, got in a quickie ZYP recap via elderly pat, R Took in candy, pens, and pads for entire clinic.

REACTION : Fantastic from staff, decent from docs.

FOLLOWUP : New info from qrtrly mtg.

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order

BATESNUMBER : ZYAKAG3 1054

NAME = Williams, Margaret
CALLDATE = 09/21/2001
CALLID = 63003489
PRESCRIBERLN = Craft
PRESCRIBERFN = Dirk
CITY = Wasilla
STATE = AK
ACTION : R ZYP for Martha pat via "mother in law" attn getter, R.
Took in candy for doc and staff.

REACTION : Excellent, doc is using ZYP for pats he thought had resistant major dep, is finding out they have some psychotic symptoms and ZYP is doing wonders for them!!! Isn't seeing as marked a response in elderly, but don't think he has much experience here...

FOLLOWUP : New infor from qrtrly mtg.

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order

BATESNUMBER : ZYAKAG3 1062

NAME = Eski, Joey L
CALLDATE = 10/02/2001
CALLID = 63312692
PRESCRIBERLN = Felton
PRESCRIBERFN = Nancy
CITY = Anchorage
STATE = AK
ACTION : Showed the elderly psyclink video from sept 2000 - maguire

REACTION : still no restrictions on meds - they claim. They enjoyed the video but Schultz thought is was a bit biased towards ZY although he agreed with the main points in the video - basically.

FOLLOWUP : discussed setting up one more video for this year - possibly in December

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order

BATESNUMBER : ZYAKAG3 1068

NAME = Williams, Margaret
CALLDATE = 10/16/2001
CALLID = 63528130
PRESCRIBERLN = Heverling
PRESCRIBERFN = Susan
CITY = Anchorage
STATE = AK
ACTION : R got in a fairly full ZYP recap, doc told me she just put an

elderly pat on ZYP, had another bipolar pat psychs had up to 40 mg, now back to 10 mg, discussed how EPS same as placebo... Took in candy for doc and staff. **********R********** Scheduled a lunch for February 2002.

REACTION : Actually, pretty good. Doc likes her info to be short and sweet, and I'm fairly good at getting the most important points across in less than a minute or two... **********R**********

: Get in details however you can, remember - quick, informative blurbs, hands-on tips good. ******R******

FOLLOWUP : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order

LEGEND : ZYAKAG3 1092

BATESNUMBER

NAME = Williams, Margaret

CALLDATE = 10/17/2001

CALLID = 63553395

PRESCRIBERLN = Ikahihifo

PRESCRIBERFN = Talita

CITY = Anchorage

STATE = AK

ACTION : Lunch and learn with Eric, Dr. I and Dr. B spent lots of time on ZYP. Did a full recap presentation**********R********** Both docs want info (Med Ltr) on ZYP use in elderly pats, particularly those suffering from dementia and/or Alzheimers, ZYP - is it used to treat patients with OCD? Pats with ADD? Also send data on co-medicating pats on ZYP with AX, to reduce potential weight gain. Last but not least, does ZYP interfere with pheochromocytoma workup? Went over and then gave doc ZYP diet & exercise pat ed tear shees and booklets.

**********R**********

REACTION : Very, very good. Docs were relaxed, had lots of questions, great discussion. Lots of dialogue and interaction.

FOLLOWUP : Follow up on all the requested ZYP Med ltrs**********R**********

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order

BATESNUMBER : ZYAKAG3 1093

NAME = Eski, Joey L

CALLDATE = 11/28/2001

CALLID = 64492946

PRESCRIBERLN = Hunter-Joems

PRESCRIBERFN = Susan

CITY = Juneau

STATE = AK

ACTION : **********R**********discussed the zy zydis

REACTION : **********R********** she brought up the zydis and said she has been using it quite a bit - in kids and elderly patients - I told he about higher dose forms and she asked about 2.5 - gave her instructions on how to dissolve - she woudl like a follow-up medical letter - if we have it.

FOLLOWUP : sc - Lynn is gone as of Nov 30 - new receptionist name is Stephanie

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order

BATESNUMBER : ZYAKAG3 1179

NAME = Cramer, Schelly D

CALLDATE = 11/28/2001

CALLID = 64508117

PRESCRIBERLN = Nelles

PRESCRIBERFN = Jean

CITY = Anchorage

STATE = AK

ACTION : waffle wed. Psychlink "Behavioral desturbances in the Elderly"

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order

BATESNUMBER : ZYAKAG3 1181

NAME = Williams, Margaret

CALLDATE = 12/10/2001

CALLID = 64706425

PRESCRIBERLN = Hulman

PRESCRIBERFN = Peter

CITY = Anchorage

006940

STATE = AK
ACTION : ZYP quickie recap regarding elderly pats per docs request, reviewed dosing, time of day to take med, etc. ********R********** Took in Christmas candy for doc and staff.

REACTION : Doc was friendly, time was just brief.
FOLLOWUP : Won't be back til FEB 2002.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1203

NAME = Williams, Margaret
CALLDATE = 12/18/2001
CALLID = 64907392
PRESCRIBERLN = Jones
PRESCRIBERFN = Leland
CITY = Anchorage
STATE = AK
ACTION : Lunch started off so slow (Dr. Child was the first person to show at 12:20 pm) that I thought I should have cancelled as I originally intended to do, ended up getting some of the best detail time I've ever gotten with most of the docs at the clinic!!! Got **********R********** ZYP 3 pat type recap detail time and Shelton reprint review with Child, Jones, Laufer, Coalwell, and Taylor, even passed on a few pointers they liked!!! Laufer also passed along some of his elderly pat success stories with ZYP... Didn't make any headway with Lanza regarding ZYP (he will only renew ZYP scripts, not initiate, wants these pats under psych supervision), **********R**********R**********
**********R**********

REACTION : Really good, actually, from docs and staff. Really glad I kept this lunch!!!
FOLLOWUP : Won't be back til FEB 2002...
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1226

NAME = Williams, Margaret
CALLDATE = 03/26/2002
CALLID = 66864704
PRESCRIBERLN = Dunckel
PRESCRIBERFN = Phyllis
CITY = Anchorage
STATE = AK
ACTION : Product mentions only with Dunckel, she was heading to the hospital to deliver a baby, I told her to "party down", the remark struck her funny bone, she liked. Got good ZYP ***R***detail time with Corrine, readressed elderly agitated pat, **********R**********
****
****

REACTION : Okay from doc, she was preoccupied. Great from Corrine.
FOLLOWUP : Have a McGuire program scheduled here 4/12/02.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1356

NAME = Williams, Margaret
CALLDATE = 03/28/2002
CALLID = 66931223
PRESCRIBERLN = Werner
PRESCRIBERFN = David
CITY = Palmer
STATE = AK
ACTION : This clinic just isn't going to Rx **R***ZYP...
**********R**********
********** ZYP review, elderly pat and more complicated mood symptoms. Doc says she has used ZYP for younger, agitated pats. Just a moment with Werner, reminded him to dose ZYP at night, 1.5 hrs before bedtime.

REACTION : Okay.
FOLLOWUP : Just don't know, will detail tidbits about ***R***ZYP...
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1362

NAME = Williams, Margaret
CALLDATE = 04/08/2002
CALLID = 67186583
PRESCRIBERLN = Jones

PRESCRIBERFN = Leland
CITY = Anchorage
STATE = AK
ACTION : It was definitely MONDAY at this clinic today!!! Took in Reeses Peanut Butter Cups, so I got back okay... Gave Dr. Child a cupcake sized peanut butter cup, he was kind of tickled. Product mentions only with all docs EXCEPT I got some good ZYP detail time with Dr. Laufer - he asked about ZYP's use in the elderly, dosing, EPS. Covered all of this and overall safety profile, dose at night due to beneficial somnolence, addressed potential for weight gain. Then went over Donna patient and pat's with complicated mood symptoms, gave doc the Donna pat type leave-behind. Left this with all the docs with a personal note. Good, especially with Laufer, and in spite of the crazy day!

REACTION : **********R**********
FOLLOWUP :
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1377

NAME = Williams, Margaret
CALLDATE = 04/17/2002
CALLID = 67399296
PRESCRIBERLN = Brown
PRESCRIBERFN = Edward
CITY = Anchorage
STATE = AK
ACTION : Had a breakfast meeting with doc, he was 35 minutes late and stressed from the get-go (was up until midnight studying for his board exams) so time was short. Got right to the point on ZYP, recapped Maguire - what pats has he used ZYP for? Elderly and younger pats who are unstable. Reviewed indications and the 3 pat types. Then pulled out the Hirschfeld Scale and got into complicated mood symptoms detail. Doc seemed interested in scale, marked the "key" page. Briefly discussed dosing strengths, dosing at night, potential for wt gain, strategies for dealing with wt gain. *****R*****

REACTION : Good, but doc is quite stresseed...
FOLLOWUP : Review dosing per pat type via pat leave-behinds. *********R*********
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1433

NAME = Williams, Margaret
CALLDATE = 05/10/2002
CALLID = 67937086
PRESCRIBERLN = Cooney
PRESCRIBERFN = Lisa
CITY = Wasilla
STATE = AK
ACTION : Got great time with Cooney, just product mentions with Beyeler. ZYP recap, then covered diabetes sheet and Japanese diabetes info. Cooney has used ZYP for elderly pats, am working on younger pats with complicated mood symptoms. **********R********** Went over Lilly Answers Program with Cooney, Rick the PA, nurses.

REACTION : Really good! ! Cooney had no problem with ZYP & diabetes, everyone impressed with Lilly Answers...
FOLLOWUP : **********R**********
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1477

NAME = Kristen Clouthier
CALLDATE = 06/11/2002
CALLID = 69010827
PRESCRIBERLN = Miknich
PRESCRIBERFN = Eric
CITY = Anchorage
STATE = AK
ACTION : luncheon with entire office ********R**********R**********and pt profile for zyprexa, elderly pt and younger anxious pt having trouble sleeping

REACTION : foland uses zyprexa quite a bit in her elderly population for depression and dimentia, and in her younger age 35 and up for anxious and trouble sleeping pts but- mood swings are usually brought to thier attention by family members.
**********R**********
****

FOLLOWUP : na
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1583

NAME = Kristen Clouthier
CALLDATE = 06/11/2002
CALLID = 69010830
PRESCRIBERLN = Hagen
PRESCRIBERFN = Derek
CITY = Anchorage
STATE = AK
ACTION : luncheon with entire office ********R********** **********R**********and pt profile for zyprexa, elderly pt and younger anxious pt having trouble sleeping

REACTION : foland uses zyprexa quite a bit in her elderly population for depression and dimentia, and in her younger age 35 and up for anxious and trouble sleeping pts but- mood swings are usually brought to thier attention by family members. **********R********** **********

FOLLOWUP : na
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1584

NAME = Kristen Clouthier
CALLDATE = 06/11/2002
CALLID = 69010831
PRESCRIBERLN = Simono
PRESCRIBERFN = Jane
CITY = Anchorage
STATE = AK
ACTION : luncheon with entire office ********R**********R**********and pt profile for zyprexa, elderly pt and younger anxious pt having trouble sleeping

REACTION : foland uses zyprexa quite a bit in her elderly population for depression and dimentia, and in her younger age 35 and up for anxious and trouble sleeping pts but- mood swings are usually brought to thier attention by family members. **********R********** **********

FOLLOWUP : na
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1585

NAME = Kristen Clouthier
CALLDATE = 06/27/2002
CALLID = 69271206
PRESCRIBERLN = Mackie
PRESCRIBERFN = Scott
CITY = Anchorage
STATE = AK
ACTION : office call - brought ****R*****zyprexa bag of goodies, chocolates, cherries, dried fruit. showed fishing pictures. Invite to both zyprexa ****R**** programs

REACTION : **********R********** dr. mackie graduated cum laude also and was in the top 10% of his medical class - very impressive - discussed zyprexa and ssri failure as his pt type but also alot of elderly. he is very aware of zyprexa and its uses. sharp man! He said he may attend the zyprexa program , give reminder.

FOLLOWUP : dvd, ***R*** zyprexa
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1635

NAME = Williams, Margaret
CALLDATE = 07/09/2002
CALLID = 69430005
PRESCRIBERLN = Perkins
PRESCRIBERFN = Byron
CITY = Anchorage
STATE = AK
ACTION : Hosted a good lunch here, full ZYP recap via the 3 pat types, got doc to detail the other HCP's and doc told them he's used ZYP with great success in bipolar pats, extremely anxious "Donna" type pats, and elderly pats. Trying to treat doc as a ZYP specialist, hope this becomes a self-fulfilling prophecy!!! ********R********

REACTION : Also reviewed the Hirschfeld Scale, went over really well. Clinic is now stocked with these... ********R********
: Great!
**********R**********
****

FOLLOWUP : Follow up on ZYP Regional Cons Conf.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1654

NAME = Kristen Clouthier
CALLDATE = 07/11/2002
CALLID = 69495263
PRESCRIBERLN = Flores
PRESCRIBERFN = Kathryn
CITY = Soldotna
STATE = AK
ACTION : **********R********** zyp desk reference and digfast - chocolate chip cookies of course for dr. anderson.
REACTION : he was leaving for a surgery in a minute so only reminders, but had some good time with kathy - discussed elderly and ssri failure pts , digfast tool and she was interested in the h questionaire - said it was good to have on hand for coding work and determining proper pt - reminded her about the program marvin.

FOLLOWUP : na
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1666

NAME = Kristen Clouthier
CALLDATE = 07/11/2002
CALLID = 69495268
PRESCRIBERLN = Davidhizar
PRESCRIBERFN = Lavern
CITY = Soldotna
STATE = AK
ACTION : intro of self and products again - left idc chart, **********R********** zyp desk ref and digfast
REACTION : was very nice, discussed marvin program - said he would be in town for it - would callit can make it - probably needs a reminder that morning so he will come. discussed zyp pt type - elderly and ssri pt, also angered or agitated, cant keep a job,marraige pt and dosing.- he said he has seen many people come through the door like that.

FOLLOWUP : reminder for program
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1667

NAME = Kristen Clouthier
CALLDATE = 07/11/2002
CALLID = 69495269
PRESCRIBERLN = Sanders
PRESCRIBERFN = Jim
CITY = Soldotna
STATE = AK
ACTION : ********R******** pens, pads, zyp desk reference, digfast, bag of goodies
REACTION : **********R**********quickly zyp digfast and proper dosing for elderly, ssri pt, donna t and the extreme mood disrder. invite to program.

