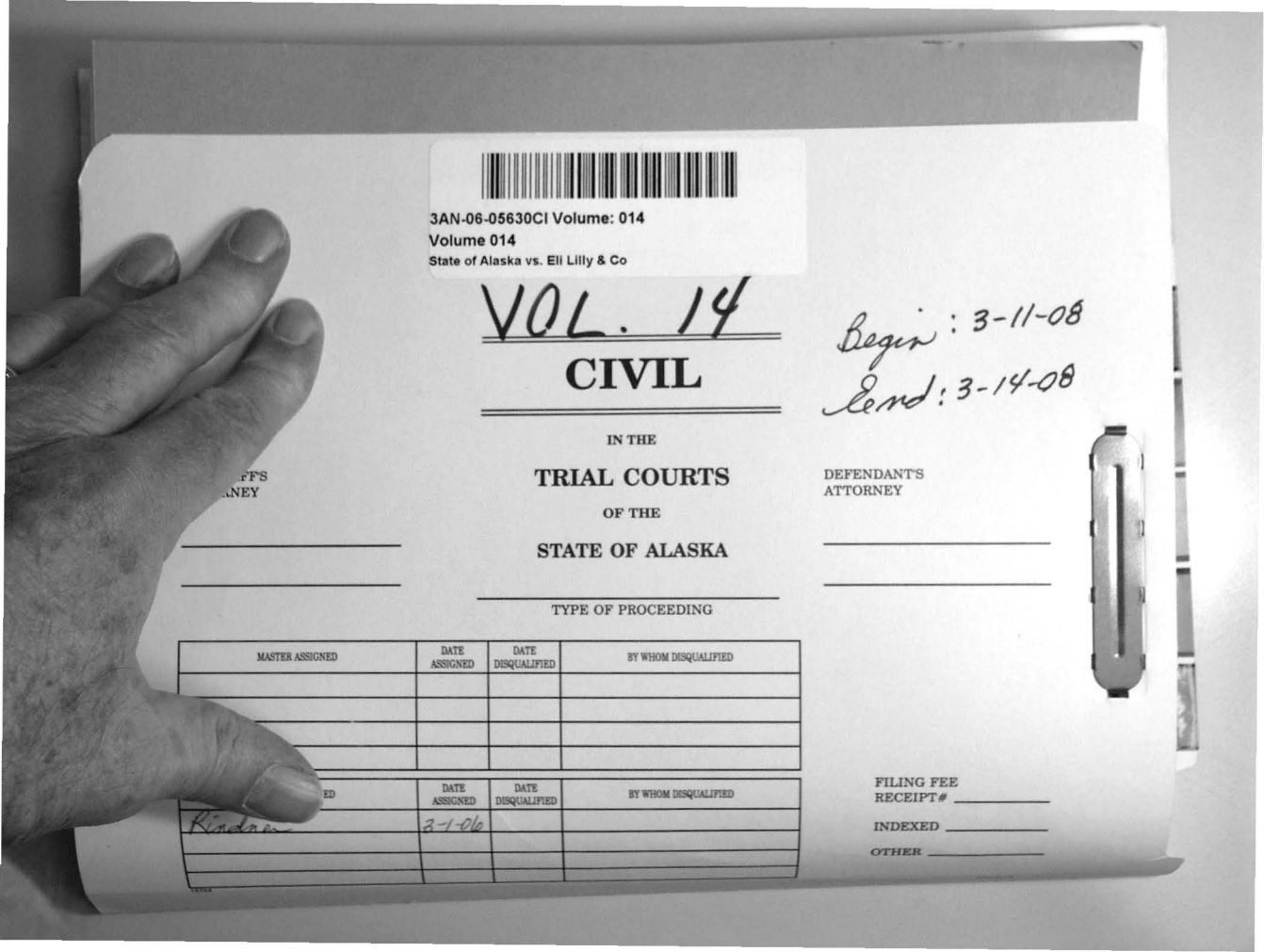

3AN-06-05630CI Volume: 014
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State of Alaska vs. Eli Lilly & Co

VOL. 14

CIVIL

Begin: 3-11-08
End: 3-14-08

IN THE

TRIAL COURTS

OF THE

STATE OF ALASKA

TYPE OF PROCEEDING

FFS
ANEY

DEFENDANT'S
ATTORNEY

MASTER ASSIGNED	DATE ASSIGNED	DATE DISQUALIFIED	BY WHOM DISQUALIFIED

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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	FILED IN OPEN COURT Date: 3-14-08 Clerk:
Plaintiff,	)	
vs.	)	
ELI LILLY AND COMPANY,	)	Case No. 3AN-06-5630 CIV
Defendant.	)	

PLAINTIFF'S OPPOSITION TO ELI LILLY AND COMPANY'S MOTION TO STRIKE TESTIMONY OF R. DUANE HOPSON, M.D.

Defendant's motion is meritless and should be summarily denied. The court should, at this point, consider whether Lilly should be subject to Rule 11 sanctions for filing its meritless motion for the following reasons:

- Lilly and its motion objects to plaintiffs having a elicited expert testimony from Dr. Hopson. However, during the course of Dr. Hopson's cross-examination, defendant through its counsel, Nina Gussack, elicited sixteen expert opinions from Dr. Hopson.

- Defendant attempts to mislead the court by falsely implying that the conduct of plaintiff's counsel was improper. The testimony elicited from Dr. Hopson by Mr. Allen was to the effect that he and Mr. Allen had never met and that testimony was both truthful and accurate. To suggest that the State is not permitted to speak with a State employee with respect to his forthcoming testimony is absurd. Further, counsel claims, without basis, that there was an "intense preparation" when, in fact, counsel has no

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knowledge of what occurred within a meeting that is protected by the attorney/client privilege.

I. Facts

First, it should be noted that with respect to Dr. Hopson, Lilly's counsel in opening statement baited the State as follows:

> And the question you should be asking yourself is: What physician is the State of Alaska bringing to this courtroom to tell us how the State got bamboozled? Because I didn't hear anything about anybody coming from the physician, no psychiatrist coming from the State to tell you how they were fooled by Lilly's label, about how it was misleading.
>
> That's because the State is not bringing any doctors from Alaska to court to tell you that they were misled, that the label's inadequate or that they were tricked into prescribing Zyprexa.
>
> Lilly is going to bring you the doctor from Alaska. In fact, you might think of him as the head doctor for Alaska, Dr. Duane Hopson, because Dr. Hopson is a psychiatrist. He is the president of the Alaska Psychiatric Association. He is also the medical director of the Alaska Psychiatric Institute, the only state-run psychiatric hospital in Anchorage, and he is an employee of the State of Alaska. And Lilly will bring Dr. Hopson to court.
>
> You might think that the State would have brought him as a witness in their case, but they won't and we will.
>
> And Dr. Hopson will tell you that he and others on his staff use Zyprexa regularly to treat patients at the Alaska Psychiatric Institute, and he will tell you that he has and continues to prescribe Zyprexa to patients right here in Alaska.
>
> He's also going to tell you that Alaska has no restrictions, no restraints on the use of Zyprexa. Two years this lawsuit has been

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> pending and for two years the State has no imposed any restriction, any restraint, any limit on the use of Zyprexa. Does that sound like somebody who has been bamboozled? If they had a complaint two years ago, you need to be asking yourself, I think, well, why haven't they done something?

Lilly's argument to the jury is of course that the State is fearful of calling Dr. Hopson because his testimony would be unfavorable to the State. Having asked the jury to draw this inference, Lilly then tried, behind the jury's back, to prevent the State from calling Dr. Hopson. It is a novel trial tactic to ascribe a motive to the State for failing to call Dr. Hopson while petitioning the court to prevent the State from meeting Lilly's challenge.

The court, after extensive argument by the parties, decided to allow the State of Alaska to call Dr. Hopson.

II. Lilly has violated *Miller v. Phillips* and local procedure to the State of Alaska's prejudice.

In its motion, Lilly complains that expert opinion testimony was elicited from Dr. Hopson. Lilly is correct. Counsel for Lilly, Nina Gussack, elicited at least sixteen separate expert opinions from Dr. Hopson during the course of the taking of his testimony on March 12, 2008. Those expert opinions do not relate to Dr. Hopson's testimony on direct and those opinions relate solely to Lilly's claimed defense. Expert opinions elicited from Dr. Hopson by Ms. Gussack include the following:

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Q: You would agree with me, wouldn't you that there is no one medication that will be effective for all of those patients?

A: Correct.

Q: And you believe it's important to have a variety of choices of medications to treat seriously mentally ill patients don't you?

A: Absolutely, yes.

[Tr. 160, lines 7 thru 14, Vol. 8, Transcript of Proceedings, March 12, 2008]

Q: You would agree with me, wouldn't you, Doctor, that no mediation can help any patient unless they are taking it, unless they're compliant with their mediation, correct?

A: Correct.

[Tr. 161, lines 6 thru 10]

Q: Okay. And you would agree with me, wouldn't you, that one of the most significant challenges in treating seriously mentally ill patients is having them become – is having them stay compliant with their medication regimen, isn't it?

A: Yes.

Q: So when a medication like olanzapine is demonstrated to have longer duration of patients staying on it, that's an important finding, isn't it?

A: Yes.

[Tr. 162, line 2 thru 13]

Q: Doctor, before I forget, there was – Mr. Allen made reference to mood, thought and behavior as bases for prescribing Zyprexa.

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You would agree with me, wouldn't you, that the reference to mood is related to bipolar disorder or bipolar disease, isn't it?

A: Yes.

Q: And you certainly describe for us, I think, in a very extensive and compelling way that the acute schizophrenic patient has many behavioral disturbances, don't they?

A: Yes.

Q: And, in fact, a bipolar patient, a manic bipolar patient has behavioral disturbances as well, don't they?

A: Yes.

[Tr. 163, line 21 thru Tr. 164, line 11]

Q: And you have always believed – you personally, that there was an increased incidence of weight gain and blood glucose elevations with patients on Zyprexa as opposed to the other atypical antipsychotics; isn't that right?

A: Yes. We began seeing that, I believe that.

[Tr. 171, lines 8 thru 14]

Q: Okay. So in 1999 it wouldn't surprise you that an article about Antipsychotic Induced Weight Gain, a Comprehensive Research Synthesis would be published and describe the effects of antipsychotics on body weight – excuse me – correct?

A: That's correct.

[Tr. 176, lines 16 thru 22]

Q: Of all the sources of information that you have about a medication, is the sales representatives' information the most

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valuable or somewhere towards t he bottom of the continuum of information?

A: I think I would consider it extremely valuable, and I – you know, would expect that it would be timely and accurate.

[Tr. 178, lines 7 thru 14]

Q: And it says here that assessment of the relationship, if you'll see the second sentence – 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.

So, let's just break that down for a minute. You would agree, sir, that the patients with schizophrenia are at increased risk for diabetes regardless of medication?

A: Yes.

[Tr. 190, lines 8 thru 20]

Q: And you would agree that there is an increasing incidence of diabetes in the population at large?

A: Yes.

[Tr. 190, lines 21 thru 24]

Q: In fact, there are those who have called it an epidemic of diabetes, correct?

A: Yes.

[Tr. 190, line 25 thru Tr. 192, line 2]

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Q: Of course we know that there's equally challenging of the American population an epidemic of obesity as well?

A: Correct.

[Tr. 191, lines 3 thru 6]

Q: And you tell us that you were well aware of the connection between being obese or overweight and the risk of diabetes?

A: Yes.

Q: There are a lot of things going on that make it hard to figure out what causes diabetes, isn't there?

A: Yes.

Q: Particularly in a patient with schizophrenia?

A: Yes.

Q: Now, it goes on to say: Given these confounding pieces that we've just talked about, the relationship between atypical antipsychiotic use and hyperglycemia-related adverse events is not completely understood.

You'd agree with that, wouldn't you, sir?

A: Yes.

[Tr. 191, lines 7 thru 25]

Q: Okay. Now, if we go to page 7 of that warning regarding hyperglycemia and diabetes mellitus, at the top of the page it says: At that time, in the September, 2003 label, that precise risk estimates for hyperglyciemia-related adverse events in patients treated with atypical antipsychotics are not available, okay.

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> And it goes on to say: The available data are insufficient to provide estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipyschotics.
>
> So, from this language in the warning of September, 2003, what physicians were being told is, there's insufficient information to make distinctions between the various atypical antipsychotics, correct?
>
> A: Yes.

[Tr. 192, lines 1 thru 18]

III. <u>The vast majority of the testimony elicited by the State from Dr. Hopson was factual in nature.</u>

A review of Dr. Hopson's testimony, which Lilly's counsel apparently has not done, reveals that the information elicited from him was primarily factual and related to how patients were treated at Alaska Psychiatric Institute and the reasons for that treatment, particularly with respect to the use of atypical antipsychotics.

Further, the following bench discussion occurred immediately preceeding the doctor's testimony with respect to the use of atypical antipsychotics:

> Ms. Gussack: We object to opinions being elicited from the witness who plainly has not been identified as an expert on the subject -
>
> Mr. Allen: I'll ask him **as a fact.** (Emphasis added)
>
> The Court: You can – I'm not going to let you ask him as an expert per expert, but he can be asked questions as a hybrid witness that – in **describing what he does as his work,** he can explain things to the jury and explain how those things affect him in his work. (Emphasis added) (End of bench discussion)

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[Tr. 76, lines 9 thru 21]

Thereafter, Mr. Allen followed the court's instruction and a reading of the full transcript makes it clear that the testimony offered "describes what thedoctor does at work." Immediately following the bench discussion with the court, Mr. Allen begins as follows:

> Q: (By Mr. Allen) Doctor, occasionally we'll have these interruptions and that's fine. I apologize.
>
> Doctor, do you, **as a practicing psychiatrist at the Alaska Psychiatric Institute**, is a warning in the package insert, in general, and on Zyprexa, in particular, important to you? (Emphasis added)
>
> A: Yes.

[Tr. 76, line 22 thru Tr. 77, line 4]

Thereafter, defense counsel's objections are sparse. However, the court is scrupulous in its instructions to counsel and the jury so that the jury understands that the testimony being given relates to Dr. Hopson's practice at the Alaska Psychiatric Institute. For example, Ms. Gussack complains:

> Ms. Gussack: This is plainly improper to have opening statements by counsel be used. It's not evidence in this case (Ms. Gussack objecting to her own opening statement.)
>
> The Court: Well, that's not evidence but his testimony – I mean, I assume he's going to ask him if he agrees and that's something he does. Actually, I don't want you to ask him if he agrees, I want you to ask him if it's something he uses in his practice.

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[Tr. 78, lines 17 thru 25]

The court is again making it clear that the doctor's testimony relates to "something he uses in his practice".

Ms. Gussack objects again:

> Ms. Gussack: Objection, eliciting an opinion from Dr. Hopson here.
>
> The Court: I'll allow that, because I think it's within his medical expertise and as part of a doctor explaining things.
>
> Q: (By Mr. Allen) Is diabetes bad for you, Doctor?
>
> A: Yes.

[Tr. 81, lines 18 thru 24]

Thereafter, the court continues to make sure that counsel and the jury understand that testimony being given by Dr. Hopson relates to his practice as follows:

> Ms. Gussack: I think the question just posed really is a Phase 2 question; it's a damage question. And haven't been given opportunity to obtain the information that would allow us to have cross-examination on this issue.
>
> The Court: I'm going to over-rule that objection, but I want you to establish that he's got sufficient information to ask that question. In other words, I've got concerns about whether – what the basis is going to be and where this is coming from and whether it's – **if it's coming from his practice, personal practice**, I'll allow him to answer the question if it's coming from the literature, he becoming an expert – (Emphasis added)

[Tr. 106, lines 9 thru 23]

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In response to the court's concern, Mr. Allen thereafter asks his next questions, which clearly relates to Dr. Hopson's practice at A.P.I. as follows:

> Q: In your professional judgment, do you believe that the protocol that you have now is a better protocol for patients' health than it used to be?
>
> A: I do.
>
> Q: And why is that?
>
> A: Because I think with our current understanding of the risks, we are better equipped to monitor for the potential side effects.

[Tr. 108, lines 3 thru 12]

And finally, at the end of Dr. Hopson's testimony, Mr. Allen continues to make it clear that he is referring to the doctor's personal practice at A.P.I. with the following question:

> Q: Doctor, based upon your personal experience and practice, do you believe prior to the time that you learned what you know about Zyprexa – and it's much difference today than it was even a year ago; is that true?
>
> A: Yes.
>
> Q: Do you believe patients who are placed on Zyprexa develop diabetes who otherwise would not have developed diabetes if you knew then what you've been told now?
>
> A: I think there are.
>
> Ms. Gussack: Objection – I said objection. For the reasons we expressed earlier.

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The Court: That's over-ruled.

[Tr. 151, lines 4 thru 17]

Ms. Gussack made no other objections during the course of Dr. Hopson's testimony relating to Lilly's claim that "improper opinions" were being given. It is clear that counsel's objections were not well-founded and each objection was handled appropriately by the court. Further, Mr. Allen was careful to comply with the court's wishes couching his questions in terms of things which affected Dr. Hopson's practice as a psychiatrist in Alaska.

IV. Conclusion

The ultimate trial tactic is to ask a jury to draw an inference based upon opposing counsel's conduct and then attempt to persuade the court to prohibit counsel from behaving in any other way. This is the taking of gamesmanship to an absurd level. Lilly, both in Dr. Hopson's deposition and at trial, sought from Dr. Hopson opinions which were completely unrelated to his practice at A.P.I. Counsel then intended to place those opinions before the jury while preventing the State from doing anything to rebut that testimony. The court has correctly decided that such gamesmanship should go unrewarded and Lilly offers no rational basis for ruling otherwise. Lilly's motion should be denied and sanctions should be imposed.

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DATED this 13th day of March, 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.

FILED IN OPEN COURT
Date: 3-13-08
Clerk: MZO

Case No. 3AN-06-05630 CI

DEFENDANT ELI LILLY AND COMPANY'S MOTION TO STRIKE TESTIMONY OF R. DUANE HOPSON, M.D.

After failing to list Duane Hopson, M.D., as either a fact, expert or "hybrid" witness in either of its witness lists, the State yesterday called Dr. Hopson and:

- Elicited expert testimony without ever disclosing a summary of his expected testimony; and
- Attempted to mislead the jury by falsely implying that this employee of the State had come to court "cold," unprepared to provide the testimony that had, in fact, been the subject of intense preparation.

This "hybrid" expert testimony constituted unfair surprise to Eli Lilly and Company and should be stricken from the record, or a mistrial should be declared.

I. FACTS

Although Lilly identified Dr. Hopson as a lay witness on its final witness list, the State failed to list him on either witness list that it has filed and, to this day, it has failed to provide any "Other Expert Opinion Testimony Summary" for Dr. Hopson, as required by the Uniform Pretrial Scheduling Order applicable to this matter. The deadline for "Other Expert Opinion Testimony Summary" passed on November 5, 2007.

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Dr. Hopson is the Medical Director of the Alaska Psychiatric Institute, which dispenses Zyprexa on a regular basis. Because the State never notified Lilly of its intention to call Dr. Hopson as an expert, Lilly prepared for trial with the understanding that he would appear as a lay witness. Following his deposition on December 11, 2007, Dr. Hopson's name never appeared on *any* of the witness lists filed by the State. His deposition testimony – and the absence of any disclosure of expert opinion – led Lilly to conclude that the State did not intend to elicit such opinions from him. Then, with less than twenty-four hours warning, the State called Dr. Hopson to the stand, where he offered expert testimony.

Counsel for the State began his direct examination by eliciting testimony that Dr. Hopson had never met with him. Then, for the first time, Dr. Hopson expressed numerous opinions regarding the adequacy of the warnings contained in the Zyprexa label, as well as his analysis of internal Lilly research and marketing documents, all of which fall outside the scope of lay witness testimony. On cross-examination, Dr. Hopson admitted that he had met secretly with the State's attorneys within the last two weeks and, during those meetings, reviewed an undetermined set of documents selected by the State's attorneys for the purpose of eliciting the expert opinions expressed by Dr. Hopson for the first time yesterday.

II. THE STATE VIOLATED MILLER v. PHILLIPS AND LOCAL PROCEDURE TO LILLY'S PREJUDICE.

Pretrial discovery enables the parties to prepare for, and eliminate unfair surprise at, trial. The requirement to disclose witnesses, both lay and expert, and to allow the parties the opportunity to depose listed witnesses enables each side to discover the testimony the other will offer at trial. The rules apply with equal force to expert and "hybrid" witnesses.

In *Miller v. Phillips*, the Alaska Supreme Court first addressed the issue of a "hybrid witness," i.e., a fact witness who, because of his profession, could render expert opinions. 959 P.2d 1247 (Alaska 1998). In *Miller*, Dr. Newton was listed only as a lay witness on the defendant's witness list. *Id.* at 1249-50. At trial, Dr. Newton's testimony expanded to the expression of expert opinions. The Millers claimed unfair surprise. *Id.* at

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1251. The Alaska Supreme Court found that the trial court did not abuse its discretion in allowing Dr. Newton to appear as a hybrid witness and express both lay and expert opinions because the Millers had ample notice that Dr. Newton was going to be a defense witness at trial, and the substance of his opinion was disclosed in advance of trial in the form of an affidavit. *Id.* at 1251.

Following *Miller*, the Anchorage trial courts added a category of disclosure to its Routine Pretrial Order to address hybrid witnesses – the "Other Expert Opinion Testimony Summary." This disclosure obligation requires any party who intends to use a hybrid witness at trial to disclose that intention and timely provide a summary of the expected testimony. The Uniform Pretrial Scheduling Order (UPSO), which applies to this case, required each party to serve:

> a summary of the anticipated testimony of any other witness offering expert testimony (e.g., treating physician), unless such expert opinion has already been disclosed in discovery.

The State ignored this rule.

Although the opinions expressed in court yesterday by Dr. Hopson fall within the category contemplated by the UPSO, the State offered no excuse for failing to summarize Dr. Hopson's opinions. Indeed, the State possessed the documents secretly shown to Dr. Hopson in the days leading up to his testimony for more than a year preceding that deadline. Likewise, if the State determined only after Dr. Hopson's deposition that it wished to elicit these opinions, it could have alerted the Court and Lilly, and provided a summary at that time, together with an opportunity for Lilly to re-depose Dr. Hopson.

Instead, the State's lawyers disguised both the fact that they would even call Dr. Hopson in the State's case-in-chief, and that he would express opinions about the documentary evidence in this case. This obfuscation bled into the State's direct examination of Dr. Hopson, who testified that he had never met, or even talked over the phone, with Mr. Allen, who was directing the examination. Only on cross-examination was Lilly able to

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discover that the State's lawyers had met with Dr. Hopson and provided him some undisclosed batch of one-sided documents.

In *Zaverl v. Hanley*, the Court recognized that in *Miller*, "we thought it significant that the Millers had received Dr. Newton's affidavit setting out the substance of his opinions 'well before trial'" whereas in *Zaverl*, the aggrieved party had "no advance notice that Dr. Borden would offer the disputed testimony or rely on expertise that he had disclaimed at his deposition." 64 P.3d 809, 815 (Alaska 2003). The Court then ruled that "[t]here is no reason in this situation to permit such undisclosed opinions." *Id.*

Here, the State chose to keep Dr. Hopson in the dark concerning its theories of the case and supporting evidence until well after Dr. Hopson's deposition. To compound this failure, the State never listed Dr. Hopson on any witness list and never filed any summary of "Other Expert Witness Testimony," as required by this Court. Lilly has never had the opportunity to discover what Dr. Hopson was shown, and never had the opportunity to depose him to discover his recently-formed opinions. This unfair surprise prejudiced Lilly by the presentation of an undisclosed expert witness. For this abuse of the discovery process and disregard of the Court's Pretrial Order, the Court should strike Dr. Hopson's testimony or declare a mistrial.

DATED this 13th day of March, 2008.

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George A. Lehner, admitted *pro hac vice*
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I certify that on March 13, 2008, a copy of the foregoing was served by hand on:

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#9437421 v2

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-06-5630 CI

FILED IN OPEN COURT
Date: 3-13-08
Clerk: MTO

RENEWED MOTION FOR MISTRIAL

I. INTRODUCTION:

Appellate courts in several states have reversed trial courts that permitted cases to proceed to verdict after a party's witness provided appropriate aid to an ailing juror. Regardless of any carefully conducted voir dire and the use of curative instructions, the appellate courts recognized the potential for prejudice in situations much like that presented here. For the reasons articulated in those opinions, Eli Lilly requests that the Court declare a mistrial.

II. FACTS:

Shortly after the jurors were brought in to the courtroom yesterday morning, Clarence Venhuizen (Juror 13) collapsed from what the Court described as an apparent heart attack. During the fall, Mr. Venhuizen hit his forehead, and began bleeding.

Thankfully, Dr. Duane Hopson was in the viewing area of the courtroom and rushed to Mr. Venhuizen's aid. A few moments later, Dr. William Wirshing arrived to assist Dr. Hopson in treating Mr. Venhuizen, who was taken from the courtroom on a stretcher and by ambulance to the hospital. The entire jury was present both when Mr. Venhuizen collapsed and when Drs. Hopson and Wirshing rushed to his aid.

Counsel for Lilly deeply appreciate the heroic efforts of Drs. Hopson and Wirshing, and wish Mr. Venhuizen a full and speedy recovery. Lilly is certain that the remaining jurors feel similarly indebted to Drs. Hopson and Wirshing. As a result, not only will these State witnesses (and therefore the State) *gain* credibility during direct examination, but Lilly will *lose* credibility during cross examination. This result may be through no fault of the jurors—and, in fact, the jurors may not even realize their bias—but the potential for the bias both *for* the State and *against* Lilly requires that the Court order a mistrial and empanel a new jury.

Courts across the country have concluded that "medical assistance furnished by a doctor who is a *witness* or a party, to a juror in the presence of the jury, seriously undermines [a trial's] integrity."[1] In *Reome v. Cortland*, a juror collapsed during a court recess and defendant doctors administered aid in full view of the other jurors.[2] The jury later learned that the stricken juror had been taken to the hospital, but had not been admitted and was "fine."[3] Although the trial court gave a curative instruction, the appellate court found that "[t]he favorable bias that [the doctors] admirably humanitarian efforts created could not have been displaced by curative instructions, however consciously given by the [trial court] and earnestly sought to be adhered to by the jury."[4] Accordingly, the appellate court ordered a new trial.[5]

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[1] *Reome v. Cortland Mem. Hosp.*, 152 A.D.2d. 773, 774 (N.Y. App. Div. 1989) (emphasis added).