FOLLOWUP : more on zyp
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1668

NAME = Kristen Clouthier
CALLDATE = 07/12/2002
CALLID = 69529146
PRESCRIBERLN = White, Jr.
PRESCRIBERFN = Roy Matison
CITY = Anchorage
STATE = AK
ACTION : lunch w/michele -

REACTION : ********** zyprexa h scale, digfast cards, preper pt focus - invites to programs
complaints from lanza, jones, taylor, schultes, coalwell if cant bring wife wont come to programs anymore.
**********R**********
********** zyprexa pt type - elderly, multiple ssri, dosing digfast cheat sheet and key and h scale information - all found scale useful and discussed safety of zyp. vs other agents - scheultes asked about zyp and diabetes - was able to respond according and discuss moa of zyprexa- increase in appetitie which may lead to obesity but no causal relationship established between zyp and diabetes - also compared to other agents there is no increased incidence with zyp - high risk rate in this population anyway - he would like medical letter- but was satified with answer.
**********R**********

FOLLOWUP : **********R**********
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1678

NAME = Kristen Clouthier
CALLDATE = 07/12/2002
CALLID = 69529148
PRESCRIBERLN = Coalwell
PRESCRIBERFN = Timothy
CITY = Anchorage
STATE = AK
ACTION : lunch w/michele -
**********R**********

REACTION : ********** zyprexa h scale, digfast cards, preper pt focus - invites to programs
complaints from lanza, jones, taylor, schultes, coalwell if cant bring wife wont come to programs anymore.
**********R**********
********** zyprexa pt type - elderly, multiple ssri, dosing digfast cheat sheet and key and h scale information - all found scale useful and discussed safety of zyp. vs other agents - scheultes asked about zyp and diabetes - was able to respond according and discuss moa of zyprexa- increase in appetitie which may lead to obesity but no causal relationship established between zyp and diabetes - also compared to other agents there is no increased incidence with zyp - high risk rate in this population anyway - he would like medical letter- but was satified with answer.
**********R**********

FOLLOWUP : **********R**********
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1679

NAME = Kristen Clouthier
CALLDATE = 07/15/2002
CALLID = 69571711
PRESCRIBERLN = Hagen
PRESCRIBERFN = Derek
CITY = Anchorage
STATE = AK
ACTION : office luncheon -
**********R**********

REACTION : ********** zyprexa reminder of ssri pt, elderly pt and thick chart donna pt, indications, dosing appropriate startting dose, digfast cards - h scale questionnaire.
maples just started here, oberstad and maples covering out of town docs pts - alot of elderly from smith whenever he is out - perfect zyp pt - they all took the digfast - found it useful and will use - especially foland -

006945

R**********
R*******
********** zyp dvd again for different pt population
**********R**********
FOLLOWUP : **********R********** State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
LEGEND : ZYAKAG3 1687
BATESNUMBER

NAME = Kristen Clouthier
CALLDATE = 08/20/2002
CALLID = 70702812
PRESCRIBERLN = Hunter
PRESCRIBERFN = John
CITY = Wasilla
STATE = AK
ACTION : office call - ********R******** zyp cme, zyp weight management guide
REACTION : said he is having success with his elderly on zyp - suggest 30% of depressed may be boipolar, food for though he said - likes new office - good for new insurance laws. mary lou very happy there - said they were kicked out of hospital because they refused to pay increase in rent. **********R**********
**********R**********
FOLLOWUP :
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1850

NAME = Williams, Margaret
CALLDATE = 08/26/2002
CALLID = 70810411
PRESCRIBERLN = Thrall
PRESCRIBERFN = Anne
CITY = Anchorage
STATE = AK
ACTION : Forgot to order Anne's med letter - can one mix 5 mg of Zyprexa Zydis in applesauce or some food or drink to dispense the medication to an elderly patient?
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1872

NAME = Williams, Margaret
CALLDATE = 09/13/2002
CALLID = 71335378
PRESCRIBERLN = Bartling
PRESCRIBERFN = Victor
CITY = Fairbanks
STATE = AK
ACTION : Took in my usual muffins, got brief but decent detail time with each key doc, focused on Maguire recap, focused on bipolar patients and how ZYP is an efficacious, safe, and easy to dose mood stabilizer... The mood stabilizer light bulb seemed to finally "turn on" for Dr. Steiner, he did not remember that ZYP is a mood stabilizer, agreed that 1 of 3 pats depressed are bipolar depressed, has had patients get manic on an SSRI, so was all of a sudden rather interested in ZYP and was surprised ZYP is indicated for bipolar mania, his issue with ZYP is wt gain, send med letter on ZYP being used for bipolar disorder in general and strategies to manage potential weight gain. Dr. Judkins stated that he thinks primary care physicians will start to treat more and more bipolar pats since the medication (ZYP) is easy to dose, very safe, and actually works! Dr. Bartling declined being trained as a speaker (did really consider this and was complimented) as he has a very busy schedule at TVC, he's also the director of the Denali Nursing Home at the FBKS Memorial Hospital, and has several children. He and I discussed ZYP use in the elderly in more detail, but bipolar as well. Bartling wants more info on using ZYP in the elderly... All 4 docs just loved my Girdwood Forest Fair parade baby float photos, I knew they would!
**********R**********
****
REACTION : Really friendly, actually. Even Dr. Steiner thanked me for kind of "interrupting" him and impressing upon him that ZYP IS indicated for bipolar mania and is a mood stabilizer...
FOLLOWUP : ZYP via handheld DVD...
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1960

NAME = Williams, Margaret
CALLDATE = 09/13/2002
CALLID = 71335382
PRESCRIBERLN = Thomas
PRESCRIBERFN = Robert
CITY = Sitka
STATE = AK
ACTION : Met doc in FBKS, he approached me when he noticed my ZYP bags, wanted ZYP info and samples, wants me to come to his clinic in Sitka. Mostly went over use of ZYP in elderly pats w/dementia, send med letter.
REACTION : Really good.
FOLLOWUP : See about going to Sitka.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1961

NAME = Kristen Clouthier
CALLDATE = 09/18/2002
CALLID = 71468546
PRESCRIBERLN = Hunter
PRESCRIBERFN = John
CITY = Wasilla
STATE = AK
ACTION : office call - very busy today
REACTION : provided cme.********R********* new nurse for office - very helpful and appreciates the pt education - put the zyp education in each pt room. dosng by samples -
FOLLOWUP : next time remind of donna - has he seen any donna lately? or just elderly ts in need of zyp?
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1978

NAME = Kristen Clouthier
CALLDATE = 09/23/2002
CALLID = 71583198
PRESCRIBERLN = Schwartz
PRESCRIBERFN = John
CITY = Anchorage
STATE = AK
ACTION : office call - zyp and lilly caes pt assistance programs - zyp digfast, ********R*********pt educationa dn disgnostic criteria chart.
REACTION : he thought the pt assisatance ery useful - asked who he was using zyp for successfully and he said he stil hasnt branched beyond the elderly pts in his nursing home - briefly explained a donna pt symptoms and how successful zyp can be in those pts as well.
**********R**********
FOLLOWUP : try to get him to try n donna - doesnt he see these pts?
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1997

NAME = Williams, Margaret
CALLDATE = 09/23/2002
CALLID = 71604819
PRESCRIBERLN = Schwartz
PRESCRIBERFN = John
CITY = Anchorage
STATE = AK
ACTION : Rode with Kristen, had her take the lead as I just returned from Mexico and feel a bit ill intestinally... Dr. Forman has just recently put a pat on ZYP, not sure if she's bipolar, but she wasn't doing any better on any AD's... Kristen worked diagnosing bipolar pats. Dr. Schwartz is still only using ZYP for elderly pats in the nursing home, but really likes the Lilly Cares and Lilly Answers program info... **********R**********
REACTION : Good. Kristen has better relationships with these two docs than I do...
FOLLOWUP : Try to get another lunch here, to do an MDQ "workshop"...
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 1999

NAME = Kristen Clouthier
CALLDATE = 12/02/2002
CALLID = 73603025
PRESCRIBERLN = Mayer

PRESCRIBERFN = Louis
CITY = Anchorage
STATE = AK
ACTION : office call- zyp ****R***** - lilly **R** answers and indigent forms, cost zyp, mdq scale and digfast
REACTION : he had a pt put o zyp by some other physicians and now he is maintaining the pt - pt is doing well - went over entre detail, dosing for different pt types, safety, efficacy and cost - he has many elderly pts that have dimentia - he asked about using in combination with other agents - in the elderly, discussed eps rates comparable to placebo, somnolence and how to manage appetitie increase. **********R**********

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 2199

NAME = Kristen Clouthier
CALLDATE = 01/16/2003
CALLID = 74456696
PRESCRIBERLN = Cates
PRESCRIBERFN = John
CITY = Anchorage
STATE = AK
ACTION : office call
REACTION : he was very open today - he said he had tried 3 patients on zyp - elderly pts all for sleep and to stop sundowners syndrom - he said all pts got extremely aggitated and agressive and he had to load them with haldol to calm them down - then he took them off the zyp - i asked dr gillete aout it he said this would be a normal occurance and instead of loading haldol just up the dose until sleep of zyp - it works and aggitation is common for possibly up to a week - get back to cates with this info. - also send medical letter. **********R**********

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 2272

NAME = Kristen Clouthier
CALLDATE = 01/31/2003
CALLID = 74821225
PRESCRIBERLN = Thomas
PRESCRIBERFN = Joan
CITY = Fairbanks
STATE = AK
ACTION : office call-
REACTION : **********R**********

********** zyp reminders - still using successfuly and interested to hear about comedication for weight gain - had already sent med letter bt he never read it - cost effective ones are the key - office also needs more 2.5mg when you get it. ticman has not seen the weight gain on zyp but he uses mostly for elderly pts and it had been working very very well for him - serrano also working well but interested in weight management - both are happy with the medication - love the purple pens for zyp - keep them coming.

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 2324

NAME = Kristen Clouthier
CALLDATE = 01/31/2003
CALLID = 74821228
PRESCRIBERLN = Ticman
PRESCRIBERFN = Patrick
CITY = Fairbanks
STATE = AK
ACTION : office call-
REACTION : **********R**********

********** zyp reminders - still using successfuly and interested to hear about comedication for weight gain - had already sent med letter bt he never read it - cost effective ones are the key - office also needs more 2.5mg when you get it. ticman has not seen the weight gain on zyp but he uses mostly for

elderly pts and it had been working very very well for him - serrano also working well but interested in weight management - both are happy with the medication - love the purple pens for zyp - keep them coming.

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 2325

NAME = Kristen Clouthier
CALLDATE = 01/31/2003
CALLID = 74821230
PRESCRIBERLN = Schag
PRESCRIBERFN = Steven
CITY = Fairbanks
STATE = AK
ACTION : office call-
REACTION :

**********R**********

********** zyp reminders - still using successfuly and interested to hear about comedication for weight gain - had already sent med letter bt he never read it - cost effective ones are the key - office also needs more 2.5mg when you get it. ticman has not seen the weight gain on zyp but he uses mostly for elderly pts and it had been working very very well for him - serrano also working well but interested in weight management - both are happy with the medication - love the purple pens for zyp - keep them coming.

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 2326

NAME = Cramer, Schelly D
CALLDATE = 03/04/2003
CALLID = 75689997
PRESCRIBERLN = Schramm
PRESCRIBERFN = Colleen
CITY = Fairbanks
STATE = AK
ACTION : Asked colleen if she has taken her psych boards yet; had appropriate dose discussion. Colleen requested med letter on higher doses (Volovka)
REACTION : The state screwed up her licence app & payment, so she doesn't know if she is technically a psych anp yet...but she did finish her boards. She isn't writing cns drugs yet, but does at Samaritan Hospital-elderly care facility. she is only psych specialist on staff there. Only about 5 low dose zy scripts per mo. She talked about one pat doing okay on zy-but could be doing better, no significant ses. Took opportunity to discuss appropriate dose; if no ses at 5 mg, data suggested it may make sense to try for better efficacy with a little higher dose-if no benefit seen, she can always back down again. differentiated from Risp on this point.
FOLLOWUP : Check on higher dose idea for the Samaritan patient she talked about'did she get med letter on volovka? Colleen is only one day a wk at CMHC, so she won't be huge for us, but incremental dose increases for better efficacy at both locations won't hurt.

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 2413

NAME = Kristen Clouthier
CALLDATE = 03/07/2003
CALLID = 75798711
PRESCRIBERLN = Cullen
PRESCRIBERFN = John
CITY = Valdez
STATE = AK
ACTION : AAFP conference
REACTION : dr hunt speaker program on bipolar mania and disgnosing mood disorders. use of zyp - common questions were how to diagnose, weight gain and how to handle it, if you have to keep pts on meds for life, use of depakote and or zyp and use of zyp with other agents - polypharm, differentiating serotonin symdrome and inducing mania, and using zyp in elderly - trd, other pts. -

**********R**********

********** doty took mdq and agreed she misses seeing and diagnosing a number of bipolar pts. foland very - schwartz i think it reassured his depakote use - ask him if him made him more comfortable with zyp.

**********R**********

********** dr mike - concerened about weight and curious about depakote - need to thwart depakote use vs zyp next week at apt.
LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 2422

NAME = Kristen Clouthier
CALLDATE = 08/14/2003
CALLID = 80110825
PRESCRIBERLN = Bosveld
PRESCRIBERFN = Robert
CITY = Anchorage
STATE = AK
ACTION : office call
REACTION : he is now in his new office and likes it - gersters old office - discussed type of pt that zyp can be used in and dosing for each type - he said he would probably see the elderly pts who need more cognition - he would like more data on that - did show him the zyp sales on efficacy of symptoms including thought content - he does not want ed letter but does want more info on this subject.
**********R**********

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 2913

NAME = Kristen Clouthier
CALLDATE = 09/10/2003
CALLID = 80884353
PRESCRIBERLN = Laufer
PRESCRIBERFN = Kenneth
CITY = Anchorage
STATE = AK
ACTION : office call - lunch
REACTION : hadnt discussed with him in a while about zyp - is it still something he uses and is happy with - yes but he has backed off a bit - because he was concerned about td with zyp - discussed safety profile and safety compared to other agents - and apa recommendation of zyp as first line for b mania - he sees pts in an elderly home as well- talked about zydis - he was really happy about that -
**********R**********
****

LEGEND : State of Alaska v. Eli Lilly and Company: Confidential - Subject to Protective Order
BATESNUMBER : ZYAKAG3 3012

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
	)	Case No. 3AN-06-05630 CI
v.	)	
	)	
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	
	)	

PLAINTIFF'S SUPPLEMENTAL RESPONSES TO DEFENDANT'S FOURTH SET OF INTERROGATORIES

PRELIMINARY STATEMENT

In response to Lilly's First Interrogatories and Requests for Production, the State provided a general description of the kinds of proof it would offer underlying its claims in this case. In response to Lilly's Fourth Interrogatories and Requests for Production, the State provided a description of similar information with respect to its claims under the Unfair Trade Practices and Consumer Protection Act (UTPCPA). However, the evidence is incomplete at this point because of Lilly's reluctance to produce meaningful discovery in response to the State's discovery requests. Lilly delayed the production of virtually any discovery until ordered by the Discovery Master to produce it. Additionally, at Lilly's request, key depositions have been delayed.[1]

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[1] The recent 30(b)(6) deposition on the issue of Lilly's marketing practices was initially noticed for December 6, 2007, but at Lilly's request was delayed until January 11, 2008.