[2] *Id.*

[3] *Id.*

[4] *Id.*

[5] *Id.* at 775.

Similarly, in *Campbell v. Fox*,[6] a juror lost consciousness during the plaintiff's opening statement. The defendant physician carried the juror to the counsel table, and the juror later recovered. The trial court conducted *voir dire* and, satisfied with the jurors' responses that they would not allow the incident to prejudice their views of the trial, denied plaintiff's motion for mistrial. The Supreme Court of Illinois reversed, holding that "the effect of the unusual events in this case was so apparent as to have unquestioned influence upon the jury's ability to try the issues in controversy fairly" that a new trial was required.[7]

The Ohio Court of Appeals followed *Campbell* in *Haukedahl v. St. Luke's Hospital*.[8] In this case, a juror lost consciousness during opening statements and at least five individuals went to his aid, including two defendants and a defendant's attorney. As in *Campbell,* the trial court conducted *voir dire* and all of the jurors stated that they "would be able to proceed and agreed that any assistance [to the juror] was unrelated" to the case.[9] The appellate court held, however, that regardless of the jurors' responses, "the jury may have been aware that appellees responded to their fellow juror, and that response would have presented appellees to the jury in a favorable light."[10] The appellate court held that "the trial judge's refusal to grant a mistrial was unreasonable, arbitrary, and unconscionable," and that the trial court abused its discretion in failing to grant a mistrial.[11]

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[6] 498 N.E. 2d 1145, 1147 (Ill. 1986).

[7] *Id.*

[8] No. L-92-011, 1993 WL 496681, at **2-3 (Ohio Ct. App. Dec. 3, 1993).

[9] *Id.* at *2.

[10] *Id.* at *3.

[11] *Id.*

Nor is this rule limited to instances where defendant physicians lend aid to members of the jury. In *State v. Rideout*,[12] an insulin-dependent juror notified a deputy sheriff during deliberations that he needed insulin immediately but that he had locked it in his car.[13] The deputy sheriff called the police department to open the juror's car. The responding officer turned out to have been "an important State witness."[14] Although the responding officer and the juror did not discuss the case,[15] the Supreme Court of New Hampshire found that the jury could have been affected by this encounter.[16] If the jury gave more "credibility and reliability" to the responding officer's testimony, it "could only bolster the State's theory of the case" and "threaten[] the integrity of [the jury's] deliberations, and hence, its verdict."[17] Similarly, in *Minnesota v. Schwartz*[18] and *New Jersey v. Hunt*,[19] physicians who testified for the prosecution rendered aid to jurors. In both instances, the state supreme courts found that the potential for prejudice, combined with other errors, required new trials.[20]

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[12] 725 A.2d 8 (N.H. 1999).

[13] *Id.* at 9.

[14] *Id.* at 9, 11.

[15] *Id.* at 9.

[16] *Id.* at 11.

[17] *Id.*

[18] 122 N.W.2d 769 (Minn. 1963).

[19] 138 A.2d 1 (N.J. 1958).

[20] *Schwartz*, 122 N.W.2d at 772, 775; *Hunt*, 138 A.2d at 12-13.

For the foregoing reasons, the Court should grant a mistrial.

DATED this 13th day of March, 2008.

Attorneys for Defendant

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LANE POWELL LLC

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ASBA No. 8411122
Andrea E. Girolamo-Welp,
ASBA No. 0211044

06-05630 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

CERTIFICATE OF SERVICE

FILED
STATE OF ALASKA
2008 MAR 13 PM 2:43
CLERK

The undersigned certifies that on March 13, 2008, a copy of Defendant Eli Lilly and Company's Renewed Motion for Mistrial was served by hand on the following:

Eric T. Sanders, Esq.
Feldman Orlansky & Sanders
500 L Street, Suite 400
Anchorage, Alaska 99501-5911

DATED this 13th day of March, 2008.

Jeri Ann Jenson

I certify that on March 13, 2008, a copy of the foregoing was served by hand on:

Eric T. Sanders, Esq.
Feldman Orlansky & Sanders
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Anchorage, Alaska 99501-5911

009867.0038/163846.1

LANE POWELL LLC
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Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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

FILED IN OPEN COURT
Date: 3-12-08
Clerk: [illegible]

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

JUDGE'S RULINGS 3/12/08 Mark Rindner

DEFENDANT ELI LILLY AND COMPANY'S DEPOSITION COUNTER-DESIGNATIONS FOR TRIAL AND OBJECTIONS TO PLAINTIFF STATE OF ALASKA'S TRIAL DEPOSITION AND EXHIBIT DESIGNATIONS

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 for David Noesges, both of which must be presented together with the State's affirmative designations to ensure proper context:

Start (Page:Line)	End (Page:Line)	
15:7	15:9	Include
114:20	115:8	May use as cross- Not include

Lilly objects to the following pages and lines of Plaintiff State of Alaska's Trial Deposition Designations for David Noesges:

O= Override
S= Sustain

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06-05630CI

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55:2 55:7	55:5 55:11	Foundation; Relevance (Alaska R. Evid. 401, 402, 602)	O
55:13	55:24	No question asked within designated portion; Relevance; (Alaska R. Evid. 401, 402)	O - Question is in next section
58:5	59:10	Relevance; probative value outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 402; 403)	O
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100:23 101:6	101:2 101:6	Relevance; hearsay (Alaska R. Evid. 401, 402, 802)	O
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Lilly also objects to Plaintiff's exhibits for use during the testimony of David Noesges:

Plaintiff's Exhibit	**Objection(s)**
Zyprexa Plaintiff's Exhibit No 1901	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: internal sales representative training material. Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)
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Zyprexa Plaintiff's Exhibit 10094	M.I.L. regarding Recent Regulatory Events Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Subsequent Remedial Measures (Alaska R. Evid. 407) Hearsay (Alaska R. Evid. 801, 802)
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Lilly reserves the right to object to these exhibits, and any others that may be introduced by Plaintiff, under the Alaska Rules of Evidence or any other applicable rule of law, based on this Court's rulings or the purposes for which Plaintiff seeks to use the exhibits at trial.

Respectfully submitted,

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Attorneys for Defendant
Eli Lilly and Company

Dated: March 12, 2008

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

FILED IN OPEN COURT
Date: 3-12-08
Clerk: [illegible]

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

06-05630 CI

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Respectfully submitted,

LANE POWELL, PC

By: _____

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Attorneys for Defendant
Eli Lilly and Company

Dated: March 12, 2008

06-05630 CI

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.

APPEARANCES

FOR THE PLAINTIFF:
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FOR THE DEFENDANT:

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PEPPER HAMILTON LLP
3000 Two Logan Square
Eighteenth and Arch Streets
Philadelphia, Pennsylvania 19103-2799

ALSO PRESENT:

Pete Zinkan, Videographer

INDEX OF EXAMINATION

INDEX OF DEPOSITION EXHIBITS

INDEX (CONTINUED):

INDEX OF DEPOSITION EXHIBITS

PREVIOUSLY MARKED EXHIBITS SHOWN TO THE WITNESS REQUESTED TO ACCOMPANY THE ORIGINAL TRANSCRIPT

MARKED AS PLAINTIFFS' EXHIBITS:

8262, 1941, 995, 9201, 5849, 1970, 1901

2368, 4121, 1926, 1939, 1949, 1961, 1962

PROCEEDINGS

THE VIDEOGRAPHER: We are now on the record. My name is Pete Zinkan. I'm the videographer for Golkow Technologies, Inc., One Liberty Place, 1650 Market Street, 51st Floor, Philadelphia, Pennsylvania.

Today's date is January the 11th of 2008. We are going on the record at 9:31 a.m.

This video deposition is being held at the law office of Ice Miller, located at One American Square, Indianapolis, Indiana in the matter of Zyprexa Products Liability Litigation.

This case is filed in the State of Alaska the Third Judicial at Anchorage, Cause No. 3AN-06-5630 CIV. The deponent is David Noesges.

Will counsel please state their appearance for the record.

MR. SUGGS: My name is David Suggs with the firm of Richardson, Patrick, Westbrook & Brickman representing the State of Alaska.

MR. MARCUM: Christiaan Marcum also with the plaintiffs.

MR. BOISE: Barry Boise on behalf of Defendant Eli Lilly & Company and the witness.

THE VIDEOGRAPHER: The court reporter is

Carolyn Smith and she may now swear the witness.
You may proceed.

DAVID THOMAS NOESGES,

having first been duly sworn to tell the truth, the whole truth, and nothing but the truth was examined and testified as follows:

EXAMINATION

QUESTIONS BY MR. SUGGS:

Q Would you state your full name for the record, please?

A Yes. It's David Thomas Noesges.

Q And how do you spell your last name?

A Last name is spelled N-o-e-s-g-e-s.

Q I thought that was probably the case, and I noticed that we had the misspelling here on the exhibit tab so I wanted to make sure that was right.
What is your occupation, sir?

A I am employed by Eli Lilly and Company.

Q And what's your job title?

A I'm currently the national sales director for our U.S. diabetes unit.

Q For the U.S. diabetes unit.
Have you previously had responsibility with

responsibility to Zyprexa?

A Yes, I have.

Q And what were your job titles? When did you work on Zyprexa projects?

A I first began working for Zyprexa in 1999 as the sales and marketing operations manager.

Q Was that based here in Indianapolis?

A Yes, it was.

Q Did you have any other jobs with respect to Zyprexa after that?

A Yes, subsequent to that in 2000 through 2001 I was the sales director for what was in our Midwest area.

Q Okay. And did you have any job responsibilities after 2001 with respect to Zyprexa?

A Yes. From 2003 -- late 2003, November, I believe of 2003, until October of 2004 I was Zyprexa marketing director.

Q And did you have any responsibilities for Zyprexa after 2004?

A Yes. Then from 2004 until the end of 2007 I was in a sales leadership role, first as the national sales director for our neuroscience retail organization from 2004 until basically the end of 2005.

Q Okay.

A And then through -- from 2005 through 2007 I was our executive sales director for the west region of neurosciences.

Q Would that include Alaska --

A Yes.

Q -- the west region?
Who did you report to?
MR. BOISE: In the last capacity?
THE WITNESS: In the last capacity?

QUESTIONS BY MR. SUGGS:

Q Um-hmm.

A I reported to Enrique Conterno.

Q Okay. And who did he report to?

A Enrique reported to Deirdre Connelly.

Q And who did she report to?

A Deirdre reported to John Lechleiter.

Q And when did you switch over to the diabetes side of the company?

A I switched over effective January the 1st.

Q Just a couple of weeks ago?

A Yes.
MR. BOISE: 2008.
MR. SUGGS: Right, I assumed that.
(Deposition Exhibit 1 marked for identification.)

QUESTIONS BY MR. SUGGS:

Q I'm going to hand you what we'll mark as Exhibit 1, which is the copy of the renotice of this deposition. And on the second page of this document it lays out -- have you seen this document before?

A Yes, I have.

Q Okay. And on the second page it indicates that Eli Lilly and Company is requested to produce the person of persons most knowledgeable about: 1) The identity Lilly sales representatives for Zyprexa in Alaska from 1996 to the present; 2) The verbatims, or sales messages, used by Lilly's sales representatives for Zyprexa in Alaska from 1996 to the present; 3) The marketing of Zyprexa in Alaska from 1996 to the present; and 4) Call notes generated by Lilly's sales representatives regarding Zyprexa from 1996 to the present.
Do you see those numbered categories?

A Yes, I do.

Q And are you prepared to answer questions regarding those areas today as the corporate representative of Eli Lilly?
MR. BOISE: Subject to the objections that were raised in response to this notice of

deposition.
MR. SUGGS: Okay. Of course, we don't necessarily accept your objections, but neither of us is going to determine the validity of those.
Q Those topics that are set forth in Exhibit 1 are going to be the principal focus of my deposition -- before we get into those, I need to ask you some questions about your personal background.
First, can you tell me just generally your educational background?
A Yes. I have an undergraduate degree from the Unites States Military Academy at West Point.
Q Okay. And what year did you graduate?
A I graduated in 1984.
Q And did you serve in the Army then for some years after that?
A Yes, I did.
Q And how long?
A I served for five years in the Army.
Q And did you have any -- when did you join Lilly?
A I joined Lilly first as a summer intern in the summer of 1990.
Q Okay. And when did you join them full-time?
A I joined full-time, then, in July of 1991.
Q Okay. Am I correct that you would have completed

your service with the Army in 1989?
A Yes, that's correct.
Q What did you do jobwise between 1989 and 1991?
A I was a full-time student, graduate student, at the Wharton School of Business in Philadelphia.
Q Did you receive a degree there?
A Yes, I did.
Q Was it a Master's in Business Administration?
A Yes.
Q When you were in the Army, did you have any involvement in medical issues -- or what branch of the Army were you in?
A No, I was combat engineer.
Q Would it be fair to say that you did not have any experience in the pharmaceutical industry before joining Eli Lilly in 1991?
A Yes, that's correct.
Q And you briefly described the job responsibilities you've had regarding Zyprexa when we first started the deposition.
It would be fair to say, would it not, that your involvement with Zyprexa primarily had to do with sales?
MR. BOISE: Object to the form.
QUESTIONS BY MR. SUGGS:

Q Is that correct?
A My responsibilities were predominantly sales and marketing.
Q Okay. And are you the person within Lilly who is most knowledgeable about the marketing of Zyprexa in Alaska?
MR. BOISE: Object to the form of the question.
THE WITNESS: Be difficult for me to answer whether I'm most knowledgeable.
QUESTIONS BY MR. SUGGS:
Q Who else would you regard as knowledgeable or more so than you are with respect to the marketing of Zyprexa in Alaska?
MR. BOISE: Object to the form of the question.
THE WITNESS: I don't know of anyone who would be more knowledgeable than I am.
QUESTIONS BY MR. SUGGS:
Q Do you know how it was that you came to be designated as the person to come to this deposition?
MR. BOISE: Please, don't reveal communications with counsel.
I don't think you are really asking for that,

are you?
QUESTIONS BY MR. SUGGS:
Q Was it a drawing of short straws or --
MR. BOISE: Object to the form.
THE WITNESS: I -- I don't know.
QUESTIONS BY MR. SUGGS:
Q Okay. Who was it that told you that you would be expected to come here for the deposition?
A I was asked by counsel if I would participate.
Q Okay. What, if anything, did you do to prepare to testify on behalf of Lilly regarding the marketing of Zyprexa in Alaska?
MR. BOISE: Instruct the witness not to disclose any interactions with counsel. He means other than -- subject to my objection, other than meeting with counsel.
THE WITNESS: I did review some promotional materials in preparation.
QUESTIONS BY MR. SUGGS:
Q Were those selected for you or did you go out and get them yourself?
A No. I asked for some materials for the period between 2001 and 2003 where I was not directly responsible for U.S. marketing of Zyprexa.
Q Do you recall which documents you reviewed?

A They were promotional materials for the 2001 to 2003 time frame for Zyprexa.
Q Would these be brochures, videotapes? What kind of promotional materials are you talking about?
A Yes, it would be promotional brochures.
Q I'm not going to mark these right now, but are these the promotional brochures that you reviewed?
I notice the one that you have in your hand there, I believe has a copyright date on the back of 2001 and the one that Mr. Boise has in his hand has a copyright mark of 2003.
A I can't say for certain that this is the exact material that I have looked at.
Q Okay. Who was directly responsible for sales of Zyprexa in that 2001-2003 time period?
MR. BOISE: Sales?
MR. SUGGS: In the U.S.
THE WITNESS: Sales for the U.S. overall?
QUESTIONS BY MR. SUGGS:
Q Yes.
A It would have been Glyn Parkin.
Q Can I have those brochures back?
MR. BOISE: Can I see that first one? Thanks.
Thanks.
QUESTIONS BY MR. SUGGS:

Q I would like to talk a bit generally about Zyprexa.
You would agree that Zyprexa was one of Lilly's biggest selling products in terms of dollar sales, correct?
MR. BOISE: Time frame?
QUESTIONS BY MR. SUGGS:
Q From the time you began working on Zyprexa until you stopped.
A Yes, that's correct.
Q In fact, during that time period from 1999 throughout 2007 it was the largest selling product in the company, was it not?
A Yes, that's correct.
Q And do you happen to know what the annual sales of Zyprexa were in 2007 approximately to the nearest billion dollars?
MR. BOISE: U.S. sales?
MR. SUGGS: Yes.
THE WITNESS: I believe U.S. sales would have been between 2 and $3 billion.
QUESTIONS BY MR. SUGGS:
Q Was that lower than it had been the previous year?
A Yes.
Q How much lower?
A I don't know on a percentage basis.

Q Do you know in terms of dollar-amount basis?
A No, I don't know.
Q Would you agree with me that sales of Zyprexa declined after 2004?
MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: Yes.
QUESTIONS BY MR. SUGGS:
Q What -- do you recall what the peak level of sales was in 2004?
MR. BOISE: Object to the form, beyond the scope.
Could I have a continuing objection on general sales questions?
THE WITNESS: I don't recall what our sales were.
QUESTIONS BY MR. SUGGS:
Q Do you recall generally, an approximation?
A No.
Q To the closest billion dollars?
MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: Without reviewing the results, I could not say specifically.
QUESTIONS BY MR. SUGGS:
Q Wasn't it in the area of about $4 billion?

MR. SUGGS: Object to the form, beyond the scope.
THE WITNESS: I don't know.
QUESTIONS BY MR. SUGGS:
Q Do you recall that the company increased the price of Zyprexa after 2004?
MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: Yes.
QUESTIONS BY MR. SUGGS:
Q And did the company do that after sales began to decline?
MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: Yes.
QUESTIONS BY MR. SUGGS:
Q Okay. Do you know who it was that made the decision to increase the sales price of Zyprexa when sales began to decline?
MR. BOISE: Object to the form, compound, beyond the scope, lack of foundation.
THE WITNESS: No, I do not.
QUESTIONS BY MR. SUGGS:
Q Do you know, roughly, the percentage of sales of Zyprexa between the 1996 time period through 2007

that were to Medicaid programs?
MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: I'm sorry. I did not understand. Could you ask the question?
MR. SUGGS: Sure.
Could you read the question, please?
(Record read.)
THE WITNESS: No, I do not.
QUESTIONS BY MR. SUGGS:
Q Wasn't it on the order of about 60 percent?
MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: I don't know.
QUESTIONS BY MR. SUGGS:
Q Were you aware that the number one driver of the budget crisis in Medicaid programs was the cost of Zyprexa?
MR. BOISE: Object to the form, beyond the scope, lack of foundation.
THE WITNESS: No. I don't know for certain if that's the case.
QUESTIONS BY MR. SUGGS:
Q Had you heard that?
MR. BOISE: Object to the form, beyond the

scope.
THE WITNESS: No, I don't know.
QUESTIONS BY MR. SUGGS:
Q My question wasn't whether you knew or not it was whether you heard that.
MR. BOISE: Same objection.
THE WITNESS: I'm sorry. Could you ask the -- could you repeat the original question again?
QUESTIONS BY MR. SUGGS:
Q Had you heard that the number one reason for a budget crisis in Medicaid programs was because of Zyprexa?
THE REPORTER: Sorry, I need your objection again.
MR. BOISE: Objection, foundation, compound, beyond the scope.
THE REPORTER: Your answer?
THE WITNESS: My answer was no.
(Deposition Exhibit 2 for identification.)
QUESTIONS BY MR. SUGGS:
Q I'm going to hand you what's marked Exhibit 2.
It appears to be a PowerPoint presentation with a title on the first page entitled "Current Situation" and below that it says, "Budget Crisis" and it has in parens, WA, slash, OR, slash, AK,

slash, HI, end paren.
Do you see that?
A Yes, I do.
Q And do you recognize those as the initials of the states of Washington, Oregon, Alaska and Hawaii?
A Yes, I do.
Q And are those states in the western region?
A Yes, they are.
Q And that was the region for which you were the head of sales, was it not, the western region?
A Yes, that is correct.
Q And is it your testimony that you were unaware that there was a budget crisis for Medicaid programs during the time that you were in charge of sales of the western region?
MR. BOISE: Object to the form of the question.
THE WITNESS: No, I did not testify to that.
QUESTIONS BY MR. SUGGS:
Q Were you aware then that there was, in fact, a budget crisis in the Medicaid programs in the western region in the time that you were head of that region's sales?
A No. I don't know that I would characterize a crisis, a budget crisis.

Q Well, what were you aware of with respect to the budget of Medicaid programs during that time?
A I know that all of the states had Medicaid challenges with their budgets.
Q They had challenges; how is a challenge different than a crisis?
MR. BOISE: Object to the form.
THE WITNESS: I don't know whether I -- I don't feel like I'm in a position to be able to determine whether one of those states has a crisis or not.
QUESTIONS BY MR. SUGGS:
Q Apparently whoever wrote this PowerPoint indicated there was a budget crisis, correct?
A Yes. That's what the document says.
Q Right below the phrase Budget Crisis it states, "#1 Driver Zyprexa (all states)."
Do you see that?
A Yes, I do.
Q And were you aware when you were the head of the western region of sales that states were concerned about the price of Zyprexa for their Medicaid programs?
A Yes.
Q And how was it that you became aware of that?

Page 22

A I was aware through direct customer feedback we had through state Medicaid officials.
Q And the state Medicaid officials were telling you that Zyprexa was their number one expense, correct?
A In many cases it was their number one expense among antipsychotic products, yes.
Q In fact, it was their number one expense of all the drugs in the Medicaid program, wasn't it? Isn't that what they were telling you?
A In which time frame?
Q The time that you were head of western regional sales, 2003 to 2007.
A I don't know for certain if that would have been the case in every state.
Q In a lot of states, right?
MR. BOISE: Objection, vague.
QUESTIONS BY MR. SUGGS:
Q And at least according to this memo it says the number one driver was for Zyprexa in all states, correct?
A Yes, that's what this memo says.
Q Okay. You know how much a Zyprexa pill costs?
MR. BOISE: Object to the form, beyond the scope, vague.
THE WITNESS: There's not one price for a

Page 23

Zyprexa pill.
QUESTIONS BY MR. SUGGS:
Q What is the range for a Zyprexa pill? What can it vary from?
MR. BOISE: Object to the form, beyond the scope, vague.
THE WITNESS: I would need to refer to our pricing documents to get --
QUESTIONS BY MR. SUGGS:
Q Doesn't it range from $8 a pill to about $10 a pill?
MR. BOISE: Objection, beyond the scope.
THE WITNESS: I could not say that all prices would be within that range.
QUESTIONS BY MR. SUGGS:
Q Are there some prices that are within that range?
MR. BOISE: Objection, vague, beyond the scope.
THE WITNESS: Yes.
QUESTIONS BY MR. SUGGS:
Q Okay. And how much does it cost to make a Zyprexa pill -- about 10 cents?
MR. BOISE: Objection, vague, beyond the scope.
THE WITNESS: I don't know.

Page 24

QUESTIONS BY MR. SUGGS:
Q I would like to direct your attention to the second page of Exhibit 2, has the title Goals, slash, Objectives, and the goal is to ensure unrestricted availability of all the Lilly products on all state formularies.
Do you see that language there?
A Yes, I do.
Q And the fact of the matter is that there were some states that were so concerned about the price of Zyprexa and the impact that it had on their Medicaid programs that there was discussion of restricting sales of Zyprexa or having Zyprexa be on the -- require prior approval, correct?
MR. BOISE: Objection, beyond the scope, compound, complex.
THE WITNESS: Yes, that's correct.
QUESTIONS BY MR. SUGGS:
Q Okay. Lilly did not want that to happen, correct?
MR. BOISE: Objection, compound, vague, beyond the scope.
THE WITNESS: Our position was clearly that we wanted to have equal and open access for all antipsychotic products including Zyprexa.
QUESTIONS BY MR. SUGGS:

Page 25

Q If you could direct your attention to the following page, it has the title on that page in quotes a misspelling of the word "strategy" and says "Stragedies," S-t-r-a-g-e-d-i-e-s, correct?
A Yes.
Q And then the first bullet point below that states, "Implement Totally Aligned Activities of State Action Teams."
Do you see that language?
A Yes.
Q And are you familiar with the phrase "state action teams"?
A Yes, I am.
Q What were state action teams?
A Our state action teams were a cross-functional team that were helping to implement our strategy of equal and open access.
Q That included, apparently, something called an MPA. What was that?
A Yes, the MPA is a manager of public affairs.
Q It would be like a public relations person?
MR. BOISE: Object to the form.
THE WITNESS: No.
QUESTIONS BY MR. SUGGS:
Q What is public affairs?

A Manager of public affairs was responsible for managing our relationship with government payors.
Q Oh, okay. And then it also included what you refer to there as Advocacy Specialists.
Is that something different than a manager of public affairs?
A Yes, that is different, a different role.
Q What is that role?
A Those roles had responsibility to work with different advocacy groups.
Q Like the National Association for the Mentally Ill?
A Yes, that would be one example.
Q Is -- are there other examples?
A The APA would be an example.
Q Okay. And with respect to the National Association for the Mentally Ill what would Lilly's advocacy specialist do with that organization which is sometimes referred to as NAMI, correct, N-A-M-I?
MR. BOISE: Objection, compound, beyond the scope.
QUESTIONS BY MR. SUGGS:
Q My question right now is: Are you familiar with the acronym NAMI?
A Yes, I am.
Q That stands for the National Association for the

Mentally Ill, correct?
A Yes, that's correct.
Q Okay. What would your advocacy specialist do with respect to NAMI?
MR. BOISE: Objection, vague, beyond the scope.
THE WITNESS: They would work with NAMI for our common goals of open access.
QUESTIONS BY MR. SUGGS:
Q And then there's also reference there to someone who is a PHDD. What is that?
A I'm not sure I can get the acronym exactly correct, but it would be a representative of our public health division.
Q And what did that person do?
A This is a person that, again, who worked with public payers.
Q And then there is also a listing there for sales.
Would that just be a sales representative?
A It could be a sales representative, could be a sales manager, or sales director as well.
Q Okay. Then there is also another member of the state action team was somebody from B2B.
What does that stand for?
A That is our business to business group.