In accordance with the Discovery Master's order of January 14, 2008, below is a recitation of the specific violations upon which the State bases its UTPCPA claims. This information will be supplemented at the conclusion of discovery, or as otherwise necessary.

Before addressing the specific Alaska violations which are the subject of Lilly's interrogatories, it is important to note that Lilly had a sophisticated, broad-based scheme designed to distort the entire body of public knowledge regarding Zyprexa's risks and benefits. Lilly formulated this scheme at its corporate headquarters in Indianapolis, and it was carried out nationwide. Sales messages and materials all originated in Indianapolis, and the sales representatives were expected to carry those messages nationwide. The scheme was implemented in Alaska, as in all other states.

Lilly's scheme included failing to warn in the product labeling accompanying each prescription about the risks associated with Zyprexa use. However, the scheme also included affirmative misrepresentations which 1) minimized the magnitude and hazards of weight gain with Zyprexa; 2) denied a causal relationship between Zyprexa and hyperglycemia or diabetes; 3) claimed that hyperglycemia or diabetes occurred with Zyprexa use at rates comparable to other antipsychotic medications; and 4) promoted Zyprexa as safe and efficacious for uses not indicated on its labeling.

At the 30(b)(6) deposition of Lilly regarding its marketing practices, deponent David Noesges testified that all sales messages delivered by Lilly sales representatives are

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developed in Indianapolis.[2] He further testified that the sales representatives are trained to and expected to deliver those messages, and are prohibited from delivering any messages that have not been approved by Lilly.[3] Sales representatives are provided with a number of sales tools, including brochures, sell sheets and scripted answers to various questions. These materials included messages which, as indicated above, affirmatively misrepresented the risks and benefits of Zyprexa. Clear evidence that Lilly sales representatives delivered these messages is available in the sampling of "call notes" produced by Lilly. A call note is a business record which contemporaneously details a Lilly sales representative's visit to a physician.[4] Sales representatives are expected to accurately detail such visits.[5]

Pursuant to the January 14 order of the Discovery Master, the State provides answers to Lilly's interrogatories below on the basis of information the State currently possesses.

INTERROGATORIES

INTERROGATORY NO. 66: State the number of times that you contend Lilly violated the Alaska Unfair Trade Practices and Consumer Protection Act, AS 45.50.471, et seq., as alleged in the Fifth Claim for Relief in the Complaint by:

(a) "represent[ing] Zyprexa had characteristics, uses, benefits and/or qualities that it did not have;"

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[2] Exhibit 1 (Deposition of David Thomas Noesges, January 11, 2008 at 38).
[3] Id. at 35-36.
[4] Id. at 197-198; Exhibit 2 (Exhibit 9 to Deposition of David Thomas Noesges).
[5] Exhibit 1 at 198; Exhibit 2.

(b) "represent[ing] that Zyprexa was of a particular standard, quality and grade suitable for consumption when in fact it was not;"

(c) "advertis[ing] Zyprexa with an intent not to sell it as advertised;"

(d) "engag[ing] in conduct creating a likelihood of confusion or a misunderstanding and which misled or damaged buyers of Zyprexa, including the State of Alaska;"

(e) "us[ing] misrepresentations or omissions of material facts with the intent that others rely on the misrepresentations or omissions in connection with the sale of Zyprexa;" and/or

(f) "violat[ing] the labeling and advertising provisions of AS 17.20."

ANSWER: The State objects to the foregoing interrogatory in that discovery is ongoing in this case. The State is still in the process of taking depositions of Lilly witnesses with information relevant to the State's claims. The State reserves the right to use any and all evidence produced by any party in discovery in this case or in the Zyprexa Multidistrict Litigation ("MDL"). Subject to and without waiving this objection, it is clear that Lilly engaged in conduct violating the above-referenced provisions of the Alaska statutory law by minimizing the magnitude and hazards of olanzapine-induced weight gain, denying a causal relationship between olanzapine and hyperglycemia and/or diabetes, and by claiming that hyperglycemia and/or diabetes occurring during treatment with olanzapine occurred at rates comparable to other antipsychotic medications. Moreover, Lilly misrepresented that

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Zyprexa was an appropriate treatment for "complicated mood disorders" and other off-label uses. This list is intended to be illustrative and not exhaustive.

At a minimum, Lilly violated the above-referenced provisions of the UTPCPA with each prescription of Zyprexa that was unaccompanied by a product label which adequately conveyed the risks of Zyprexa use, including but not limited to the risks of weight gain, hyperglycemia or diabetes, and other metabolic disturbances.[6] Each and every prescription of Zyprexa to any Alaska resident is a violation of the provisions of the UTPCPA, because each prescription failed to warn of the true nature and extent of Zyprexa's risks. Through the year 2006, there were 208,780 prescriptions to Alaska Medicaid patients alone. The State believes the total number of prescriptions (to both Medicaid and non-Medicaid patients) will be significantly higher but is still in the process of discovering the total number prescriptions to all Alaska residents.

In addition to each prescription without an adequate warning being a separate violation of UTPCPA, it was also a separate violation of the Act for any sales call in which the sales representative minimized the hazards with weight gain and diabetes, misrepresented the facts about the drug, or improperly promoted the drug off-label. Identified herein are a

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[6] It is important to note here that the Discovery Master found that "[t]he State's responses, including all incorporated materials, adequately identify the factual bases for inadequate warnings and Lilly's knowledge of the alleged hazards of Zyprexa."

number of additional violations related to affirmative misrepresentations of Zyprexa's risks, benefits or uses which are detailed in call notes by sales representatives.[7]

Searching the call notes database with specific terms reveals numerous violations of the UTPCPA. The State will provide examples below of such searches and exhibits detailing the results of those searches. These exhibits detail specifically the dates and substance of the UTPCPA violations in response to these interrogatories.

A search of the call notes using the search term "weight gain" reveals 98 instances of Lilly sales representatives discussing the issue of Zyprexa-related weight gain with Alaska physicians between 1999 and 2004.[8] In none of these instances did the Lilly sales representative indicate the true extent and magnitude of Zyprexa weight gain to the physician. Instead, the sales representatives were delivering the company message that weight gain was manageable and that any risk of it was far outweighed by Zyprexa's superior efficacy. Each of these notes establishes a violation of the UTPCPA.

A search of the call notes using the terms "diabetes," "glucose," "no differences," "comparable," "cause" or "causal" reveals 170 instances of Lilly sales representatives discussing high glucose or diabetes with Alaska physicians between 2000 and 2004.[9] Lilly sales representatives did not advise physicians of the true risks of high glucose or diabetes in

[7] The State has only received a sampling of call notes to date. It will require a full production of all call notes through the present to fully address the spectrum and magnitude of UTPCPA violations in Alaska.

[8] Exhibit 3 (Alaska call notes reflecting discussion of weight gain).

[9] Exhibit 4 (Alaska call notes reflecting discussion of diabetes, glucose or diabetes messages).

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these visits, but instead used company messages regarding "comparable rates among atypical antipsychotics" or "no causal link between Zyprexa and diabetes" to reassure physicians and encourage prescribing Zyprexa. Each of these notes establishes a violation of the UTPCPA.

Not only do the call notes establish violations of the UTPCPA for failing to advise of the full nature and extent of weight gain and diabetes risks associated with Zyprexa, they also establish violations of the UTPCPA in the form of Lilly's illegal off-label promotion of Zyprexa for symptoms or conditions for which it was never indicated. For example, using the search term "SSRI" reveals 20 instances between 2002 and 2003 in which a Lilly sales representative promoted Zyprexa as a mood stabilizer for someone whose symptoms were aggravated by an SSRI or in whom SSRI treatment failed.[10] Further, using the search term "elderly" reveals 51 instances between 2001 and 2002 in which Lilly sales representatives promoted Zyprexa for use in elderly patients for various symptoms or disorders such as agitation, hostility, dementia or improved cognition.[11] Searching for "children" or variations thereof reveals 11 instances between 1999 and 2000 of Lilly representatives promoting the use of Zyprexa in adolescents.[12] Finally, searching for the names of various Lilly patient exemplars or "patient types" such as "Martha," "Melvin," "Donna" or "Kelly" reveals 159 instances of Lilly representatives between 2001 and 2002 using these patient exemplars to

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[10] Exhibit 5 (Alaska call notes reflecting discussion of use of Zyprexa in patients treated with SSRI).
[11] Exhibit 6 (Alaska call notes reflecting discussion of use of Zyprexa in elderly patients).
[12] Exhibit 7 (Alaska call notes reflecting discussion of use of Zyprexa in adolescent patients).

promote the use of Zyprexa in patients who were not diagnosed with bipolar disorder or schizophrenia, the only indications for Zyprexa.[13]

All of the call notes above establish numerous violations of the UTPCPA, but not all violations. Until discovery is complete, the State cannot establish with precision the total number of violations.

INTERROGATORY NO. 67: Identify every alleged violation enumerated in response to Interrogatory No. 66 which was the result of Lilly's representing that "Zyprexa had characteristics, uses, benefits and/or qualities that it did not have, in violation of AS 45.50.471(b)(4)," as alleged in paragraph 53(a) of Complaint. For each representation, your response should identify who made the representation, the recipient(s) of the representation, the method of communication, the date of the representation, the content of the representation, and the basis for your contention that the representation was false, including but not limited to identifying what characteristics, uses, benefits and/or qualities Lilly represented Zyprexa to have, which it did not have.

ANSWER: The State objects to the foregoing interrogatory in that discovery is ongoing in this case. The State is still in the process of taking depositions of Lilly witnesses with information relevant to the State's claims. The State reserves the right to use any and all evidence produced by any party in discovery in this case or in the Zyprexa Multidistrict Litigation ("MDL"). See response to Interrogatory No. 66, above.

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[13] Exhibit 8 (Alaska call notes reflecting discussion of various patient types).

By way of further response, there are many instances of Zyprexa sales representatives minimizing the magnitude and risks of weight gain on Zyprexa. For example, Alaska sales representatives told physicians that weight gain was "manageable," provided "strategies" and "solutions" for combating weight gain, and generally touted Zyprexa's "superior" or "broad spectrum" efficacy as a benefit which outweighed the risk of weight gain.[14] This conduct occurred regularly from 1999 to 2004, a time during which Lilly acknowledged internally that it did not know how to effectively manage weight gain, that weight loss programs worked only five percent of the time in healthy – i.e., mentally stable – volunteers, that it was actively attempting to minimize the liability of weight gain while at the same time increasing the focus on Zyprexa's superior efficacy, and that it would be ludicrous to state that some patients who gained clinically significant weight on Zyprexa would not be at long-term increased cardiac risk as a result. Further, Lilly taught its sales representatives to "weaken [the] link" between weight gain and diabetes.[15]

Lilly's Alaska sales representatives also misrepresented to physicians on numerous occasions that there was no causal relationship between Zyprexa and diabetes, or between weight gain on Zyprexa and diabetes. These detailing visits occurred between 2000 and 2004, a time when the company was attempting to eliminate the risk of diabetes from the risk/benefit equation. It is clear from the call notes that when Lilly representatives shared

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[14] Exhibit 3.
[15] Exhibit 1 at 113; Exhibit 9 (Zyprexa MDL Plaintiffs' Exhibit 1901).

diabetes information with physicians in Alaska, it was the same tortured data claiming there was no causal link between Zyprexa and diabetes.[16]

Lilly sales representatives also used the "comparable rates" message with Alaska physicians and denied that there was a causal connection between Zyprexa and diabetes.[17] These messages were designed reduce the perception that diabetes was linked to Zyprexa and to eliminate the diabetes risk from the risk/benefit equation. The message was delivered with frequency to Alaska physicians, beginning in 2001 and continuing through at least January 2004.[18] However, at all times Lilly had relevant information belying the "comparable rates" message that it refused to share with physicians. Even after Lilly was required to change its label in September 2003, Lilly continued to trumpet the message to physicians to minimize the negative effect of the label change on Zyprexa. Not only was this message belied by available data – a point made clearly in 2004 by the ADA Consensus Statement, which ranked the atypicals by weight gain and diabetes risk – but Lilly was forced in October 2007 to acknowledge this in a revised Zyprexa warning label. Internal company documents cited in the State's "backgrounder" make it clear the company knew this for years prior to 2007, and the recent 30(b)(6) deposition of Lilly regarding the label change confirmed the same.

Finally, there are numerous instances in the "call notes" of Lilly sales representatives promoting Zyprexa as safe and efficacious for uses far beyond its approved indications.

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[16] Exhibit 1 at 103-111; Exhibit 10 (Exhibits 4 and 5 from the Deposition of David Thomas Noesges).
[17] Exhibit 1 at 58-60, 63; Exhibit 11 (Zyprexa MDL Plaintiffs' Exhibit 1941).
[18] Exhibit 4.

Often through the use of patient exemplars with names like "Donna," "Martha," "Marty" and "Melvin," the representatives would promote Zyprexa for use in combating non-indicated mood and thought disorders such as depression, anxiety, and "complicated mood disorder," and for use in patient populations such as the elderly and children for whom Zyprexa had not been established as safe or effective.[19] Lilly sales representatives were taught to do this, though the drug was never approved for any of these conditions.[20]

This evidence clearly establishes violations of the above-referenced UTPCPA provision. Lilly's sales representatives in Alaska were carrying out the company's orchestrated national plan to minimize the magnitude and hazards of olanzapine-induced weight gain, deny any causal relationship between olanzapine and hyperglycemia and/or diabetes, convince physicians that hyperglycemia and/or diabetes occurring during treatment with olanzapine occurred at rates comparable to other antipsychotic medications, and promote Zyprexa was an appropriate treatment for "complicated mood disorders" and other off-label uses. Until discovery is complete, however, the State is unable to perform and exhaustive recitation of such evidence and additional violations.