Q What do they do?
A They have responsibility for -- really for our marketing promotions and all of our pricing negotiations with payers.
Q And were these state action teams organized by region, by state or -- I guess they would have to be by state, because they are called state action teams, aren't they?
A Yes, they were organized by state.
Q Each state including Alaska would have an MPA, an advocacy specialist, a PHDD, a salesperson, or a sales manager, and a B2B person who were a member of the state action team whose goal was to ensure the unrestricted availability of all Lilly products on all state formularies, correct?
MR. BOISE: Object to the form, foundation.
THE WITNESS: Their goal would be to ensure open access for Zyprexa and all of the antipsychotics.
QUESTIONS BY MR. SUGGS:
Q Okay. Another one of these strategies of this goal was the strategic campaign to support key legislators.
Did I read that correctly?
MR. BOISE: Object to the form.

THE WITNESS: That's what this document says.
MR. BOISE: The question was: Did you read it correctly?
MR. SUGGS: Yes.
Q What kind of campaign support is being referred to there?
MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: I don't know the answer to that.
QUESTIONS BY MR. SUGGS:
Q Is this political campaign support?
MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: I don't know.
QUESTIONS BY MR. SUGGS:
Q How would key legislators be supported if not giving them money for their campaigns?
MR. BOISE: Object to the form, beyond the scope, calls for speculation.
THE WITNESS: I don't know the answer to that. I can't tell who's written the document or what it's referring to.
QUESTIONS BY MR. SUGGS:
Q Who are the key legislators that Lilly was supporting in Alaska?

MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: I'm not aware of -- of any legislators we were supporting but -- in Alaska.
QUESTIONS BY MR. SUGGS:
Q If I could direct your attention to the following page, it has the heading Tactics. And it has several bullet points below that, the last of which is, "Target 5-6 Key Legislators As Champions."
Those would be champions for Lilly's goal of maintaining unrestricted availability of its products, correct?
MR. BOISE: Object to the form of the question, compound, beyond the scope.
THE WITNESS: I can't tell what this document is referring to beyond what it says there.
QUESTIONS BY MR. SUGGS:
Q You were the regional sales manager for the western region, and it's your testimony you don't know what this refers to when talking about targeting five to six key legislators as champions; is that correct?
MR. BOISE: Objection, asked and answered.
THE WITNESS: My testimony is that I don't know what this document is referring to.

QUESTIONS BY MR. SUGGS:
Q If I could direct your attention to the following page -- I take it back. It's several pages back. It's the second to last physical page. There is a PowerPoint that has "Sales Support Needed," and it refers to "Coverage of DUR Board Members."
Do you see that?
A Yes.
Q That refers to Lilly's sales force having contact with drug utilization and review board members of Medicaid programs, doesn't it?
MR. BOISE: Object to the question, beyond the scope, vague.
THE WITNESS: I can't tell from the document whether they are referring to a Medicaid drug utilization review board or not.
QUESTIONS BY MR. SUGGS:
Q What other types of drug utilization review boards were there besides those for Medicaid?
A Often managed care organizations that are private paid would have different types of drug utilization review processes as well.
Q Now, the private organizations you talked about wouldn't be having the type of budget crisis that was referred to on the first page of this document,

would they?
MR. BOISE: Object to the form.
THE WITNESS: I think managed care organizations are in a various state of budget circumstances.
QUESTIONS BY MR. SUGGS:
Q This document talks about, on the first page, various governmental issues -- democratic control of legislature, negative activity by the governor, persistent legislators. There are references to the government activities throughout this document. Wouldn't that indicate that this is regarding a public system rather than a private managed care organization?
MR. BOISE: Object to the form of the question, foundation.
THE WITNESS: Potentially does, but I can't say for certain.
QUESTIONS BY MR. SUGGS:
Q Well, when you were head of the western region of sales in the U.S., were you aware that sales representatives were expected to -- to have contacts with drug utilization review board members --
MR. BOISE: Object to the form.

QUESTIONS BY MR. SUGGS:
Q -- of Medicaid programs?
MR. BOISE: Object to the form of the question, beyond the scope, vague.
THE WITNESS: Yes, certainly our sales representatives would have been calling on some members of drug utilization review boards.
QUESTIONS BY MR. SUGGS:
Q Let's focus on sales activities in Alaska in particular.
Do you know who the Lilly sales reps were in Alaska from 1996 to the present?
A I can't recall, from memory, all of the sales reps during that time period.
Q Can you tell me the ones that you recall from 2000 to the present?
A No, I can't give you a comprehensive list.
Q Can you give me a list of some of them?
A Yes.
Q Okay. Who can you list for me?
A I know Joey Eski.
Q He is the only one?
A That's the only one I can recall from memory.
Q How long has he been a sales rep in Alaska?
A Joey is a she, actually.

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.

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

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.)

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

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?

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

that there was something on the database that they have to be aware of? Like, 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:

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

that refer to?
A I can't say specifically what these tools would have been then but formulary is basically a drug list of medicines that are available.
Q Well, how would a sales rep use a formulary tool?
MR. BOISE: Object to the form, vague.
THE WITNESS: In this time frame potentially if a customer asked for formulary information, was involved in a formulary decision, the sales representative could provide them with information in the context of a formulary packet.
QUESTIONS BY MR. SUGGS:
Q And below those boxes that we have been talking about, there's a heading in the middle of the page numbered 1 with larger font, and it's bold and it's all caps and it says, "ALL PROMOTIONAL MATERIALS MUST BE APPROVED BY A BRAND TEAM," correct?
A Yes, that is correct.
Q And then in the item below that No. 2, in the second half of that paragraph it states, "Approved materials must not be copied or altered in any other way for use with customers. No highlighting, underlining or adding notes," correct?
A Yes, that's correct.
Q No. 3 was "The use of homemade materials is

forbidden."
That's in all caps, correct?
A It's not in all caps; it's bold.
Q I'm sorry. It's bold. I misspoke.
It's in bolded font, correct?
A Yes.
Q Also in bolded font in that paragraph is the sentence "Homemade Materials are anything not approved by the Brand team for use with customers," correct?
A Yes.
Q Fair to say that the promotional materials that came out of Lilly were designed and intended -- strike that.
The promotional materials that came out of Lilly came out of corporate headquarters here in Indianapolis and were expected to be used as developed by the brand team without exception and without change or alteration, correct?
A Promotional materials were developed by the U.S. brand team and it certainly works -- all of our sales representatives were expected to use them consistent with the promotional guidelines.
Q They were expected to use them, too, weren't they?
MR. BOISE: Object to the form.
THE WITNESS: Yes, they were expected to use

the promotional materials.
QUESTIONS BY MR. SUGGS:
Q Let's talk about the content of the sales messages that were used by Lilly sales reps for Zyprexa, in particular, regarding hyperglycemia and diabetes.
Were you -- I believe you said you began working on Zyprexa in 1999; is that correct?
A Yes, that's correct.
Q What month?
A I believe it would have been October or November of 1999.
Q Okay. And at that time you were aware that there had been concerns expressed in the marketplace and in published medical articles that weight gain associated with Zyprexa could cause patients to develop diabetes, correct?
A Yes, I'm aware of those concerns.
Q Okay. And weight gain and possible hyperglycemia was recognized as a major threat to hyper -- strike that.
Weight gain and possible hyperglycemia was recognized as a major threat to Zyprexa, correct?
MR. BOISE: Object to the form of the question.
THE WITNESS: Weight gain was a known side

effect of Zyprexa and was in our label as such from launch.
MR. SUGGS: Move to strike as nonresponsive.
Q Sir, weight gain and possible hyperglycemia was recognized as a major threat to Zyprexa, which was a critically important product to the company, correct?
MR. BOISE: Object to the form of the question, compound.
THE WITNESS: I would not regard -- major threat would not be a characterization that I made at that time.
QUESTIONS BY MR. SUGGS:
Q Let me hand you what's been previously marked as Plaintiffs' Exhibit No. 8262. For the record this is a string of E-mails in November of 1999.
I would direct your attention, in particular, sir, to the E-mail at the bottom of the first page, which is a November 9, 1999, E-mail from Alan Breier to a number of individuals, looks like about a dozen or more, including several top executives, such as John Lechleiter and August Watanabe.
Do you recognize the names of any of those individuals, sir?
A Yes, I do.

that Alan Breier was the head of Zyprexa product team?
A Yes, I am.
Q And John Lechleiter was at that time the chief operating officer of the company, was he not?
MR. BOISE: Object to the form, foundation.
THE WITNESS: No. I don't believe in 1999 he was the chief operating officer.
QUESTIONS BY MR. SUGGS:
Q Do you recall what his title was back at that time?
A No, I do not.
Q He is currently the CEO of the company, correct?
A No, he is currently president and chief operating officer.
Q I thought I heard he was the new CEO or has that not become effective yet?
A He will be the new CEO effective April 1st.
Q Okay. In a couple of months he is going to be the CEO?
A Yes, he will.
Q What other names on there do you recognize?
MR. BOISE: Objection, beyond the scope.
THE WITNESS: I recognize Charles Beasley. I recognize Gary Tollefson, Norma Ascroft and August Watanabe.

QUESTIONS BY MR. SUGGS:
Q And in the first sentence in this E-mail from November 1999 it states, quote, Olanzapine-associated weight gain and possible hyperglycemia is a major threat to the long-term success of this critically important molecule.
Do you see that language?
A Yes, I do.
Q And apparently no one ever informed you of that back in November of 1999; is that correct?
MR. BOISE: Object to the form, foundation.
THE WITNESS: If you are asking whether I saw this E-mail, no.
QUESTIONS BY MR. SUGGS:
Q I was not asking about that E-mail. I figured you probably would not have seen this E-mail. Earlier you said you took over your position with Zyprexa in October of 1999 and you said that you would not characterize Zyprexa weight gain and possible hyperglycemia as a major threat to the long-term success of Zyprexa.
So my question was: Fair to say that no one ever informed you in the words of this E-mail that olanzapine-associated weight gain and possible hyperglycemia is a major threat to the long-term

success of this critically important molecule?
MR. BOISE: Objection.
QUESTIONS BY MR. SUGGS:
Q No one ever told you that?
MR. BOISE: Objection, foundation, compound question, beyond the scope.
THE WITNESS: I don't believe in 1999 that weight gain and possible hyperglycemia were characterized to me as a major threat to a long-term success.
QUESTIONS BY MR. SUGGS:
Q So apparently people like Alan Breier and John Lechleiter were aware of that, but you were not in your position --
MR. BOISE: Object to the form.
QUESTIONS BY MR. SUGGS:
Q -- correct?
MR. BOISE: Foundation, beyond the scope.
THE WITNESS: I don't believe they characterized weight gain or hyperglycemia as a major threat to me in November of 1999.
QUESTIONS BY MR. SUGGS:
Q Okay. Did anyone ever tell you that olanzapine-associated weight gain and possible hyperglycemia was a major threat to the long-term success of

Zyprexa?
A I certainly have had ongoing discussions since this time that weight gain is a side effect, was a significant issue for Zyprexa.
Q Okay. And when did you first become informed that there was a concern that the weight gain associated with Zyprexa could result in hyperglycemia?
MR. BOISE: Object to the form of the question, foundation, compound, beyond the scope.
THE WITNESS: I don't know the answer to that.
QUESTIONS BY MR. SUGGS:
Q Were you ever informed that weight gain associated with Zyprexa -- strike that.
Were you ever informed that there was a concern that the weight gain associated with Zyprexa could result in hyperglycemia?
MR. BOISE: Objection, beyond the scope.
THE WITNESS: Yes, I'm certainly aware of a lot of customer concerns about the weight gain and what the metabolic effects, including the impact of hyperglycemia, might be.
QUESTIONS BY MR. SUGGS:
Q And hyperglycemia is indicative of diabetes, correct?
A Hyperglycemia is -- again, I'm not a clinician, but

hyperglycemia reflects elevated glucose levels beyond normal levels.
Q And, in fact, the -- are you -- were you aware that the American Diabetes Association has said that a fasting glucose of a hundred twenty-six milligrams per deciliter or higher is the diagnostic for diabetes?
MR. BOISE: Object to the form of the question, foundation.
THE WITNESS: Yes, I am aware of that.
QUESTIONS BY MR. SUGGS:
Q Okay. Were you aware that the American Diabetes Association has said that the random blood glucose in excess of 200 milligrams per deciliter is diagnostic for diabetes?
MR. BOISE: Object to the form, foundation.
THE WITNESS: Yes, I am aware.
QUESTIONS BY MR. SUGGS:
Q And when did you become aware of that, sir?
MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: Difficult to answer because some of those guidelines have changed over time, but I have been aware from the time I was a new Lilly sales representative of what the diagnosis of diabetes

and hyperglycemia is.
QUESTIONS BY MR. SUGGS:
Q And when did you become aware that there was a concern that the weight gain associated with -- with Zyprexa could result in hyperglycemia?
MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: I don't know that I could answer specifically when that issue was raised, but certainly weight gain is a known risk factor for diabetes among many others. I was aware of that from the beginning of my work with Zyprexa.
QUESTIONS BY MR. SUGGS:
Q And you used a term there, risk factor.
What does the word "risk factor" mean to you?
MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: You are asking me to get beyond my marketing expertise so --
QUESTIONS BY MR. SUGGS:
Q No. I'm asking you to explain what you mean by words that you first brought up. You were the one that first said that it was your understanding that weight gain was a risk factor for diabetes. I never used the phrase risk factor before in this

deposition. You brought it up.
What do you mean by it?
MR. BOISE: Object to the form of the question.
THE WITNESS: Again, I'm not a clinical expert. I would rely on my colleagues but I know that weight gain among other factors is -- I don't know how else to describe it -- as a risk factor for diabetes.
QUESTIONS BY MR. SUGGS:
Q Risk factor means if a person has that factor or that condition that they have an increased risk of developing the disease, correct?
MR. BOISE: Object to the form of the question, foundation.
THE WITNESS: I don't know that that's -- that I could answer that question.
QUESTIONS BY MR. SUGGS:
Q Well, you used the phrase "risk factor."
What do you mean by it when you use that term?
MR. BOISE: Object to the form, asked and answered, harassing.
THE WITNESS: Weight gain is a known risk factor for diabetes --
QUESTIONS BY MR. SUGGS:

Q No. I'm not --
MR. BOISE: Let him answer the question. Let him answer the question. You can ask another one, David. I think you are harassing him.
MR. SUGGS: I'm not --
MR. BOISE: Were you finished with your answer?
THE WITNESS: No.
MR. BOISE: Finish your answer, please.
THE WITNESS: Weight gain is a known risk factor for diabetes. In my marketing and sales roles at Lilly, I rely on our medical and regulatory and legal colleagues to help me characterize that as a risk factor for diabetes.
QUESTIONS BY MR. SUGGS:
Q What do you mean when you use the words risk factor?
MR. BOISE: Objection, asked and answered.
THE WITNESS: I mean that it's a risk factor for diabetes.
QUESTIONS BY MR. SUGGS:
Q A risk factor means it's a risk factor.
Can you give me any other help with -- what's in your mind when you use the term risk factor?
A You are asking me to make a judgement that I don't

think I'm qualified to make from a medical standpoint.
Q No, I am just asking you to explain the words that you used for yourself for the first time in this deposition.
MR. BOISE: Objection, asked and answered, harassing.
THE WITNESS: Risk factor meaning quite simply that weight gain is a risk factor for diabetes.
QUESTIONS BY MR. SUGGS:
Q Sir, am I correct that throughout the times that Zyprexa has -- strike that.
Am I correct that throughout the time that you were involved with Zyprexa from 1999 through the end of 2007 that Lilly sales representatives have been trained to say that Zyprexa does not cause diabetes?
MR. BOISE: Object to the form, foundation, beyond the scope.
You can answer.
THE WITNESS: No. We have trained our representatives throughout that time that -- that our data is not able to answer the question as to whether Zyprexa can -- causes weight gain -- I'm sorry, causes diabetes.

QUESTIONS BY MR. SUGGS:
Q In fact, your sales reps have been taught to say that there is no causal relationship between Zyprexa and the onset of diabetes, isn't that true, sir?
MR. BOISE: Objection, foundation.
THE WITNESS: Our position as communicated to the sales representatives is that based on our analysis of the data we cannot determine a causal relationship between Zyprexa and diabetes.
QUESTIONS BY MR. SUGGS:
Q I'm going to hand you what's been previously marked as Plaintiffs' Exhibit 1941. For the record this is a document entitled "ZYPREXA 'FREQUENT AREAS OF CONCERN' OR 'FAOC.'" I'll also represent to you, sir, that the database that has been provided to us by Lilly states that this document was generated on June 28, 2002.
And I'll also represent to you that Lilly has stated in answers to interrogatory in this case in Alaska that this document was in the knowledge management database and made available to sales representatives.
Do you have any basis to dispute either the

date that was provided to us by Lilly or their representation that this document was in the knowledge management database?
MR. BOISE: Take a minute to look at the document.
THE WITNESS: Okay.
QUESTIONS BY MR. SUGGS:
Q Do you have any basis, sir, to dispute the date that was provided to us as June 28, 2002, as the date this document was generated?
A No, I do not.
Q Do you have any basis to dispute that the answers to interrogatories in this case which stated that this document was made available to the sales reps in the knowledge management database?
A No.
Q I'd like to direct your attention to the bottom of the first page. There is some language there that's actually on the bottom of every one of the pages that says, "For internal use only. Not for use in detailing."
Do you see that language?
A Yes, I do.
Q Sir, when it says, "Not for use in detailing" that means that this is something that was not meant to

be left with a physician, correct?
MR. BOISE: Object to the form of the question.
THE WITNESS: "Not for use in detailing" means that this document can't be used for promotional purposes with a clinician.
QUESTIONS BY MR. SUGGS:
Q You don't want the doctors to even see this, do you?
MR. BOISE: Object to the form of the question.
THE WITNESS: This has not been approved for promotions for representatives to promote to sales representatives.
QUESTIONS BY MR. SUGGS:
Q A sales rep would not provide this to the doctor, he would not hand this to the doctor, correct?
A No, a sales representative would not be allowed to hand this document to the doctor because it has not gone through the promotional approval process.
Q Well, not only that, it would be embarrassing if the doctors knew that the sales reps had a script, wouldn't it?
MR. BOISE: Object to the form of the question.

THE WITNESS: This document can't be used with clinicians because it has not been approved for promotional use.

QUESTIONS BY MR. SUGGS:

Q What this document does is identify various concerns that physicians had about Zyprexa and then tells the sales rep how to respond, correct?

A Yes. This document is a training document to help provide sales representatives to answers to frequently asked questions of physicians.

Q One of the questions is Question No. 6 on page 2. The question is: "I am concerned about diabetes." And below that it says "Cushion."

What does cushion mean?

A Cushion quite simply means to -- as it describes here to thank the doctor for the concern and to show empathy for the doctor, that this is a valid concern that we want to address.

Q And then it says "Clarify," and there to clarify it says, "Is this something you have seen or heard about?" Correct?

A Yes.

Q And then there is -- below that it says, "Address AOC." AOC stands for area of concern, correct?

A Yes, that's correct.

Q And in this response -- pardon me, and in that section there the sales rep is told what to tell the doctor, correct?

A Yes, that's correct.

Q And in the third sentence of that paragraph it states, quote, In every study examining this subject, no causal relationship has been established between patients being treated with Zyprexa and the onset of diabetes, correct?

A Yes, that's correct.

Q And do you know when it was that -- well, strike that.

It's fair to say, sir, that the sales reps were taught and told to inform physicians that there was no causal relationship between Zyprexa and the onset of diabetes throughout the time period you were involved with Zyprexa, correct? Between 1999 and 2007 that's what sales reps were expected to tell physicians, correct?

MR. BOISE: Object to the form of the question, mischaracterized his testimony, asked and answered.

THE WITNESS: No. That's not correct.

In fact, in this time frame what they were instructed to say was, In every study examining

this subject, in this time frame, no causal relationship has been established between patients being treated with Zyprexa and the onset of diabetes.

QUESTIONS BY MR. SUGGS:

Q Have sales reps ever to your knowledge been instructed to go out and admit to physicians that Zyprexa can cause diabetes?

A No, that has never been a specific verbatim for our sales representatives.

Q In fact, they go on to say in this document, the following sentence says, "The incidence of diagnosed treatment-emergent diabetes with patients taking Zyprexa was comparable to those patients treated with Risperdal, Haldol and Depakote in every clinical study conducted by Lilly ir by our competitors."

Did I read that correctly?

A Yes, you did.

Q And Risperdal, Haldol and Depakote are other psychiatric drugs, correct?

A Yes, Risperdal and Haldol are antipsychotic medicines and Depakote is a mood stabilizer.

Q And that message of comparable rates of diabetes between Zyprexa and other drugs has been a

consistent message coming from the company, correct?

MR. BOISE: Object to the form.

What time frame?

QUESTIONS BY MR. SUGGS:

Q Throughout the time you were involved with Zyprexa.

A Comparable rates has not been a message throughout the time frame that I have been involved with Zyprexa.

Q When was it not?

A We currently do not have a message that --

THE REPORTER: I can't hear you.

THE WITNESS: We currently do not have a message for diabetes for comparable rates of diabetes with Zyprexa.

QUESTIONS BY MR. SUGGS:

Q I bet not in light of the labeling change that came out in October. When did Lilly --

MR. BOISE: Hold on. Was that a question?

QUESTIONS BY MR. SUGGS:

Q When did Lilly stop having comparable rates be part of their message?

MR. BOISE: Object to the form of the question, compound, move to strike the observations of counsel.

THE WITNESS: I don't know the exact time

frame.
QUESTIONS BY MR. SUGGS:
Q Can you give me an approximate time frame?
A It would have been prior to my assuming responsibilities in 2003 for Zyprexa in the U.S.
Q It's your testimony that after 2003 Lilly did not make a claim of comparable rates?
A We did not have a promotional message for comparable rates after 2003 is my recollection, yes.
Q Sir, do you see a difference between the phrase "comparable rates" and "no consistent differences"?
MR. BOISE: Object to the form.
THE WITNESS: You are really asking a medical question that I would rely on my medical colleagues to answer.
QUESTIONS BY MR. SUGGS:
Q Sir, isn't it a fact that even after 2003 Lilly told physicians that there were no consistent differences among atypicals in the incidence of diabetes?
A I would want to review the specific promotional material to know exactly what our communication was in each time frame.
Q Okay. We'll get to that.

If I could direct your attention to the first page of this document. Let's stay with the page that we were on, at least the question we were on. This document, after instructing the sales reps to address the area of concern, then says that the sales reps should check for agreement and then get back to selling, correct?
A I'm sorry. Where are you reading from now?
Q Page 3.
A Okay. Okay.
Q That's what the sales reps were told, give this message here that was developed out in Indianapolis -- strike that.
The sales reps were told that if a doctor said he was concerned about diabetes they should address that area of concern using that language that we've talked about here and after doing that they should then check for agreement and get back to selling, correct?
A Yes, that's correct.
Q Okay. If I could direct your attention to the first page, the first area of concern that reflected there was "I do not treat that type of patient."
Do you see that?

A Yes, I do.
Q And under Important notes it says "Make sure the PCP" -- by the way that stands for primary care physician, correct?
A Yes, that is correct.
Q Make sure the primary care physician recognizes the type of patient we are talking about today, not the psychotic patient or severely ill patient, but the complicated mood patient who has symptoms of irritability, anxiety, poor sleep and mood swings. This is most likely a patient he has seen for a few years and has felt comfortable treating.
Do you see that language here?
A Yes, I do.
Q Zyprexa was never indicated for the treatment of irritability, was it?
MR. BOISE: Object to the form.
THE WITNESS: No.
QUESTIONS BY MR. SUGGS:
Q It was never indicated for the treatment of complicated mood, was it?
MR. BOISE: Object to the form.
THE WITNESS: No.
QUESTIONS BY MR. SUGGS:
Q It was never indicated for the treatment of

anxiety, correct?
MR. BOISE: Object to the form.
THE WITNESS: No.
QUESTIONS BY MR. SUGGS:
Q It was never indicated for poor sleep, correct?
MR. BOISE: Object to the form.
THE WITNESS: No.
QUESTIONS BY MR. SUGGS:
Q It was never indicated for mood swings, correct?
MR. BOISE: Object to the form.
THE WITNESS: No.
QUESTIONS BY MR. SUGGS:
Q Okay. By the way, just so the record is clear, when you are saying "no" you are agreeing with me that it was not indicated for any of those?
A Yes, that correct.
Q Just so we have a clear record.
MR. BOISE: If you are done with the document, I would like to take five minutes.
MR. SUGGS: Sure.
MR. BOISE: Okay.
THE VIDEOGRAPHER: We are off the record. It is 10:42. This is the end of Tape No. 1 of the deposition of David Noesges.
(Recess.)

THE VIDEOGRAPHER: We are back on the record. This is beginning of Tape No. 2 of the deposition of Dave Noesges. It is 10:54.
QUESTIONS BY MR. SUGGS:
Q Sir, I'm going to hand you two exhibits now. One is -- has been previously marked as Plaintiffs' Exhibit 995 and the other one is Plaintiffs' Exhibit 9201.
For the record Exhibit 995 is a memo from Alan Breier, Jack Jordan, Dennis Torres, Mike Bandick to the policy committee dated July 7, 2003.
MR. BOISE: Denice.
MR. SUGGS: Pardon?
MR. BOISE: Denice.
MR. SUGGS: Yes. What did I say?
MR. BOISE: Dennis.
MR. SUGGS: I thought I said Miss. I could be wrong.
Q Let's talk about that document first.
You are familiar with what the policy committee is at Lilly, are you not, sir?
A Yes, I am.
Q It's the principal governing body of the corporation made up of top level executives, correct?

A Yes, that my understanding.
Q It's chaired by the CEO of the company who at the time this memo was written was Mr. Sidney Taurel, correct?
A Yes, that is correct.
Q And Alan Breier was the head of the Zyprexa product team, correct?
A At this time, yes.
Q And Jack Jordan at that time was head of U.S. marketing, correct?
MR. BOISE: Object to the form, foundation.
THE WITNESS: Yes, that's correct.
QUESTIONS BY MR. SUGGS:
Q And in this time period July 7, 2003, what were your responsibilities with respect to Zyprexa?
A This time frame of July 7, 2003, I was the general manager of Lilly Australia and New Zealand.
Q So you would have not had involvement with Zyprexa in the U.S., correct?
A That's correct at this time.
MR. BOISE: Object to the form.
QUESTIONS BY MR. SUGGS:
Q Did you ever work with Jack Jordan or Denice Torres?
A Yes.