INTERROGATORY NO. 68: Identify every alleged violation enumerated in response to Interrogatory No. 66 which was the result of Lilly's representing that "Zyprexa was of a particular standard, quality and grade suitable for consumption when in fact it was not, in violation of AS 45.50.471(b)(6)," as alleged in paragraph 53(b) of Complaint. For

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[19] Exhibits 4 – 7.

[20] Exhibit 1, p. 164:15 – 177:15. Exhibit 12 (Zyprexa MDL Plaintiffs' Exhibit 4121).

each representation, your response should identify who made the representation, the recipient(s) of the representation, the method of communication, the date of the representation, the content of the representation, and the basis for your contention that the representation was false, including but not limited to identifying what characteristics, standard, quality and grade Lilly represented Zyprexa to have, which it did not have.

ANSWER: See response to Interrogatory Nos. 66 and 67, above.

INTERROGATORY NO. 69: Identify every alleged violation enumerated in response to Interrogatory No. 66 which was the result of Lilly's "advertis[ing] Zyprexa with an intent not to sell it as advertised, in violation of AS 45.50.471(b)(8)," as alleged in paragraph 53(c) of the Complaint. Your response should identify each and every representation you contend constitutes an advertisement, the content of the advertisement, where the advertisement was published, transmitted, or otherwise communicated, the date of the advertisement, who received the advertisement, and the basis for your contention that Lilly's intent contradicted the content of the advertisement.

ANSWER: See response to Interrogatory Nos. 66 and 67, above.

INTERROGATORY NO. 70: Identify every alleged violation enumerated in response to Interrogatory No. 66 which was the result of Lilly's "engag[ing] in conduct creating a likelihood of confusion or a misunderstanding and which misled or damaged buyers of Zyprexa, including the State of Alaska, in violation of AS 45.50.471(b)(11)," as alleged in paragraph 53(d) of the Complaint. Your response should describe in detail each

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incidence of alleged conduct, identify who engaged in the conduct and describe their involvement, identify when the conduct occurred, identify where the conduct occurred, and identify what was confusing or misleading about the conduct, and identify what buyers were misled and/or damaged by the conduct.

ANSWER: See response to Interrogatory Nos. 66 and 67, above.

INTERROGATORY NO. 71: Identify every alleged violation enumerated in response to Interrogatory No. 66 which was the result of Lilly's "us[ing] misrepresentations or omission of material facts with the intent that others rely on the misrepresentations or omissions in connection with the sale of Zyprexa, in violation of AS 45.50.471(b)(12)," as alleged in paragraph 53(e) of the Complaint. For each representation, your response should identify who made the representation, the recipient(s) of the representation, the method of communication, the date of the representation, the content of the representation, and the basis for your contention that the representation was false. For each omission, your response should identify the information that was omitted, the date that the information should have been communicated, and the person(s) to whom the information should have been communicated.

ANSWER: See response to Interrogatory Nos. 66 and 67, above.

INTERROGATORY NO. 72: Identify every alleged violation enumerated in response to Interrogatory No. 66 which was the result of Lilly's "violat[ing] the labeling advertising provisions of AS 17.20, in violation of AS 45.50.471(b)(48)," as alleged in

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paragraph 53(f) of the Complaint. Your response should identify each provision of AS 17.20 that you contend was violated, describe in detail each incidence of alleged conduct resulting in that violation of AS 17.20, identify who engaged in the conduct and describe their involvement, identify when the conduct occurred, and identify where the conduct occurred.

ANSWER: See response to Interrogatory Nos. 66 and 67, above. Additionally, per the Discovery Master's January 14, 2008 order, the State's prior responses and incorporated materials "adequately identify the factual bases for inadequate warnings and Lilly's knowledge of the alleged hazards of Zyprexa."

INTERROGATORY NO. 73: For each individual violation enumerated in response to Interrogatory No. 66, identify the "ascertainable loss of money or property" that you contend resulted from that specific violation.

ANSWER: The State objects to this interrogatory as discovery is ongoing and that any response to this interrogatory is premature in that damages are not at issue in the first phase of trial currently scheduled for March 3, 2008. By way of further response, the State is entitled to any and all damages to be determined by the Court and/or jury at the trial on damages in this case. The State will prove at the first trial that Zyprexa presents serious risks of weight gain, hyperlipidemia, hyperglycemia and/or diabetes, and related health conditions for which the State has the burden of paying the cost of medical treatment. In the second trial, the State will prove the extent of these injuries and the State's damages, and evidence relevant to that proof will be provided to Lilly in accordance with the Court's January 4,

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2008 order regarding discovery unrelated to liability. Additionally, the State will prove in the first trial that Lilly promoted Zyprexa for numerous symptoms and conditions for which Zyprexa had no indication, and the State will prove at the second trial that it suffered damages as a result of increased prescriptions for off-label uses.

Respectfully SUBMITTED and DATED this 24 day of January, 2008.

FELDMAN, ORLANSKY & SANDERS
Counsel for Plaintiff

BY _____
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Certificate of Service
I hereby certify that a true and correct copy
of the foregoing **Plaintiff's Supplemental Responses to Defendant's Fourth Set of Interrogatories**
was served by messenger on:

Brewster H. Jamieson
Lane Powell LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648

Barry Boise, via email (boiseb@pepperlaw.com)
Pepper Hamilton

By Annette R. Cartier
Date 1-24-08

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Filed in the Trial Courts
STATE OF ALASKA, THIRD DISTRICT
JAN 22 2008
Clerk of the Trial Courts
By _____ Deputy

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,
Plaintiff,
v.
ELI LILLY AND COMPANY,
Defendant.

Case No. 3AN-06-05630 CI

ELI LILLY'S NOTICE OF FILING DEPOSITION DESIGNATIONS UNDER SEAL

Defendant Eli Lilly, by and through counsel of record, files its deposition designation pages, Exhibits A-J, under seal, attached to this notice. Portions of the deposition designations may be confidential under the Court's April 6, 2007 oral ruling.

DATED this 22 day of January, 2008.

See Judge Rindner's order of 6/13/08, page 22, #21 Documents unsealed made 8/11/08

PEPPER HAMILTON LLP
Andrew R. Rogoff, admitted *pro hac vice*
Eric J. Rothschild, admitted *pro hac vice*
and
LANE POWELL LLC
Attorneys for Defendant

By _____
Brewster H. Jamieson, ASBA No. 8411122
Andrea E. Girolamo-Welp, ASBA No. 0211044

I certify that on January 22, 2008, a copy of the foregoing was served by hand-delivery on:

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Feldman Orlansky & Sanders
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Case No. 3AN-06-05630 CI

DEFENDANT ELI LILLY AND COMPANY'S DEPOSITION DESIGNATIONS FOR TRIAL

Defendant Eli Lilly and Company ("Lilly") designates for trial the following deposition transcript excerpts:

I. **Deposition of Charles Beasley, Jr. M.D.—Volume 1,** designated pages Exhibit A.

Start (Page:Line)	End (Page:Line)
26:10	27:16
30:11	33:3
33: 4	33:19
34:19	38:24
46:5	52:15
53:2	55:3
57:1	57:20
112:8	114:7
137:24	139:15
139:16	141:14
141:15	142:2
153:8	156:8
156:9	158:7
161:18	161: 20
161:22	162: 7
162:9	162:17
162:22	163:5
163:7	163:11

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Start (Page:Line)	End (Page:Line)
191:23	192:7
192:10	193:2
196:16	197:24
199:17	201:3
261:18	262:21
365:24	366:11

II. **Deposition of Charles Beasley, Jr. M.D.—Volume 2**, designated pages Exhibit B.

Start (Page:Line)	End (Page:Line)
520:7	521:13
530:19	531:3
532:1	532:16
532:22	533:9
535:5	536:14
537:24	540:13
540:14	541:16
541:17	543:8
543:9	544:13
544:14	545:11
545:12	546:13
546:14	547:22
547:23	548:22
549:16	550:1
550:17	551:2
551:9	553:13
553:14	555:15
555:16	556:24
557:1	557:9
557:10	557:19
557:20	558:4
558:5	559:24

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560:1	561:20
561:21	562:22
562:23	564:13
564:14	564:20
564:21	565:7
565:8	567:9
567:13	567:20
567:21	569:11
569:12	570:13
570:14	572:21
572:22	573:12
573:13	575:12
575:13	578:1
578:5	578:6
578:18	580:21
580:22	582:20
583:4	583:16
584:1	586:1
586:2	586:23
586:24	590:10
722:8	723:11

III. **Deposition of David Campana—Volume 1**, designated pages Exhibit C.

Start (Page:Line)	End (Page:Line)
5:8	5:14
7:15	7:23
8:18	9:1
9:6	11:12
34:4	34:8
169:3	169:9

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IV. **Deposition of David Campana—Volume 2**, designated pages Exhibit D.

Start (Page:Line)	End (Page:Line)
191:19	192:14
208:13	208:20
209:13	209:19
210:13	211:15
214:12	214:25
215:16	216:5
218:2	219:13
222:25	223:13
224:3	224:6
228:6	228:21
229:4	229:6
229:11	229:13
242:25	248:2
249:10	250:20
250:24	252:9
252:10	255:24
256:13	259:11
265:7	270:6
271:3	271:7
271:18	272:12
281:24	282:17
307:23	308:22
309:21	310:20
311:17	312:5
313:6	313:19
314:16	315:15
332:5	333:21

Start (Page:Line)	End (Page:Line)
18:21	19:7
19:17	20:1
20:20	22:23
61:11	62:7
62:10	62:24
64:10	66:19
68:1	68:16
72:18	73:18
73:21	74:14

VII. **Deposition of Duane Hopson, M.D.**, designated pages Exhibit G.

Start (Page:Line)	End (Page:Line)
5:21	6:3
6:22	10:16
11:5	11:25
12:4	17:8
17:12	29:5
29:8	34:2
35:19	37:20
38:15	41:22
42:14	46:13
48:14	50:22
51:8	54:12
55:1	56:9
56:12	59:2
59:14	60:4
61:23	61:25
62:14	69:22
70:3	78:6
79:15	91:3

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Start (Page:Line)	End (Page:Line)
91:13	93:15
94:2	95:16
96:12	99:23
101:3	105:4
105:17	106:14
106:1	106:1

VIII. **Deposition of Karleen Kay Jackson**, designated pages Exhibit H.

Start (Page:Line)	End (Page:Line)
5:17	5:22
6:13	7:2
7:3	7:14
8:5	8:11
8:22	9:3
9:24	10:7
14:23	15:4
15:21	16:2
23:24	25:3
30:3	31:13
31:19	32:9
33:20	34:12

IX. **Deposition of Gary Tollefson, M.D.**, designated pages Exhibit I.

Start (Page:Line)	End (Page:Line)
11:19	11:23
13:6	13:9
13:18	15:3
29:19	32:4
35:10	37:3

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37:21	43:10
51:11	51:24
52:3	52:19
52:22	55:3
55:6	55:9
105:16	105:20
105:23	106:20
106:23	107:8
111:1	111:3
111:6	111:14
115:14	117:9
117:17	118:4
182:13	183:6
183:9	183:22
187:3	188:4
297:19	298:9
298:16	298:21
369:19	370:1
370:4	370:7
370:10	370:11
380:11	383:14
383:17	388:2

X. **Deposition of Robin Pitts Wojcieszek**, designated pages Exhibit J.

Start (Page:Line)	End (Page:Line)
6:10	6:17
9:19	11:3
11:6	12:17
130:2	130:19
130:21	131:4
167:15	169:23

Start (Page:Line)	End (Page:Line)
170:1	171:5
171:7	172:6
172:13	173:1
173:3	173:22
173:24	174:2
174:4	177:4
177:6	177:14
177:16	180:10
180:12	182:18
182:23	182:25
183:2	183:17
183:19	189:12
189:14	192:5
192:7	192:23

Lilly reserves the right to introduce any of the deposition testimony set forth in plaintiff's deposition designations. Lilly further reserves the right to affirmatively designate any deposition testimony not yet taken in this or any other matter. Lilly further reserves the right to introduce additional deposition testimony not included above, if deemed necessary for the rebuttal of testimony from witnesses called by plaintiff or exhibits introduced by plaintiff at the trial of this action.

DATED this 22nd day of January, 2008.

PEPPER HAMILTON LLP
Andrew R. Rogoff, admitted *pro hac vice*
Eric J. Rothschild, admitted *pro hac vice*
and
LANE POWELL LLC
Attorneys for Defendant

By A.E. Girolamo-Welp
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Andrea E. Girolamo-Welp, ASBA No. 0211044

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A B C D E

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: MDL-1596

ZYPREXA PRODUCTS

LIABILITY LITIGATION

THIS DOCUMENT RELATES TO:

ALL CASES

C O N F I D E N T I A L

- - -

July 26, 2006

- - -

Videotape deposition of

CHARLES BEASLEY, JR., M.D.

- - -

GOLKOW LITIGATION TECHNOLOGIES
1600 John F. Kennedy Boulevard
Suite 1210
Philadelphia, Pennsylvania 19103
(877) DEPS-USA

- - -

CHARLES BEASLEY, JR., M.D., after having been duly sworn, was examined and testified as follows:

- - -

EXAMINATION

- - -

QUESTIONS BY MR. SUGGS:

Q. Good morning, Dr. Beasley. Would you state your full name for the record, please?

A. Yes, my name is Charles M. Beasley Jr.

Q. And how old are you, sir?

A. I am 56.

Q. And are you married?

A. Yes, I am.

Q. And do you have any children?

A. No, I do not.

Q. Okay. And are you currently employed by Eli Lilly?

A. Yes, I am.

Q. And what's your current job

title?

A. My current job title is Distinguished Lilly Scholar and Chief Scientific Officer For Global Product Safety.

Q. And how long have you held that position?

A. I've held that position since the spring of 2003.

Q. Okay. And do you currently have any responsibilities regarding the drug Zyprexa?

A. No, sir, not directly. I -- my current function is a consultant within Global Product Safety across a number of compounds as people would come and consult to me.

Q. Okay. What, if anything, have you done to prepare for this deposition?

A. I have met with my attorney during the last week, and the early part of this week.

Q. Okay. And about?

THE OPERATOR: Scott Bailey has joined the conference.

MR. SEE: Mr. Bailey, this is Andy See, I'm representing Lilly, could you indicate who you represent and whether you have signed on or agreed to be bound by the protective order?

MR. BAILEY: We have agreed to the protective order and I represent Dr. Wanda Lee in the Howard case pending in, I believe, Fulton County, Georgia.

MR. ALLEN: Mr. See, I don't want to get on the record this early, but it's not your fault. But we have these interruptions throughout the day, I promise you that won't be the last one, and I just want to make it clear for the record those interruptions should not count against our time.