Q Did you report to either or both of them?
A No, I did not.
Q How did you work with them?
A When I was the sales director in the U.S. I was a colleague of Jack's. He was the marketing director at that time and I worked with Denice in my capacity as U.S. marketing director.
Q Okay. What years were those?
A I was the U.S. marketing director from November of 2003 through, basically, October of 2004.
Q Okay. So this memo would have been written a couple of months before you took over as U.S. marketing director, correct?
A Yes. This is written before I took over.
Q Did you succeed Jack Jordan, then, in that position?
A Yes, I did.
Q And it states that "The purpose of this document is to provide additional information" to the policy committee "on topics associated with Zyprexa and perceptions surrounding weight gain and diabetes," correct?
A It would be helpful if I could take a minute to read this. It will be easier to answer your questions if I could see the context.

Q I don't think you need to read the entire document to answer the questions that I have for you. And since time is a factor here, what I would suggest is this, sir: Why don't I ask you the question, if after hearing that question you feel you need to read the entire document in order to answer the question I have asked, I will be happy to give you that time. I really don't think it is going to be necessary.
A With due respect, sir, it would be helpful for me to know the context of the document to answer your questions.
Q Sir, you don't know what my questions are. So why don't you wait and listen to what my question is first.
My first question is: The first sentence of this memo to the policy committee states quote, The purpose of this document is to provide additional information on topics associated with Zyprexa and perceptions surrounding weight gain; is that correct, sir?
MR. BOISE: Your question is that is what the first sentences reads?
MR. SUGGS: Yes.
THE WITNESS: Yes.

QUESTIONS BY MR. SUGGS:
Q If you could direct your attention to about the middle of the page there is a line across the page that says, "New Zyprexa 'Focus' Team."
Do you see that?
A Yes.
Q Then right below that the memo states in that first paragraph, in part, quote, As discussed during the recent Policy Committee meeting, there are already multiple initiatives underway. In order to intensify our efforts, we have organized a Focus team whose charge is to deliver, by July 28, a more assertive, fully integrated and customer-tested approach to changing the way key stakeholders view and address this issue.
Do you see that language, sir?
A Yes.
Q Was that focus team still in existence when you took over as head of U.S. marketing in November of 2003?
A I'm going to have to read further to understand what the focus team is they are referring to in order to answer that question.
Q Okay. Go ahead.
A I'm not aware of that focus team being in existence

during my time as marketing director. No.
Q Okay. Directing your attention to the following paragraph that states, quote, Our goal is to influence key stakeholders (clinicians ... sales representatives, patients, Wall Street, the media, Lilly senior management, caregivers and thought leaders) with the facts about diabetes relative to the seriously mentally ill, Zyprexa, and other atypical agents. Our message: "-- and then they list five different--pardon me, seven points, correct?
A Yes, that's correct.
Q And point No. 4 was stated as a, quote, Data do NOT -- it's in all caps and bold font.
"Data do NOT support a causal link between Zyprexa and diabetes; while the scientific literature is mixed, there does not appear to be consistent differences among atypicals"; is that correct?
A Yes, that's what the document reads.
Q Again the message is there is no causal relationship?
MR. BOISE: Object to the form of the question.
MR. SUGGS: Correct.
THE WITNESS: No. What this statement says,

is that data do not support a causal link between Zyprexa and diabetes; while the scientific literature is mixed there does not appear to be consistent differences among atypicals.
QUESTIONS BY MR. SUGGS:
Q And what it says there, there does not appear to be consistent differences, that is essentially the same thing as saying comparable rates, correct?
MR. BOISE: Object to the form of the question.
THE WITNESS: No, I think this is a different statement.
QUESTIONS BY MR. SUGGS:
Q Different words, but it conveys the same sense, doesn't it?
MR. BOISE: Object to the form.
QUESTIONS BY MR. SUGGS:
Q Zyprexa is no worse than anybody else?
MR. BOISE: Object to the form.
A No. What this says, quite simply, is that data do not support a causal link between Zyprexa and diabetes; while the scientific literature is mixed, there does not appear to be consistent differences among atypicals.
Q When it says "there does not appear to be

consistent differences among atypicals," doesn't that mean the company was saying that Zyprexa was no worse than anybody else in terms of diabetes?
MR. BOISE: Object to the form of the question, asked and answered.
THE WITNESS: No, I think --
QUESTIONS BY MR. SUGGS:
Q That's common sense isn't it, sir?
MR. BOISE: Object to the form of the question.
THE WITNESS: No, sir. I think that the statement is very clear that what we are saying is data do not support a causal link between Zyprexa and diabetes and that scientific literature is mixed and through that analysis, there does not appear to be consistent differences among the atypicals.
Q If you are saying there are no consistent differences among the atypicals, doesn't that mean that Zyprexa is no worse than anybody else?
MR. BOISE: Object to the form.
Dave, you asked it three times.
MR. SUGGS: I'm trying to get a straight answer.
MR. BOISE: He has given you a straight answer. Move to strike your command.

Page 74

MR. SUGGS: No, he hasn't.
Q Doesn't -- when it says there is no consistent differences, isn't that the same thing as saying that Zyprexa was no worse than anybody else?
A No, sir, it's not.
Q I would like to direct your attention to the second page of the document. In about the middle of the page there is a heading there for Corporate Response Letter. And 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 representative. The letter is written on behalf of Lilly and signed by Dr. Alan Breier."
Do you see that language, sir?
A Yes, I do.
Q If I could direct your attention to the following -- the other exhibit I handed you, which is Exhibit 9201, which is sitting on the table in front of you.
A Um-hmm.
Q That is, in fact, the letter that was being referred to there by Alan Breier, is it not?
A I can't say for certain that this is the letter that this document is referring to.

Page 75

Q I'll represent to you, sir, that we have had testimony from Dr. Breier himself that this is indeed a letter that he wrote that was, in fact, distributed.
Do you have any basis to dispute that?
A No, sir, I do not.
Q Okay. If I could direct your attention to -- by the way, do you recall that, in fact, a letter from Dr. Breier, this letter, was distributed to the sales -- pardon me, distributed by the sales force to physicians?
A No, sir, I do not.
Q But you were not in the country then at that time in July or August or September of 2003, correct?
A Yes, that's correct. I was in Australia.
Q Okay. If, in fact, the sales reps did distribute this letter to physicians, they would be using it as a promotional piece, correct?
MR. BOISE: Object to the form of the question.
THE WITNESS: No, sir, that's not necessarily the case.
QUESTIONS BY MR. SUGGS:
Q Well, this letter does, in fact, promote the message that Zyprexa is safe, does it not?

Page 76

MR. BOISE: Object to the form of the question. The document speaks for itself.
THE WITNESS: I am going to have to read the letter. Now you have asked the question that is going to require me to read it in order to be able to answer your question.
QUESTIONS BY MR. SUGGS:
Q Let me withdraw that question and ask you another question.
Do you see how in Dr. Breier's letter there are several paragraphs that start off with bolded font questions?
A Yes, sir.
Q The first one was: "Does Zyprexa cause diabetes?"
MR. BOISE: That's not the first.
MR. SUGGS: I'm sorry. First --
MR. BOISE: First one that you asked about.
THE WITNESS: Sir, I'm going to read the letter if you are going to ask me questions about it.
QUESTIONS BY MR. SUGGS:
Q Sir, you have not heard my question yet.
MR. BOISE: It's a page and a half letter, Dave, why don't you let him read it?
MR. SUGGS: We have a lot of documents to get

Page 77

through here. We are not going to be able to get done in time. It just seems kind of odd that we take a break and right when we come back from the break, all of a sudden this witness now has to read page by page every document that we put in front of him. Is that just a coincidence? I think not.
MR. BOISE: David --
MR. SUGGS: Let me ask the questions.
MR. BOISE: Your statement is offensive.
MR. SUGGS: If he needs to read the entire document to answer the question I pose, I am happy to give him the time. I already did with the prior question. I don't think he's going to need it for this. Here is my question --
MR. BOISE: Ask him the question. If he needs to read it, I ask you to respect that; and I find your comments offensive and I move to strike them.
MR. SUGGS: I did. Well, it seems more than a little coincidental to me.
MR. BOISE: Move to strike your comment.
QUESTIONS BY MR. SUGGS:
Q Directing your attention to Exhibit 9201, there is in the third paragraph a bolded question says: "Does Zyprexa cause diabetes?" Do you see that language, sir?
A Yes, sir I do.

Page 78

Q And the answer to that in the first sentence is: "The available data do not establish a causal link between diabetes and Zyprexa -- or any other antipsychotic, for that matter."
Do you see that language?
A Yes, sir I do.
Q And that's essentially saying the same thing that we saw before in Exhibit 1941, when in response to a doctor saying that he was concerned about diabetes, the sales reps were told to say, "In every study examining the subject, no causal relationship has been established between patients being treated with Zyprexa and the onset of diabetes." Those are certainly saying the same thing, isn't it, sir?
MR. BOISE: You are reading from 1941 now?
MR. SUGGS: Yes.
MR. BOISE: Read from this one over here.
THE WITNESS: He is asking me to compare?
MR. BOISE: He is asking you to compare 1941 under Item 6, David?
MR. SUGGS: Yes.
THE WITNESS: Sir, in the context of what our reps can say promotionally, the words that we choose are important. If the words are identical I would agree with you it is the same statement. If

Page 79

they are not identical then the different words are important.
QUESTIONS BY MR. SUGGS:
Q So you think there is a significant difference between saying, "The available data do not establish a causal link between diabetes and Zyprexa," in the 2003 letter, and the language in the 2003 Area of Concern document. "In every study examining the subject, no causal relationship has been established?" What's the difference there? I guess I'm just not getting it.
MR. BOISE: Object to the form of the question.
QUESTIONS BY MR. SUGGS:
Q In both instances the company is denying that Zyprexa causes diabetes, correct?
MR. BOISE: Object to the form of the question.
THE WITNESS: No, sir, that is not correct. What the company is saying, "The available data do not establish a causal link between diabetes and Zyprexa."
QUESTIONS BY MR. SUGGS:
Q And it's your testimony that that does not deny that Zyprexa causes diabetes?

Page 80

A Yes, sir. What we are saying is that the available data do not establish a causal link between diabetes and Zyprexa.
Q And if you are making that claim then you are denying that there's a causal relationship, correct?
MR. BOISE: Object to the form, asked and answered.
THE WITNESS: No, sir, we are saying that the available data do not establish a causal link between diabetes and Zyprexa.
QUESTIONS BY MR. SUGGS:
Q Well, does the company admit that Zyprexa can cause diabetes?
MR. BOISE: Object to the form, asked and answered.
THE WITNESS: No, sir. Our position is that the available data do not establish a causal link between diabetes and Zyprexa at this time.
QUESTIONS BY MR. SUGGS:
Q Then if I could direct your attention back to Exhibit 9201, at the bottom of the first page there is a paragraph with the bolded question, "Given the weight gain profile of Zyprexa, how can Lilly claim 'no consistent differences' for treatment-emergent

Page 81

diabetes among patients treated with atypicals?"
Do you see that language?
A Yes, sir, I do.
Q And then in about the middle of the paragraph there is a sentence that states, "The fact is, head-to-head clinical studies and epidemiology studies show no consistent or clinically significant difference in the risk of diabetes among patients treated with different atypical antipsychotics, despite differences in the respective weight gain profiles."
Do you see that language, sir?
A Yes, sir, I do.
Q And that was the message that sales reps were expected to use with physicians, correct?
MR. BOISE: Object to the form of the question, vague.
You are in this time period?
MR. SUGGS: Yes.
MR. BOISE: Okay.
THE WITNESS: No, sir. This -- this document is not an approved document for a sale representative to communicate. It's a document with Alan Breier's statements to physicians.

QUESTIONS BY MR. SUGGS:
Q Well, sir, the sales reps, according to Exhibit 995, were instructed to deliver this to clinicians, correct?
A Yes, sir, that's correct.
Q And if they deliver it to the physicians and they leave it with the physician, that's the message that's being delivered by the sales rep, correct?
MR. BOISE: Object to the form, vague.
THE WITNESS: No, sir --
MR. BOISE: Compound.
THE WITNESS: The sales representatives would deliver this letter to the doctor and they would use the promotional materials which have been approved for our medical-legal regulatory process for their promotional and communication of the message.
QUESTIONS BY MR. SUGGS:
Q Well, the message that was communicated by Lilly to the physicians in this letter was, there is no consistent differences between the atypicals, correct?
MR. BOISE: You are referring back to 9201 now?
MR. SUGGS: Yes.

THE WITNESS: Do you want me to read this to you, sir? Is that what you are asking?
MR. SUGGS: No. Let me withdraw that question.
Q Sir, do you recall that the comparable rates message was developed in 2000?
A I don't know specifically the time frame where the comparable rates message was developed.
Q Let me hand you what's been previously marked as Plaintiffs' Exhibit 5849, which for the record is a PowerPoint presentation bearing the date December 14, 2000. On the bottom left-hand corner, there's also a handwritten note at the top saying "meeting 12-14-2000, Zyprexa strategy with increased glucose and weight gain."
I'll also represent to you, sir, that this document was according to the database that was provided to us by Lilly came from the files of Dr. John Holcombe.
Do you know Dr. John Holcombe?
A Yes, I do.
Q Who is he?
A I'm not sure what Dr. Holcombe's title is. I'm not sure if he is still with Lilly but he is a physician.