MR. SEE: We'll all work with what we have here and do our best.

MR. ALLEN: Thank you.

QUESTIONS BY MR. SUGGS:

Q. Dr. Beasley, about how many hours did you spend meeting with your attorneys before the deposition?

A. During the last week and-a-half, I think, it was either four or five partial days that were running usually from about 9:30 or 10 o'clock to about 3 o'clock or 3:30 in the afternoon.

Q. Okay. And have you talked with anyone else besides your attorneys in order to prepare for the deposition?

A. No, I have not.

Q. Were there any individuals present at those meetings you had with your counsel besides attorneys?

A. No, there were not.

Q. Did you review any documents in those meetings that refreshed your recollection?

A. Yes, I did.

Q. Okay. And have you -- do you have any agreement to work with Lilly or its attorneys in connection with this litigation apart from your regular employment agreement?

Page 30

A. No.
Q. Okay. As part of your preparation for the deposition were you asked to practice question -- pardon me. Were you asked practice questions and did you give practice answers?
A. No, I did not.
Q. Okay. Was any part of your preparation videotaped?
A. No, it was not.
Q. Thank you. I'd like to go over some of your background. I believe you were born in 1950 in Tokyo, Japan; is that correct?
A. That's correct.
Q. And I assume your father was stationed there in the military?
A. That's correct.
Q. And how long did you live in Japan?
A. Six months.
Q. Not much of a memory there?
A. No, sir.
Q. Okay. And then you received

Page 31

your undergraduate degree in psychology at Yale University in 1977?
A. That's correct.
Q. Now, at that point you would have been about 27 years old; is that correct?
A. That's correct.
Q. That's somewhat older than most undergraduates who go to college right after high school. Did you do something else before you went to college?
A. There was a period where I had left Yale and attended the University of Kentucky, taking extensive work in computer science at the University of Kentucky, before returning to Yale and completing my degree in psychology.
Q. Okay. And you received your medical degree in 1983 from the University of Kentucky College of Medicine; is that correct?
A. That's correct.
Q. Okay. And then I believe you did an internship at Yale University in the

Page 32

Department of Psychiatry for a year?
A. That's correct.
Q. So that would take us up to 1984?
A. That's correct.
Q. Okay. And then you did a three-year residency in psychiatry at the University of Cincinnati in Ohio between 1984 and 1987; is that correct?
A. That would be correct. I completed the residency in June of 1987.
Q. Okay. And I believe you became board certified in psychiatry in 1988; is that correct?
A. That would have been correct. It's a two-step process and I believe that I completed the second part in, I believe, it was October of 1988.
Q. Okay. And you joined Eli Lilly as an Associate Research Physician in July of 1987; is that correct?
A. That's correct.
Q. Were you ever in private practice in psychiatry after you completed

Page 33

your residency and before joining Eli Lilly?
A. No, I was not. I came directly to Lilly from my residency.
Q. Okay. And can you briefly describe in general terms the positions you've held at Eli Lilly since joining the company in 1987?
A. Well, there's been about a 19-year evolution --
Q. I understand that.
A. -- evolution here. I joined with the title of Associate Research Physician. And my first work in the company was with Fluoxetine, trade name of Prozac, the antidepressant, and I managed and developed, supervised a number of clinical trials for Prozac. I don't remember the specific number, I believe it was someplace in the order of eight or ten.
Q. Can I interrupt you for just one second. Were those clinical trials done in support of the -- the application to FDA for -- in connection with the new drug application?

A. No, sir. These were trials that were completed and -- both initiated and completed following the submission of the new drug application.

Q. Okay. So they would have been post-marketing studies?

A. They would have been post-marketing studies.

Q. I'm sorry. I interrupted you.

A. To -- one slight technical correction on that, although, again, they did not support the original NDA, one of the trials was a maintenance study which was required in order to gain approval of the long-term efficacy of the compound. So that was, in essence, a type of registration trial.

Q. Okay. And then continue, if you would, describing the positions you've held.

A. Okay. While I was working on Fluoxetine, I also had responsibilities as the, as trial designer and -- for the

molecule that was then referred to as atomoxetine. It was being developed as an antidepressant. This molecule was not taken completely through development at the time as an antidepressant. And this work occurred simultaneously with my work on Fluoxetine, and took me -- this takes me up through, approximately, 1991.

Q. Okay.

A. I did receive a promotion during that time from associate research physician to Research Physician. So we've got several things going on here, both my title changes and my work changes. I'm trying to describe --

Q. Okay. I appreciate that.

A. -- both of those. In 1991, was the point where I was assigned responsibilities for the continued development of olanzapine or trade name Zyprexa. And I worked in this program on a global basis, both in the United States and in coordination with other physicians outside of the United States, up through 1997 as part

of the olanzapine team.

And there was an -- there was an evolution from the drug being developed as -- as part of the general Neuroscience team to a team focused, specifically, on the development of that molecule. So I took part in both of those.

Q. And during that period, were you developing and monitoring clinical trials that were in support of the new drug application?

A. Yes, I was.

Q. Okay.

A. In 1997, there occurred a significant organizational change. I also had been promoted in that period twice to Senior Research Physician and then to Lilly Advisor.

In 1997, there was a -- a reorganization. The team leader for the Zyprexa team, Dr. Gary Tollefson, was promoted to President of the entire Central Nervous System Unit. Dr. Breier was placed in charge of the team, and I transitioned off

the team to report directly to Dr. Tollefson in a consultative role. I was still rather much involved with olanzapine but in this different organizational system.

It was in about, I think, 1998 or '99, that I was assigned to be team leader for the development of a -- we call a transition team for another molecule, again, a central nervous system molecule intended for the treatment of anxiety disorders.

Q. Let me interrupt for a second. What year was that that happened?

A. I believe that was either 1998 or 1999. I don't recall the specific date. And this was a molecule that did not come to NDA, and, in fact, I was transitioned off that team prior to the the -- completion of that project.

In 2001, I transitioned completely out of the Neuroscience area. I was requested to take the position of Medical Director for our compound to tadalafil, also known as Cialis, in the cardiovascular area.

Page 38

And as I said, that work began in early 1991.
In 1990 -- I also had one promotion in this period to the position of Lilly Fellow.
In 1993, January of 1993, I --
MR. SEE: Excuse me, did you mean to say '93 or 2003?
A. Excuse me, 2003. In 2003, I transitioned back to a -- a consultative position, pretty much across all the therapeutic areas within Lilly, although I reported directly to Dr. Gary Tollefson. So my home organizational base was within central nervous system but worked across a broad number of compounds.
And then in 2004, was -- during another company reorganization, was asked to take the -- a position in global product safety.
Dr. Tollefson had retired and I was both, once again promoted to my current position and given my current functional organizational responsibilities.

Page 39

Q. Okay. I'd like to ask you some questions about Dr. Tollefson. Do you recall what his title was in the late 1990s?
I think at one point you said he was head of the entire CNS division, am I mistaken?
A. That's correct. I think he was president of the Central Nervous System Global Business Unit.
Q. Okay. And would that -- I've heard the term Neuroscience Division, is that the same thing or a subpart of that?
A. No. We could use the terms central nervous system or Neuroscience, essentially, interchangeably. What these would -- what this would include would be the areas of both psychiatry and neurology.
Q. Okay.
A. As medical specialties.
Q. Okay. And was Dr. Tollefson then senior to Dr. Breier?
A. Yes, he was.
Q. Did Dr. Breier report to Dr. Tollefson?

Page 40

A. I believe that he did. And both Dr. Breier and myself reported to Dr. Tollefson. And I don't know who else might have reported to Dr. Tollefson.
Q. And who did Dr. Tollefson report to?
A. I believe he reported to Dr. John Lechleiter.
Q. Okay.
A. Again, during this -- during this period that we're talking about.
Q. Very good. And who did Dr. Lechleiter report to?
A. I'm not sure who Dr. Lechleiter reported to at that time.
Q. Okay. I believe Dr. Lechleiter is now president of the company, is that correct, or am I mistaken?
A. I -- it's a complex relationship between himself and the -- his supervisor, and I think it's a chief executive officer position.
Q. That he has or --
A. That he has. And that

Page 41

Mr. Taurel, I'm not sure their exact titles.
Q. Okay.
A. Mr. Taurel still maintains the position that is above Dr. Lechleiter.
Q. Okay. Given what you've just told me, I'm assuming that you're pretty familiar with the general history of the development of Zyprexa, would that be correct?
A. I would certainly characterize that as correct. At least through the initial NDA and then, again, to some extent through '97 to some slightly different extent through 1991. And then I'm much less familiar with the molecule.
Q. Okay. I need to just remind myself, I need to ask you some questions on your background at Lilly before I proceed into the history of Zyprexa's development. During the time -- up -- well, let me ask this, up until 2001, would it be fair to say that you reported to Dr. Tollefson?
MR. SUGGS: Strike that. It's a bad question.

Page 46

attention to Page 5, if you would. And there there's a heading entitled Development Milestones. Do you see that page?
A. Yes, I do.
Q. Okay. And it indicates there that the molecule olanzapine which was later marketed under the trade name Zyprexa, was first synthesized in April of 1982. Does that square with your understanding?
A. That would be my understanding.
Q. Okay. And then the investigational new drug application was filed in 1986; is that correct?
A. To the best of my knowledge, yes, that would be correct.
Q. And that's sometimes referred to as an IND, correct?
A. That's correct. That's how it is abbreviated here.
Q. And an IND is something that a drug company has to file with the FDA in order to begin testing on human subjects; is that correct?

Page 47

A. Yes. And, of course, that would be within the United States --
Q. Correct.
A. -- since it's filed with the FDA.
Q. And the document also indicates that the first human dose was in September of 1986; is that correct?
A. Yes, it does.
Q. Okay. And the first open label clinical dose was in December of 1988, correct?
A. December of 1988, yes.
Q. Okay. And that phrase "First open label clinical dose" refers to a type of study where the drug is given to subjects in a clinical setting, correct?
A. Yes. This would also be what we would call an uncontrolled clinical trial. It is a very preliminary observation of the medication in -- in patients with the disease that is that the drug hopefully treats or is intended to treat.
Q. Okay. And in order to

Page 48

receive approval from the FDA to market a drug, drug companies have to perform various clinical trials, typically, involving placebo controlled and double blind studies; is that correct?
A. That's correct.
Q. Okay. And in this case, the first double blind placebo controlled dose was given in November of 1991; is that correct?
A. That's correct.
Q. And I believe you said you started working with Zyprexa in 1991. Were you involved in that very first clinical testing?
A. Yes, I was. Although I did not design those -- those clinical trials, I took over responsibility for the supervision of the molecule as those trials were beginning.
Q. Okay. And then the document indicates that the completion of core studies occurred in February of 1995. And can you describe for us what is meant by the term

Page 49

"core studies"?
A. Yes. These would have been the studies that would have been included in both the new drug application, the NDA in the United States, as well as the regulatory submissions in other countries.
Q. Okay. And the document also indicates that worldwide regulatory submission was filed in September of 1995; is that correct?
A. That's correct.
Q. And was there more than one regulatory submission filed at that time?
A. The two submissions that were filed almost simultaneously, were the U.S. submission and the European submission.
Q. Okay. And in Europe it was submitted to what agency?
A. It was submitted to the European Medicines Agency.
Q. Okay. Is that sometimes referred to as EMEA?
A. EMEA.
Q. Okay. And am I correct that

Page 50

the largest of the core studies that was done was a study that was referred to as HGAJ?
A. That was the largest.
Q. And it had, approximately, how many subjects in it?
A. It had 1,996 subjects.
Q. Okay. And was it the largest, by far, of the various clinical studies that were done in connection with the drug?
A. It was.
Q. Okay. Fair to say that the vast majority of the data that you had from clinical trials regarding Zyprexa was the data from HGAJ?
A. Given the four other trials, I think, it remained the -- probably, the majority -- again, I don't have a precise number, but I think it was, probably, just slightly over the majority.
Q. Okay.
A. In fact, if I can just -- in thinking, I think there were a total of 2500 patients treated in clinical trials that were

Page 51

included in the NDA. And I believe there were 1300 in -- treated with olanzapine, Zyprexa in that trial. So I think that is slightly more than half.
Q. Okay. And in the HGAJ study, am I correct that patients were treated in that study up to a year with Zyprexa?
A. Well, if I may, it, actually, had a rather complex design from a time perspective. There was an acute treatment period of six weeks. So all patients were treated up for -- for six weeks. If patients were not doing well, either because of tolerance or efficacy, and they remained in the trial for three weeks they could discontinue and be placed on open label olanzapine. But that would have continued to be within this trial.
There was then a -- what we call an extension that, actually, ran past a year. It ran until the time that the drug was, actually, approved. So there was definite terminal period. The option available to patients was for them to

Page 52

actually be continued for longer than a year.
Q. Okay. And the other studies that were done in connection with the NDA, were they as long-term as HGAJ?
A. Yes, they were. In fact, longer term. We had placed for patients the -- within all of the studies -- the ability to take medication until the time that we either discontinued the, the development project or the medication was approved in their specific countries.
Obviously, for patients that were doing well on the medication that was viewed as an appropriate opportunity for them to continue to receive treatment.
Q. Okay. Am I correct that Zyprexa was a drug that was intended to be used, perhaps, for a considerable period of time with any given patient?
A. Yes.
Q. In fact, was it anticipated that Zyprexa might well be used, at least in the case of schizophrenia patients, for a lifetime?

Page 53

A. That would be possible, yes.
Q. Okay. If I could direct your attention to Page 6.
Before we get to that, am I correct -- you said that the -- the prior page that we were talking about referred to the completion of core studies in February of 1995 and then the submission was filed in September of 1995.
Am I correct that in that gap of time between February and September of 1995 the data was essentially cut off, collection of data was cut off and that there was then a period of time where the data was written up for submission?
A. That's partially correct. As I said, we allowed the studies to run until the drug was approved. So there was a time when we declared the collection of data for submission to the NDA to be finalized. And that was a period where those data were unblinded, a term we refer to as locked. So those data were finalized, they were totaled and written up.

Although, again, patients were continued and data were continued to be collected in these -- in these studies that were ongoing.

Q. Okay. And at the time that the data was "locked up" or "cut off" for write-up purposes, if I can use that phrase, Page 6 of this exhibit indicates that there were about 3,000 people who had received more than one dose; is that correct?

A. That's correct.

Q. But only about 2,000 had received more than one month?

A. That's correct.

Q. And only about 875 had received more than six months?

A. That's correct.

Q. And only slightly more than 300 had actually used the drug for more than a year; is that correct?

A. That's correct.

Q. Okay.

A. These were very much intended to be designed to be in excess of what were

recommended by ICH, International Committee on Harmonization, numbers for various lengths of treatment to go into an NDA.

Q. Okay.

A. Is how the decision was made for --

Q. Certainly. So although there were over -- slightly over 3,000 subjects involved in those studies only about 10 percent or about 300 had actually used the drug for more than one year?

A. That's correct.

Q. Okay. Now, we've referred to the new drug application and the approval by the FDA of a new drug application. I'd just like to talk generally about that process.

Would you agree with me, sir, that generally the FDA does not do safety testing of new drugs to determine if they should be marketed?

THE WITNESS: I'm having a bit of difficulty understanding the question.

MR. SUGGS: Let me rephrase

it then.

THE WITNESS: Okay.

QUESTIONS BY MR. SUGGS:

Q. You've described various testing that was done on Zyprexa before it was -- went on the market. That testing was done by Eli Lilly, correct?

A. I would characterize it as being done by the -- by the investigators. It was designed and administered by Lilly.

Q. Okay.

A. Now, I understand your --

Q. Okay.

A. The FDA didn't actually do the studies or contract to have them done.

Q. Exactly. In fact, the FDA never does?

A. I think under very limited circumstances the FDA may, actually, consult or design some studies, but that's on a very, very limited basis.

Q. And that was certainly not done with respect to Zyprexa, correct?

A. No, it was not.

Q. Okay. And in this case what Lilly did was it retained or hired investigators, clinicians, out in the U.S. and elsewhere, to enroll subjects in studies that were designed by Lilly, correct?

A. They were designed by Lilly in collaboration with the investigators participating in the studies and other consultants.

Q. Okay. And those investigators then collected various data that they had been directed to do as part of the study and sent that data to Lilly, correct?

A. That's correct.

Q. And Lilly wrote up that data into a series of reports that is often referred to as a new drug application, correct?

A. That's correct.

Q. Okay. And this new drug application, it's not just a five-page application form, it sometimes can fill a boxcar, correct?

Page 110

retained by Lilly, correct?
A. I believe they were hired, paid for their attendance at these meetings.
Q. So you flew them down to San Juan, Puerto Rico, in December, which isn't too bad a gig, right?
MR. SEE: Object to the form.
A. I believe that we would have paid for their transportation.
Q. And you paid for their time while they were down there, right?
A. I assume for their meeting time with us.
Q. And these folks are regarded by the company as experts, were they not?
A. That's correct.
Q. Okay. And it's fair to say that they were concerned about the issue of weight gain with respect to the use of Zyprexa, correct?
MR. SEE: Object to the form.
A. They certainly expressed interest in this and advised us to investigate and analyze the data.

Page 111

Q. Um-hum. And sir, when Zyprexa came on the market in 1996, in October, am I correct?
A. I believe that was the case, 13 months after the NDA filing.
Q. And the labeling that was in effect at that time when the product came out on the market, did not warn physicians that your clinical studies had found statistically significant increased incidence of high glucose in Zyprexa users, correct?
MR. SEE: Object to the form.
A. That is correct. But my recollection of the data as you have -- have asked your question, is that we would not have found that.
We would have, and what we did, was we analyzed both the placebo controlled data and the haloperidol controlled data. There were three studies that include haloperidol on what we call an integrated basis. And my recollection is that those integrated analyses did not show or support the finding that we'd been

Page 112

discussing in J.
MR. SUGGS: Move to strike that portion of your answer which was nonresponsive which is everything after the answer "that is correct."
QUESTIONS BY MR. SUGGS:
Q. Did you recall that the FDA approved Zyprexa for marketing in September of 1996?
A. I don't recall whether it was late September or early October.
Q. Okay. And am I correct that one of the last things that happens before a drug is marketed is the drafting of labeling for prescribing physicians?
A. Well, there is, actually, a draft that is prepared as part of the new drug application.
Q. And it's submitted to the FDA as part of the new drug application. The FDA then comes back and says whether they approve that language or not, correct?
A. That's correct.

Page 113

Q. And oftentimes, and there is interchange between the company and the FDA as to what's going to be in the content of the language, correct?
A. That's correct.
Q. And when the FDA saw the data, the FDA -- well, let me back up for a second.
When we talk about the labeling, that's the package insert material, correct?
A. That's correct.
Q. It's also contained in the Physician's Desk Reference, which is a big thick book which contains the labeling for all prescription products, correct?
A. I think for the majority. It's not all. And those are copies of, obviously, intended to be kept current, the prescribing information or the package insert.
Q. Okay. And that information, the prescribing information that is contained in the labeling is very critical for doctors

Page 114

to have; isn't that correct?
A. It is intended to be a summary of the data that would allow the effective and safe use of the medication. That is correct.
Q. And it's absolutely necessary that the information in there is complete and accurate, correct?
A. Again, it's important that it allow for the safe and effective use of the medication. From a concept of complete, again, all 1.5 million pages can't be contained.
So the intent is that it is a summary of the most pertinent information that will allow the drug to be prescribed appropriately.
Q. And the doctor uses that information contained in the package insert to weigh both the risks and the benefits of using a drug and make an evaluation as to whether it is appropriate for him to prescribe that drug to his patient, correct?
A. That's correct.

Page 115

Q. Okay. And in the labeling there is a hierarchy of significance of information about adverse reactions or potential safety issues, is there not?
MR. SEE: Object to the form.
A. There are a series of different sections in the U.S. label.
Q. For example, there's, there can be a warning section in the drug label, correct?
A. Generally, there is a warning section.
Q. And there's also what's referred to as a precaution section, correct?
A. That's correct.
Q. And there's also what's referred to as an adverse reaction section, correct?
A. That is correct.
Q. And that is a decreasing hierarchy of significant, if the you will, is it not?
MR. SEE: Objection to the form.

Page 116

A. I'm not exactly sure what you mean by significance. If I may?
Q. Sure.
A. Significance could be the extent of which there is understood to be an association, so degree of association. That can be one thing that you might mean by significance.
The other thing that you could mean by significance would be the clinically significance of an -- of an individual term or observed event.
If you mean the latter, then those three sections don't have decreasing significance.
Q. Okay. Well, if, for example, your -- if, for example, you've got an adverse reaction or that can occur with a drug, let's call it syndrome X, okay? If you've got syndrome X that's -- and it's listed in the --
MR. SUGGS: I want to wait for the fire engine to go by.
MR. ALLEN: That won't be the

Page 117

last one of those either.
MR. SUGGS: There was one this morning at 5:30.
MR. ALLEN: We have at least three a day.
MR. SUGGS: I heard the one this morning at 5:30. Okay. I think we're safe now. Let me go back to my question.
QUESTIONS BY MR. SUGGS:
Q. Let's assume that a particular drug has something bad that can happen with it that's called syndrome X. Okay? If it's just listed in the adverse reaction section, then that means that it has been seen, syndrome X has been seen in people who have used the drug, correct, and it really means not much more than that, isn't that true?
MR. SEE: Object to the form.
A. It means that it has been seen. I believe that the standard language that the Food and Drug Administration would include in a preamble to that is that that

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B C D E

Page 134

And then the FDA went on to say, "The information on weight gain was indeed included in the approved label, but as adverse event, not a therapeutic benefit. Since the product was approved at the time of this teleconference, Dr. Tollefson knew or should have known what information the approved labeling contained and in what section it appeared, his statements therefore were false and misleading," correct?

A. Yes, it does.

Q. Okay. Now did you know that Dr. Tollefson was going to make that argument before he did so?

A. In the specific context of this teleconference, which I must assume was a nonscientific teleconference, no. We had certainly discussed this matter of whether or not weight gain could represent a therapeutic benefit for some patients.

Q. You had discussed that with Dr. Tollefson yourself?

A. We had discussed it with a -- with a number of individuals. I cannot

Page 135

recall, specifically those individuals. And it came out of our analysis of the data showing differential weight gain based on body mass index, which is a ratio of weight to height at baseline.

Q. Were you aware that Dr. Tollefson was going to make that false and misleading claim before the conference?

A. Again, I was unaware of the teleconference nor what Dr. Tollefson intended to state in that teleconference.

Q. You only found out about it afterward; is that correct?

A. That's correct.

Q. Do you recall that by 1998 Lilly had almost 200 reports of blood sugar elevation?

MR. SEE: Object to the form.

A. Are you speaking about spontaneous adverse event reports?

Q. Yes.

A. And the year was?

Q. 1998.

A. 1998. I cannot give you the

Page 136

specific number in 1998. But that would seem to me to be, approximately correct.

MR. SUGGS: Okay. I'm going to hand you what's been previously marked as Exhibit 988.

(Whereupon, Deposition Exhibit(s) 988 previously marked, was presented to the witness.)

THE WITNESS: I need to get my --

MR. SUGGS: Okay. Take a moment there and put them in a file.

THE WITNESS: One's falling apart here so --

MR. ALLEN: You give the one falling apart to me, I'll go get it put back together.

MR. SEE: I think the one just needs a staple.

MR. ALLEN: I'll go get it done.

THE WITNESS: It just needs a staple.

Page 137

MR. SUGGS: I'm, again, handing you Exhibit 988.

For the record, this is a 26-page document bearing on the title page the title Census of Spontaneous Reports for Olanzapine During the First Two Years of Marketing September 27, '96 to September 30, 1998.

It was apparently prepared by Ken Hornbuckle and Man Fung of the Worldwide Pharmacovigilance and Epidemiology Department at Eli Lilly and Company. And it is marked confidential.

QUESTIONS BY MR. SUGGS:

Q. Have you seen this particular document before, sir?

A. I can't recall seeing this document.

Q. Okay. Did you review this document in the last two weeks?

A. No, I did not.

Q. Okay. Do you know who

Page 138

Dr. Ken Hornbuckle was?
A. Yes.
Q. And who is he?
A. He is a veterinarian and epidemiologist, he's our chief epidemiologist --
Q. Okay.
A. -- at Lilly.
Q. And is he still in that capacity?
A. Yes, he is.
Q. Okay. And who was Dr. Man Fung?
A. He was --
Q. By the way, am I pronouncing his name correctly?
A. Yes, that's correct, Man Fung. Dr. Fung was the physician responsible for Zyprexa, olanzapine in the Pharmacovigilance and Epidemiology Division within the company.
Q. And what is the Worldwide Pharmacovigilance and Epidemiology Division?
A. This is a unit that serves a

Page 139

number of functions in terms of monitoring the safety of products, both drugs and administration instruments. They deal with the collection of the spontaneous adverse event reports, their organization, their analysis. They -- it's been an evolving organization.

They're also involved in potentially setting up epidemiological studies intentionally suggesting prospective studies and then interfacing with regulatory, in a sense part of regulatory. This is, actually where, with a different name my current position resides within this organization.

Q. Okay. Do you know who back in 1998 Dr. Hornbuckle and Dr. Fung would have reported to?
A. No, I'm not certain at this time.
Q. Okay. Did you have interaction with either of those gentlemen back in '98?
A. Yes. I would have.

Page 140

Q. With respect to Zyprexa?
A. Yes.
Q. Okay. And describe the nature of your interaction with those folks back in '98.
A. Well, again, although I was not part of the olanzapine team, I did review aspects of safety from a product team perspective. So I would have interacted with these individuals who also served to review safety data.

So it was a -- we, in essence, formed a larger team across several components of the corporation.
Q. Okay. And who was the "we" that you're referring to?
A. Would have been Dr. Hornbuckle, Dr. Fung, other members of product team, medical members of the U.S. Affiliate, members of their -- additional members of the Worldwide Pharmacovigilance and Epidemiology staff.
Q. And did that collection of individuals you just described, did they have

Page 141

name for that team or group?
A. No, there was no specific name for that group of individuals.
Q. Is there -- was there anyone who sort of led or headed up that group?
A. It was driven, I think as sort of a joint effort with Dr. Fung, Dr. Hornbuckle, and myself.
Q. Okay. And I've seen reference to a Dr. Kenneth Kwong. Was he part of that pharmacovigilance and epidemiology group, as well?
A. When Dr. Fung moved on to other assignments, Dr. Kwong took his place.
Q. Okay. Am I correct that one of the -- well, let's talk about these spontaneous reports and what they are. These are sometimes referred to as adverse reaction reports, or adverse event reports, correct?
A. Adverse event reports, yes.
Q. And they can come in to the company from doctors or from consumers?
A. Among other people. There are a lot of sources. They can also come in

Page 142

from literature, for example, as well as other sources.
Q. Okay. And are you aware, sir, that it's generally estimated that only 1 percent, maybe 10 percent of the number of adverse events that, actually, occur in the use of a drug ever get reported?
MR. SEE: Object to the form.
A. The literature that I am familiar with estimated between 1 in 5 and 1 in 30 cases would be reported. This was in this time frame when I was more involved with doctors Funk and Hornbuckle. I believe that more recent literature has suggested it may be as low as one in a hundred.
Q. Okay. So if, for example, you got ten adverse event reports of -- I'll use syndrome X that we were talking about before, based on the current literature that would indicate that probably out in the real world there's maybe a hundred times that amount, which would be what, a thousand?
MR. SEE: Object to the form.
Q. I take it back. You said one

Page 143

in a hundred.
A. I said you would multiply, and the best understanding that I have of the literature is that there is not a good estimator for what this is, but you could multiply by between 5 and 100, that would be the range.
Q. Okay, between 5 and 100.
A. So if you had 10 it might be 50.
Q. Or it might be --
A. Or it might be a hundred -- thousand.
Q. Okay.
A. A pretty wide range.
Q. Okay. In any event, the main thing is though, that if you get one adverse event report you've got to assume that there's a bunch more out there.
MR. SEE: Object to the form.
Q. How big that bunch is we're not sure about but there's, probably, a bunch more out there, right?
MR. SEE: Object to the form.

Page 144

A. There may be. One thing that we take into consideration when we consider that, and it's supported by some of the literature, is to what extent the drug -- a drug is having an event reported is new, how serious the event is, and to what extent the event has been described in either the medical literature or the -- or the public nontechnical literature.
So there are a number of things that we take into consideration when we do an estimate of this range.
Q. Okay. If I could direct your attention, sir, to page, I believe it's 14. And as it turns outs there is --
A. May I --
Q. -- there's two sets of numbers on these pages.
A. May I, just since I opened this document up.
Q. Sure.
A. It has refreshed my memory with respect to the reporting structure for Doctors Hornbuckle and Fung. There is a

Page 145

reference to Edmundo, so I believe that they would have reported to Dr. Muniz.
Q. How do you spell that?
A. I must confess I have difficulty with spelling Beasley on occasion, so, I believe it would be M-U-N-I-Z.
Q. Okay.
MR. ALLEN: Or something thereabout.
A. It's a -- he's originally from the Dominican Republic. It's a Latin name. It's hard for me to spell.
Q. If I could direct your attention to Page 14, and I'm referring to the bottom most number of Page 14.
A. Okay.
Q. I believe you're on the same.
A. Is it --
Q. It has two numbers, one -- it's my 14 as opposed to the 13 that was on the original document. You're there. This is the section on showing blood sugar elevation, correct?
A. Clintrace Database. This

Page 150

MR. ALLEN: Object to everything after "I don't know" as being nonresponsive.

MR. SUGGS: I concur with the objection.

QUESTIONS BY MR. SUGGS:

Q. Do you recall that by December of 1998, just a couple of months after the cutoff period for this report, Lilly was struggling about what to say regarding the link between weight gain and diabetes?

MR. SEE: Object to the form.

A. Again, in the -- I don't recall any specific information or discussion about what Lilly was going to say in any specific context in that time period.

MR. SUGGS: Let me hand you what's been previously marked as Plaintiff's Exhibit 6890.

(Whereupon, Deposition Exhibit(s) 6890 previously marked, was presented to the witness.)

Page 151

MR. SUGGS: For the record this is an e-mail from Mary Ann Adams to Michael Bandick, Charles Beasley, Dr. Alan Breier, Alan Clark, Annmarie Crawford, Charles Feehan, there may be another name that's cut off, and the subject is Agenda Zyprexa Medical Marketing Meeting.

QUESTIONS BY MR. SUGGS:

Q. And it's -- the agenda is dated December 9, 1998.

A. Yes.

Q. And have you seen this document before, sir? Do you recall receiving it?

A. No, I do not.

Q. Do you have any reason to doubt that you would have received it back in December of 1998?

A. Given that I was an addressee, I would believe that I received it.

Q. And have you reviewed this

Page 152

document more recently, say, in the last two weeks?

A. No, I have not.

Q. Okay. Is that group of individuals -- well, first of all, who is Mary Ann Adams?

A. She was an administrative assistant. I'm not sure to whom she was an administrative assistant at the time.

Q. Are the people who are listed as receiving this e-mail were they members of any particular group at Lilly?

A. Well, this is a -- it's a group of individuals that I'm having difficulty characterizing as belonging to any specific, any specific group.

I believe that there is a mix of U.S. marketing people, myself, outside the product team, Alan Breier, team leader or head of the product team, Alan Clark -- I almost misread that, Alan Clark was also U.S. marketing, and then Annmarie Crawford was a statistician on the product team. So again, I'm having difficulty saying this was group

Page 153

X.

Q. Okay. Were you -- do you know whether there was a regularly constituted group referred to as medical marketing?

A. I don't recall a specific fixed group that was given that name.

Q. Okay. You referred several times to a group known as the product team that was led by Alan Breier, am I correct?

A. That's correct.

Q. And can you describe for us what that product team consisted of or who was on that team?

A. That was a very large team of individuals that was responsible for this molecule exclusively from a worldwide and corporate perspective, primarily, directed at doing research but also with a global marketing component.

And that is in contrast to the, I guess, 190 international affiliates who actually did, also did research and, actually, directly marketed the compound. So

Page 154

this is a group that did general work with the compound. And I hope that's an adequate explanation.

Q. I'd like to probe a bit more in terms of you said it's a large team, and I don't expect you to remember all the particular individuals, but were there different departments that comprised the components of that team?

A. Yes. There would have been a medical component. So there were a number of physicians that were on the team.

Q. And you mentioned Dr. Breier. He's, obviously, a physician.

A. He was a physician but he was the head of the whole organization.

Q. Do you recall whether doctors Kinon and Dr. Robert Baker were members of that product team?

A. I think they were, actually, members of the U.S. Affiliate. So they would not have been members of the product team, at least at this point in time.

I don't think -- I think

Page 155

Dr. Kinon was briefly a member of the product team early when he came to the company but then moved to the U.S. Affiliate.

And I don't think -- I think Dr. Baker when he came was, came directly into the U.S. Affiliate.

Q. Okay. I interrupted you. You were telling me that part of the product team was a medical -- well, it was led by Dr. Breier, there was a medical component, and that's when I interrupted you.

A. There would have been a medical component -- I hope I get most of these.

There would have been a statistical component.

There would have been a very large component that we -- there would have been a systems component, people that actually work with the computers in contrast to the statistical individuals.

There would have been what we call, for instance, medical plans. These are the individuals usually with bachelor's or master degree training that actually support physicians in the conduct and the interface with doing research.

There would have been a medical writing component.

Those are the ones that I'm familiar with. I may be missing a component or two.

Q. Okay. Let me direct your attention back to Exhibit 6890 and this agenda for Zyprexa Medical Marketing in December of 1998. Do you recall this particular meeting?

A. No. Almost seven and-a-half years ago, I don't recall this specific meeting.

Q. Okay. Do you see that under the agenda there's several bullet points. The middle one is weight gain and link to diabetes, question mark, what does the data say and what is our action plan, question mark. Do you see that reference?

A. Yes, I do.

Q. And then there's a

Page 156

Page 157

handwritten note at the bottom relating to weight gain, correct?

A. Yes, there is.

Q. By the way, do you recognize that handwriting?

A. No, I don't.

Q. The handwritten note says: "Weight gain and genetic vulnerability lead to hyperglycemia," correct?

A. Yes, it does.

Q. And do you agree with that medical concept?

A. I would characterize this as being not correct.

Q. Okay. In what way do you say it's not correct?

A. I would view both weight gain and genetic variability as risk factors for the development of hyperglycemia. Individuals who have these risk factors may or may not go on to develop hyperglycemia.

A lot of people gain weight who don't become diabetic, as with people, there are people who become diabetic who

Page 158

don't gain weight.
Presumably there is this element of genetic variability. Certainly a strong hypothesis built on epidemiologic studies noting that it runs in families but we have not identified the gene abnormality that invariably leads to hyperglycemia.
Q. Okay. Am I correct in assuming that it is your view that both weight gain and genetic variability are independent risk factors for the development of hyperglycemia?
A. Thinking about that. Because we don't understand this issue of genetic vulnerability, we do not have a good understanding of how it might interact, either in lock step or in association with weight gain or independent of weight gain.
My own personal belief is that they are, probably, independent. I say that because we know that there are patients, such as myself, who may become diabetic who don't gain substantial weight.
Q. Okay. And would you agree,

Page 159

sir, that regardless of whether they are independent risk factors or not, or the alternative of being independent would be that they were somehow linked, would you agree that if an individual has both weight gain and is -- has genetic vulnerability then they would be at increased risk for hyperglycemia?
MR. SEE: Object to the form.
A. I don't know precisely. I believe that the data suggests that the more risk factors you have the higher potential there is for the development of diabetes, whether these are simply additive or they reinforce each other we don't know.
Q. Okay. Clearly, you wouldn't want a person to have both weight gain and genetic vulnerability, at least with respect to their risk for diabetes or hyperglycemia, correct?
MR. SEE: Object to the form.
A. No. I mean, you don't want weight gain or genetic vulnerability.
Q. Okay. And, sir, do you

Page 160

recall there were people back in your company in 1998 who wanted to avoid linking weight gain and diabetes or hyperglycemia?
MR. SEE: Object to the form.
A. No, I do not.
Q. Do you recall talking to people in the marketing department in December of 1998 about the issue of weight gain and diabetes?
A. I don't recall, specifically. I may well have done so in the process of trying to educate individuals that were specializing in neuroscience as opposed to diabetes care about sort of the basics of diabetes.
Q. Do you recall telling people in the marketing department back in December of 1998 that the use of antipsychotic drugs could result in weight gain and that people who gain weight may develop insulin resistance which can lead to hyperglycemia and diabetes?
A. I may have been explaining that -- that there are these associations.

Page 161

Q. Okay. Was it your belief at the time, back in December of 1998, that the use of antipsychotic drugs could result in weight gain?
A. Yes. I think the data for that are rather clear as reflected in our package insert, specifically, for our drugs and I think the David Allison article that I think was published by this time, to which we'd contributed, looked at antipsychotics in general and suggested that.
Q. And was it your view back in December of 1998 that people who gain weight may develop insulin resistance which can lead to hyperglycemia and diabetes?
A. I would characterize it as a risk factor for developing.
Q. And if someone has a risk factors that means that they may develop that problem, correct?
MR. SEE: Object to the form.
A. That puts them at increased risk. To be very precise, that puts them at increased risk relative to patients or

Page 162

individuals without that risk factors.
Q. And if, in fact, you have a group of people who are at increased risk, then those people, some of them, you may not be able to tell who, but some of them will, indeed, come down with the, with the adverse event at the end of the day, right?
MR. SEE: Object to the form.
A. I can't absolutely conclude that because again, these things remain risk factors. Some of them, actually, having a relatively low incidence of increased risk.
So I cannot automatically know that because someone has risk, or that a large group of individuals has risk factors that somebody will definitely develop the condition within that --
MR. ALLEN: Okay. Objection, nonresponsive.
MR. SUGGS: Let me restate the question.
Q. Would you agree, sir, that if you have a group of people who are at increased risk of having some adverse event

Page 163

occur that it is more probable than not at the end of the day, that some of those people will, in fact, develop the adverse event as a result of using the drug that increased their risk?
MR. SEE: Object to the form.
A. All I can say is that there is increased probability among those individuals with that risk factor of developing the condition if they -- than if they did not have the risk factor.
MR. SUGGS: Okay. I'm going to hand you what's been previously marked as Plaintiff's Exhibit 1215.
(Whereupon, Deposition Exhibit(s) 1215 previously marked, was presented to the witness.)
MR. SUGGS: By the way it's about 12:20. I suggest we finish the exam about this document and then maybe break for lunch.
MR. SEE: Sure, that would be fine.

Page 164

THE WITNESS: I could stand a bathroom break at some point.
MR. ALLEN: Let's take it now then. Do you need it now?
MR. SUGGS: Now is fine.
MR. ALLEN: It's up to you because you know, I am just telling you, you said on the camera you could stand a bathroom break and who knows what you might say in a minute. Then, you know what I'm saying? You could say I didn't really understand you, I needed a bathroom break. So let's go ahead and take a bathroom break.
THE WITNESS: Excuse me. I'm sorry about that.
MR. ALLEN: That's okay. You are right.
MR. SUGGS: We'll break for lunch. And we'll do the bathroom break.
MR. ALLEN: Off the record.

Page 165

parties at this time.)

Q. Why is there a slash between there? Were those two joined at the hip or something?
A. Well, pharmacovigilance department was part of regulatory, so --
Q. Okay.
A. -- I don't have an explanation why he wrote it this way.
Q. Okay.
A. Again, that's not part of medical.
Q. Okay. And then he refers to the Zyprexa team. Was that the Zyprexa Product Team that you were referring to before?
THE WITNESS: Let me read this.
MR. SUGGS: Sure.
A. In the Zyprexa Team. Yes, I believe that would have been the product team.
Q. Okay. And then Dr. Muniz states under that section, "while Val Simmons, Man Fung, Kenneth Kwong and Charles

Beasley have been working closely together on this issue, it was felt that a broader involvement of regulatory pharmacovigilance Mike Clayman, Tim Franson, and Greg Brophy, and Edmundo Muniz, was needed to evaluate a short-term plan." Did I read that correctly?
A. Yes.
Q. Would it be fair to say, sir, that this memo reflects that in November of 1999 the hyperglycemia issue had -- with Zyprexa had become quite an issue, correct?
MR. SEE: Object to the form.
A. I think what this reflects is the company had very clearly intended to increase the resources, both number and level of resources, that were being brought to bear to assess the topic.
Q. Um-hum. By the way, when the clinical trials for Zyprexa were done, was it a specific focus --
MR. SUGGS: Strike that.
QUESTIONS BY MR. SUGGS:
Q. When the clinical trials for Zyprexa were done before it was marketed, was

the evaluation of the risk of diabetes with Zyprexa a specific goal of those clinical studies?
A. Although it was not a -- stated as a primary outcome in the protocol, it was clearly one of the many aspects of safety that was evaluated.
MR. ALLEN: Objection, nonresponsive.
Q. If diabetes or hyperglycemia had been the specific goal of the study, would you have recommended that fasting glucose blood tests be taken as opposed to random blood glucose testing?
A. Actually, I would not have made that recommendation.
Q. Okay. And why is that?
A. My concern is with the compliance of patients that suffer severe mental disease, and knowing that you could get the possibility of really significant noncompliance in this patient population, so that if you thought you had fasting glucoses, in many instances you may well not have

fasting glucoses. That was my opinion at the time.
Q. Okay. It's pointed out by Dr. Muniz in the background section of this e-mail, that, "The discussion regarding hyperglycemia slash weight gain and antipsychotic drugs goes back as far as the early 1950s," and that, "For more than two decades, until the 1980s there was a large number of publications but the interest in the scientific community and the regulators decreased until very recently." Do you see that language, sir?
A. Yes, I do.
Q. And were you aware of that discussion of hyperglycemia and weight gain being linked with antipsychotic drugs going back to the early 1950s?
A. This was, actually, part of my residency training.
Q. Okay. And right below that section in Item B in the background, Dr. Muniz states, "Two regulatory agencies, EMEA and CANDA, have proactively asked

questions about hyperglycemia and Zyprexa."
Do you see that?
A. Yes.
Q. And were you involved in responding to those questions raised by the regulatory agencies and EMEA in Europe and Canada?
A. I certainly would have been involved, along with the pharmacovigilance people, who would have developed the primary response.
Q. And were the regulatory agencies in Canada and Europe concerned about hyperglycemia and being linked with Zyprexa?
MR. SEE: Object to the form.
A. They had certainly asked us to conduct specific evaluations of our post-marketing surveillance statement.
Q. And in fact, by this point in time, November of 1999, the European regulatory agencies had already requested that hyperglycemia be a precaution in the European label; isn't that correct?
A. I -- the European label does

not make a distinction between warnings and precautions. There's one unified section. I don't have specific recollection of when they requested that it be included as a warning.
Q. If I were to suggest to you that it was requested in late 1998 and that Lilly finally added it to the warnings slash precaution section of the European labeling in July of 1999, would that refresh your recollection?
A. I could well believe that that was correct. Again, I don't remember the specific.
Q. Okay. You don't have any reason to doubt those times I stated there, do you?
MR. SEE: Object to the form.
A. No, I do not.
Q. And regardless of the precise month, you would agree with me that at least by this point in time, November of 1999, hyperglycemia had been added to the precaution slash warning section in Europe, correct?

A. Tha[illegible], there's even
Q. Ok[illegible] at the bottom of this a hand written note on the e-mail saying precaution in Europe, correct?
A. Yes.
Q. Okay. And by this point in time, hyperglycemia was mentioned in the U.S. labeling but only in the adverse reaction section, correct?
A. Hyperglycemia, among other diabetic related terms, yes.
Q. In the adverse reaction section, not in the precaution section, not in the warning section, correct?
A. That's correct.
Q. Okay. And Item C in this e-mail it states, "Charles Beasley reassured us that regulators have felt satisfied with Lilly's explanations and Lilly's commitment to conduct new clinical trials and to continue to do proactive post-marketing safety surveillance." Did I read that correctly?
A. Yes, you did.

Q. And who did you work with on that project?
A. There were a number of people that I -- and this, actually, represents a number of projects. And, again, I don't recall specific conversation with Edmundo, but there were several activities that were going on at the time.
I worked with the pharmacovigilance individuals and the team, the product team, to produce a review, very detailed review of both the spontaneous data and the -- and the clinical trial data, that -- substantial amount of which had accumulated since the drug had been released.
We had also made the decision to conduct -- and this was in part of agreeing with this senior leadership cross-functional team, to conduct some studies of potential mechanisms of inducing hyperglycemia. So that we -- we had intended to study ways in which the medication might cause patients to become hyperglycemic if it did.

Q. Okay. Now, you said you worked with the pharmacovigilance individuals and the team to produce a very detailed review of the spontaneous data and clinical trial data. Can you tell me which individuals those would have been?

A. Well, it would have -- for the pharmacovigilance side, it would have certainly been at the time Dr. Kwong and, probably, a number of other individuals that would have produced reports, summarized them. I don't know those -- the other individuals's names.

Q. Okay. And when you said in your earlier answer that, that group that you were working with was also going to do a very detailed review of the clinical trial data, was that existing clinical trial data?

A. That was existing clinical trial data. I think, by this time we had completed a very large number of studies.

Q. Okay. And this would be data from the H -- the continuation of the HGAJ study among other things?

A. Among other things, yes.

Q. Okay. And you had some other clinical trial that had been ongoing since the drug was on the market?

A. I think there were, probably, someplace between 50 and a hundred.

Q. Okay. And when did you start that review? Had it -- let me ask --

MR. SUGGS: Strike that.

QUESTIONS BY MR. SUGGS:

Q. Had your review of the spontaneous data and the clinical trial data to deal with this --

MR. SUGGS: Well, let me back up for a second.

QUESTIONS BY MR. SUGGS:

Q. This, as you referred to it, detailed review of the spontaneous data and the clinical trial data in 1999, was that for the purpose of addressing the hyperglycemia issue?

A. The topic of hyperglycemia, yes.

Q. Okay. And who was it that directed you to undertake that review?

A. No one, actually, directed that review to be undertaken, to the best of my recollection. It was Dr. Kwong in pharmacovigilance, his group, and myself that felt it would be appropriate to conduct a very, very thorough --

Q. Okay.

A. -- and comprehensive review. I believe that it began in early 1999.

Q. Okay. And would it be fair to say that you and Kenneth Kwong were the principal drivers for undertaking that review?

A. Yes, directly. But again, Dr. Breier had put together this team that, I believe, he, actually, convened earlier than 1999, I'm not sure when he, actually, convened this team to look at clinical data, preclinical data for both weight gain, which there was recognized data an association, and potentially develop treatment methods, potentially do studies to investigate potential treatment methods, and that this

piece of work that Dr. Kwong and I decided to undertake, we, actually, viewed as a component of this overall activity.

MR. ALLEN: Objection, nonresponsive.

Q. And who did you believe you needed to report the results of your analyses to?

A. Many people. Obviously, senior management, both regulatory, medical and, of course, Dr. Tollefson. Other individuals, and then potentially, and quite likely, regulatory agencies.

Q. Okay. Did you have discussions with Dr. Tollefson, yourself, regarding the hyperglycemia issue?

A. I don't recall specific conversations. I would believe that I did since I viewed this as an important topic.

Q. Okay. In the Section 3 of the e-mail from Dr. Muniz, there's a reference to short term action plan. And there are a number of items listed below there, including continuing to strengthen the

Page 258

know who the statisticians were that were working with her.
Q. Okay. I want to make sure I understand the time frame here. In February of 2000, a year before this e-mail, you and Kenneth Kwong do an analysis which finds an incidence of treatment-emergent hyperglycemia three and-a-half times higher in Zyprexa users versus placebo users, correct?
MR. SEE: Object to the form.
A. And again you've characterized that, I believe, as a final finding.
Q. I'm not characterizing as final, partial, whatever. You did an analysis that you thought was important enough and you felt confident enough in to submit to the Global Product Labeling Committee which said that the incidence of treatment-emergent hyperglycemia was three and-a-half times higher in Zyprexa users as compared to placebo users, correct?
A. That is correct and I'm trying to provide the context.

Page 259

MR. SUGGS: Move to strike the nonresponsive portions.
Q. Three months later, you and others jen-up language that goes into the labeling under the special supplement changes being effected, which shows, essentially, no difference between the incidence of hyperglycemia in Zyprexa users versus placebo users. And five months after that, FDA makes you take out that language because they say it's -- it gives an implied sense of safety, correct?
MR. SEE: Object to the form.
A. And I would agree with you --
Q. You need to answer the question, first, sir.
MR. SEE: I think he's answering your question.
A. I agree with you with respect to the action of the FDA. In your question you characterized our actions in a certain fashion that I would disagree with.
Q. And then five months after the FDA makes you take out that language,

Page 260

which they said was expressing a certain level of implied safety with respect to treatment-emergent hyperglycemia, you do another analysis which finds a statistically significant mean increase in random glucose for Zyprexa relative to placebo and haloperidol, correct?
A. That was my understanding at the time having not been involved in those analyses.
Q. And, sir, if I could direct your attention to the remaining language in that paragraph, you go on to state, "These increases are occurring as early as week one," correct?
A. Yes.
Q. That would be week one after beginning use of the drug?
A. That's correct.
Q. And you say "These changes are accounted for, in part but not entirely, by weight increase," correct?
A. I think you have excluded a parenthetical in the -- in this but -- that

Page 261

states, "may not represent a true deterioration in glycemic metabolism but simply an increase in food intake since these are random and not fasting glucoses."
Q. And then you go on to say, "These changes are accounted for, in part but not entirely, by weight increase," correct?
A. That's correct.
Q. And then you say: Categorical analyses to values above a set of thresholds, 126, 140, 160, 200 milligrams per deciliter, do not reveal significant findings, but trends are there, except for the comparison of clozapine to olanzapine to the lower two thresholds, clozapine more, correct?
A. That's correct.
Q. And so, when you do categorical analyses like that, you are splitting the data up into different chunks, correct?
A. That's correct. We have been talking -- most of what we've been talking about so far has been categorical analysis.

Q. And when you --
A. You define a certain value that makes a distinction between normal and abnormal. At this time, 126 was the ADA criteria, so if you were 125 you would be considered normal, if you were 126 or above you would be considered abnormal.
Q. And describe for the jury what the difference is between a categorical analysis and a continuous analysis?
A. A continuous analysis is where you take averages, you have a certain number of individuals who have a baseline or a before treatment value, and each one of those patients has an individual value, and then they are observed to have multiple values, because it's measured while they're on treatment. And each of those patients will then have a change at each point of the observation and those changes are taken as an average.
Q. And, sir, it was your continuous analysis that you're referring to here which showed that olanzapine does result

in statistically significant mean increases in random glucose relative to placebo and haloperidol, correct?
A. That was my understanding of the work that had been done at that time, yes.
Q. Okay. And, sir, it was continuous analyses which your company's own outside experts recommended that you needed to be looking at, correct?
A. Yes. And I think that was the reason they were looked at.
Q. And let's talk about -- let's talk about that right now. Do you recall that in October of 2000, you and various representatives of Eli Lilly had a meeting with a group of outside experts in Atlanta?
A. Yes, I do.
Q. Okay. And those were -- those people that you met with, those outside experts, were an academic advisory board, correct?
A. That's correct.
Q. Now, Eli Lilly is a drug

company which makes, not only psychiatric drugs, but also makes and distributes a number of drugs for the treatment of diabetes, correct?
A. That's correct.
Q. In fact, Lilly sometimes refers to itself as the diabetes care company; isn't that correct?
A. I have not heard that characterization but the company is involved in producing both insulin and other drugs.
Q. And Lilly was involved in, in fact, didn't Lilly come up with one of the first insulin drugs ever?
A. Lilly didn't discover insulin, but Lilly was instrumental in developing the process for extracting it and stabilizing it so it could be used in humans.
Q. And how far back was that done?
A. I think that goes back into the late 1910s or, probably, the early 1920s.
Q. And the company had been intimately involved with diabetes and

diabetes drugs since that time, correct?
A. That's correct.
Q. So by 2000, almost 90 years of experience in the field of diabetes, correct?
A. That's correct.
Q. Your company had reams, dozens of doctors and scientists who did nothing but specialize in diabetes issues, correct?
A. That's correct.
Q. But they were in a different division than the division that was dealing with Zyprexa, correct?
A. That's correct.
Q. Okay. And when you had this meeting with the outside experts in Atlanta in October of 2000, these were outside experts that the diabetes side of the company had been using as consultants for some period of time, correct?
A. That's correct.
Q. And in fact, this group of folks -- do you remember the names of the

Page 362

manufactured by the parent company.
Q. Which is Eli Lilly here in Indianapolis, Indiana?
A. That's correct.
Q. Okay. You said, just another little answer you said, on the Zyprexa Product Team there was a medical writing component. Do you recall using the term medical writing?
A. Yes, I do.
Q. The medical writing component is what, sir?
A. There are two parts to that component.
Q. Can you tell us as briefly as possible?
A. Yes.
Q. Okay. Thank you.
A. There is the component that, actually, develops and keyboards our regulatory documents. And then there is a component that will keyboard some of our scientific publications.
Q. Yes. There are people in

Page 363

your company that are not medical physicians or scientists, necessarily, who help draft medical articles and other individuals names are subsequently added to the article as an author; isn't that true?
A. Again, my characterization, and the people that I've worked with, have been doctorate level individuals who would work with me. Frequently, I would draft my articles and they would keyboard them.
Q. So this phenomena which I've outlined for you, that somebody in medical writing actually writes the article and the author's name is later put on the article is something you're not familiar with?
A. I am not familiar with the range of how these scientific articles would be developed. What I can speak to is my experience.
Q. Would it be right or ethical for someone to ghost write an article for another person and then put their name on that article?
MR. SEE: Object to the form

Page 364

of the question.
A. That would depend upon the input that the individual had who was included as an author.
Q. Yes, sir.
A. In fact, in my experience the medical writers have also been included as authors.
MR. ALLEN: Objection, nonresponsive. Because I didn't ask that.
QUESTIONS BY MR. ALLEN:
Q. My question is this, if, in fact, an individual goes ghost writes an article, does not put his or her name on it and gives it to somebody else to stick their name on it as the author would that be ethical?
MR. SEE: Object to the form of the question.
A. Again, you have characterized the process as one of ghost writing without the name of the writer, and my experience has not been of that nature.

Page 365

MR. ALLEN: Objection, nonresponsive.
Sir, I'm not asking about your experience. I'm asking you a question.
THE WITNESS: But I was then going to answer your question.
MR. ALLEN: Well, I just want an answer to my question. I object to -- let me rephrase the question.
QUESTIONS BY MR. ALLEN:
Q. Would it be ethical for someone to write an article, ghost write it, not have their name on the article, and have someone else put their name on the article as the author, is that ethical?
MR. SEE: Object to the form of the question.
A. Yes, if the individual whose name appeared as the author had scientific input into the article.
Q. Okay, sir. We'll move on. We have limited time.
Is schizophrenia a risk

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Page 366

factor for diabetes?
A. The data appears to be that there is an increased risk in the patient population with schizophrenia so that it would constitute a risk factor.
Q. So it's Dr. Beasley's opinion that schizophrenia is a risk factor for diabetes?
A. That's my understanding of the literature and, therefore, that is my opinion.
Q. How long has that been your understanding?
A. I think I first became aware of the literature in this area when we began the review of the --
Q. My question was when did you--
MR. SEE: Hold on please. Doctor --
MR. ALLEN: It doesn't require this lengthy of a discussion. Let me rephrase my question.

Page 367

QUESTIONS BY MR. ALLEN:
Q. When did it become your understanding that schizophrenia was a risk factor for diabetes?
A. Okay. Then my short answer would be I do not know. I could provide you with some approximate information.
Q. Give me an approximate date.
A. Probably, someplace in the 1998, 1999 time course.
Q. Approximately, 1998 or 1999, you were familiar with the fact that schizophrenia, at least your opinion, who is working at Eli Lilly on Zyprexa, it was your opinion that schizophrenia was a risk factor for diabetes, right?
A. That would be correct.
Q. Okay. Which -- in your opinion, a risk factor puts someone at additional risk of developing the medical condition; is that correct?
A. That's correct.
Q. Is -- do you, also, feel the same way about diabetes -- I mean,

Page 368

schizophrenia being a risk factor for hyperglycemia?
A. As -- again, I have not reviewed literature that speaks direct --
Q. My question to you simply was --
A. I don't know.
MR. ALLEN: Thank you very much.
MR. SEE: Please have the courtesy to let him finish his answer.
MR. ALLEN: He knows he's wasn't answering the question. He just said, "I don't know." That's an answer.
MR. SEE: I'm just asking for simple courtesy. I don't want to argue with you.
MR. ALLEN: I'm not -- I'm being very courteous. I'm asking for answers to my questions.
THE WITNESS: And I am trying to provide the most complete --

Page 369

MR. ALLEN: Yes, sir. But if my question calls for a question, "do you know," and the answer is, "I don't know," that's a good answer. Okay?
MR. SEE: Object to the statement.
QUESTIONS BY MR. ALLEN:
Q. All right. Now, you've told us in your opinion in the late 1990s you understood that schizophrenia, at least in your opinion, was a risk factor for diabetes, right?
A. That's correct.
Q. Do you like to have as many risk factors as possible for a disease or do you like to reduce the number of risk factors for a disease?
MR. SEE: Object to the form of the question.
A. As, I think, I testified a few minutes ago it would be optimal from a health care perspective to reduce risk factors that you could reduce to a minimum.