Q He was working on Zyprexa at that time in 2000, was he not?
MR. BOISE: Object to the form.
THE WITNESS: I can't confirm that. I'm not certain.
QUESTIONS BY MR. SUGGS:
Q And he is not a psychiatrist, is he?
A No, sir, he is not.
Q He is an endocrinologist, isn't he?
A I believe that's correct, yes.
Q In fact, he was originally working on the side of the company that was dealing with diabetes, correct?
MR. BOISE: Object to the form.
THE WITNESS: Yes, that's correct.
QUESTIONS BY MR. SUGGS:
Q He was brought into the Zyprexa -- strike that.
He was brought in to work on Zyprexa issues in connection with the diabetes issue, correct?
A I don't know, sir.
Q If I could direct your attention to page 2 of the document. There is a heading there Market Research. It starts off by saying, "There are two groups of MDs -- the 60% who do not see diabetes as a particular concern with APs and the 40% who

are concerned."
Do you see that language, sir?
A Yes, sir, I do.
Q Was it your understanding that the acronym "APs" stands for antipsychotics?
A Yes, sir, that's correct.
Q Was it your understanding in late 2000, early 2001 that there were two groups of M.D.s, the 60 percent who do not see diabetes as a particular concern and the 40 percent who were concerned?
A Yes, that's consistent with my recollection.
Q If I could direct your attention to page 5.
By the way, have you ever seen this document before?
A I don't recall having seen it before, no.
Q If I could direct your attention to page 5. There is a heading at the top that says, "Zyprexa and Diabetes -- what we want physicians to think."
Do you see that?
A Yes, sir, I do.
Q It has at the top the Key Message, and the key message was: "Diabetes may occur in patients on antipsychotics and/or MSs" -- does that stand for mood stabilers -- mood stabilizers?
A Yes, sir, it appears that's what that is referring

to.
Q It says, "Diabetes may occur in patients on antipsychotics and/or mood stabilizers including Zyprexa, at rates that are comparable to each other."
Do you see that language, sir?
A Yes, sir, I do.
Q Do you recall that in 2000 that was what Lilly wanted doctors to think?
A No, sir, I can't tell that from this message for a couple of reasons. One is that this is -- I can't tell who the author of this is and whether this is a promotional decision or recommendation. Also there are portions of the document that refer to it as a draft. I think it's somebody's draft proposal for what a key message would be -- would be my interpretation of the document.
Q Okay. Sir, if a document is on the knowledge management database, does that mean that the document has received approval from the brand team?
A No, sir. Every document on knowledge management is not a promotional document, nor is it necessarily a document that's been approved for use with customers.
MR. BOISE: Dave, I will note that you

represented the document came from the files of John Holcombe, right?
MR. SUGGS: This document came from John Holcombe.
MR. BOISE: I don't want you to mislead him. That's all.
MR. SUGGS: Okay. I'm not misleading him.
MR. BOISE: I just want to make sure that you weren't suggesting that this was off the knowledge management.
MR. SUGGS: No, the next one I want to talk about is.
MR. BOISE: Ask him the question. That's all.
QUESTIONS BY MR. SUGGS:
Q Who was it that would post documents on the knowledge management database?
A I don't know the specific associate who would post that, but there would be an associate in Indianapolis that would post the knowledge management documents.
(Conference room phone ringing.)
MR. BOISE: Off the record for a moment.
MR. SUGGS: Off the record.
(Discussion off the record.)
THE VIDEOGRAPHER: We are back on the record.

QUESTIONS BY MR. SUGGS:
Q Could anyone post information on the knowledge management -- strike that.
Could anyone post documents or information on the knowledge management database?
A Sir, I'm not certain what the specific requirements are for a knowledge management posting.
Q Well, it couldn't just be some rogue person throwing up something on a database, could it?
MR. BOISE: Object to the form of the question, vague, foundation.
THE WITNESS: No, sir.
QUESTIONS BY MR. BOISE:
Q It would -- anything that was going up on the knowledge management database would have been reviewed within the company to make sure it was consistent with the message of the company with respect to the product, correct?
MR. BOISE: Object to the form of the question, foundation.
(Sirens sounding.)
THE WITNESS: It's important to note -- there is a lot of information in knowledge management that has nothing to do with our interactions with our customers or our marketing message. There is

information around expense reporting, information around company car utilization. It's a widespread useage of knowledge management that is well beyond just our promotion message.
MR. SUGGS: Are you picking up the sirens?
THE VIDEOGRAPHER: We are off the record.
(Discussion off the record.)
THE VIDEOGRAPHER: We are back on the record.
QUESTIONS BY MR. SUGGS:
Q Okay. Sir, to the extent documents found on the knowledge management database did talk about company products like Zyprexa and did talk about the messages of a product like Zyprexa, would it be fair to say that those materials would have been reviewed by management before they were put on there for the sales reps to -- to view?
MR. BOISE: Object to the form of the question, foundation.
THE WITNESS: For any document that's -- on knowledge management that is designed for the reps to use promotionally with their customers would have gone through our normal medical/legal/regulatory process.
There may also be informational documents that are clearly not intended for representatives to use

with their -- with clinicians which would not be part of the promotional message.
QUESTIONS BY MR. SUGGS:
Q Okay. But if there are documents that are on the knowledge management database for sales reps to use to inform them about the product, even if the document was not intended for use in detailing per se, the information in that document would have been reviewed by management before it was put out there for sales reps, wouldn't it?
MR. BOISE: Object to the form of the question, foundation.
THE WITNESS: Yes, sir, that's correct.
QUESTIONS BY MR. SUGGS:
Q Thank you. I'm going to hand you what's been previously marked as Plaintiffs' Exhibit 1970. For the record Exhibit 1970 bears the date of February 2, 2001.
And I'll represent to you, sir, that Lilly has stated in answers to interrogatories in the Alaska case that this document was on the knowledge management database and made available to sales reps.
Do you have any basis to dispute either the date of the document or that it was, in fact, on the knowledge management database?

MR. BOISE: Is your date based on the fax line or some other data point?
MR. SUGGS: It's based not only on the fax line but also on the date that is on the database for the document.
THE WITNESS: I can't determine the specific timing of the document, but I have no reason to dispute the date that you indicated.
QUESTIONS BY MR. SUGGS:
Q Okay. If I could direct your attention to page 5. There are a number of different numbers on this document. I'm going to be referring to the numbers that are sort of in bold font in the lower right-hand corner about an inch and a half or so from the bottom.
A Okay.
Q Okay. And on that page in the right-hand column in the first paragraph it starts off by saying, "Market research" -- you see where I'm at?
A Yes.
Q Starts off by saying, "Market research has shown that there are two groups of physicians with whom we must be prepared to deal. First, there is a group representing about 60% of psychiatrists who do not view diabetes as a particular concern with

antipsychotics."
Do you see that language, sir?
A Yes, sir, I do.
Q That's essentially the same market research that we saw referenced in the earlier document, the one just before this, Exhibit 5849.
And it's also consistent with what your understanding was back in that time frame, correct?
A Yes, sir, that's correct.
Q Okay. Then in the bottom part of that paragraph, four and a half lines up above from the bottom, it states, quote, The other 40% of our psychiatrists have specific concerns about ZYPREXA and diabetes, and perhaps half of this group has begun to shy away from ZYPREXA because of their concerns.
Do you see that language, sir?
A Yes, sir, I do.
Q And was that consistent with your understanding back at that time?
A Yes, sir, that's correct.
Q If I could direct your attention to page 7 in the upper left-hand corner. There is a box -- actually, there's two boxes; but there is one with text in it.
"Briefly, diabetes may occur in patients

taking antipsychotics and/or mood stabilizers including ZYPREXA, at rates that are comparable to each other."
Do you see that language, sir?
A Yes, sir, I do.
Q So at least by February of 2001 the sales reps would have had this information made available to them in the knowledge management database, correct?
A Sir, I can't tell from this document whether this was information made available to the sales representatives. It's not clear where this document came from or least in the portions you have allowed me to read thus far who it was intended for.
And also there is a comment saying that the document has not been proofread -- proofread, which suggests to me that perhaps it's not a final document, maybe in draft form.
Q Well, sir, I'll represent to you that in its answers to interrogatories in this case Lilly has stated on the record to us that this document was on the knowledge management database and made available to sales reps. That's my understanding of what their answers to interrogatories are with respect to this document.

You don't have any basis to dispute that, do you?
A No, sir, I don't, other than the sentence on there about the document not having been proofread would be inconsistent with what I would expect to be in knowledge management.
Q Okay. If I could direct your attention to page 8. In the right-hand column there is a heading, Market research testing, and then there are two paragraphs below that, correct?
MR. BOISE: Under that heading?
MR. SUGGS: Correct.
THE WITNESS: Yes.
QUESTIONS BY MR. SUGGS:
Q And the second paragraph it starts off by saying, "If we deliver the right message to the depth required, we can get physicians thinking. And with the "air cover" that is being provided in CME programming and other peer-to-peer programs, it is our intent to reframe this issue over time so that fear of diabetes does not become a reason to avoid starting a patient on ZYPREXA."
Do you see that language?
A Yes, sir, I do.
Q Now, when it refers to CME programming, that refers

to continuing medical education programs?
A Yes, sir, that does.
Q And am I correct that Lilly hired physicians to deliver presentations at continuing medical education meetings where the issue of diabetes would be addressed?
MR. BOISE: Object to the form of the question, foundation.
THE WITNESS: No, sir. Lilly does not hire physicians to make presentations at CME programs.
QUESTIONS BY MR. SUGGS:
Q What is the "air cover" that is being referred to there?
A This is referring to peer-to-peer speaker programs; and it's also referring to CME programs.
Q Well, what is a peer-to-peer programs?
A Peer-to-peer program in this context would be a promotional program. And in that case it would be a speaker, part of the Lilly speaker bureau, speaking on Lilly's behalf in a promotional program.
Q Okay. And what is the air cover that was being referred to there?
A Air cover appears to be describing the CME programming and other peer-to-peer programs.

Q What does it mean when it talks about air cover?
A Means CME programs and other peer-to-peer programs.
Q How is that air cover?
A I'm not sure how to answer your question other than it's -- that it's the -- characterizing CME programming and other peer-to-peer programs is air cover.
Q And Lilly did have what you referred to as a Lilly speakers bureau, correct?
A Yes, sir, that's correct.
Q And that is composed of physicians, correct?
A Yes, physicians and other healthcare providers.
Q Hired by Lilly, correct?
A Lilly has a contract with the physician to speak on our behalf.
Q As part of that or their speaking they would give presentations on this issue of the relationship between Zyprexa and diabetes, correct?
A Yes. That could be a portion of the message they would be delivering to customers.
Q So Lilly would hire doctors to speak to other doctors discussing the issue of diabetes and Zyprexa and those physicians that were hired were expected to give the message that there were comparable rates of diabetes; isn't that correct?

MR. BOISE: Object to the form of the question, vague, compound, time frame.
THE WITNESS: My interpretation of "hire" means that these physicians were Lilly employees, which would not be the case.
QUESTIONS BY MR. SUGGS:
Q I was not saying they were Lilly employees.
Lilly paid the physicians to go out and give those presentations, correct?
MR. BOISE: Objection, vague.
THE WITNESS: Yes, the physicians were compensated for the presentations they made.
QUESTIONS BY MR. SUGGS:
Q Let's talk about what they said.
The reason why this memo or this document refers to those peer-to-peer programs as being air cover was because the doctors that were giving those presentations were being paid by Lilly to give presentations that gave the comparable rates message; isn't that correct?
MR. BOISE: Object to the form of the question, compound.
THE WITNESS: I cannot tell from this document in this paragraph what message the doctors were delivering. I would have to go back and look at

the approved slides, which would be approved for those programs, to look at what the specific message doctors were delivering.
QUESTIONS BY MR. SUGGS:
Q Well, Lilly did not pay doctors to go out and talk to other doctors and say that Zyprexa had a higher rate of diabetes, did it?
A No, sir, we didn't.
Q No.
If I could direct your attention to page 25. The title on that page is "Hyperglycemia Sell Sheet Message Script," correct?
MR. BOISE: Let him get to the page.
THE WITNESS: Okay.
QUESTIONS BY MR. SUGGS:
Q The title on page 25 is "Hyperglycemia Sell Sheet Message Script," correct?
A Yes.
Q This was a script -- this message script was for sales reps, was it not?
A Yes. This is clearly designed for sales representatives; but, again, I can't tell from the document whether it's a final version or not. I would have to refer to the actual promotional material.

Q When sales reps were provided scripts, they were expected to follow the script, were they not?
A The scripts were part of their training documents, so certainly their message is required to be consistent with the final message script that would support the promotional document; but we didn't expect sales representatives to memorize a script like this and then to communicate it word for word to the doctors.
Q They did not have to do it word for word; but you certainly did not expect or intend for them to give any presentation that differed in substance from what was provided, correct?
A Yes, that's correct.
Q If I could direct your attention to the left-hand column of page 26. There's a heading about a third of the way down called "High Ground Opener."
A Yes.
Q And there's two paragraphs below that heading, correct?
A Yes.
Q And the second one starts off by saying, quote, "There are two main points that I want you to walk away with."
And this is -- would be a sales rep talking to

a doctor, correct?
A Yes.
Q So there were two main points that he wanted the doctor to walk away with. And he goes on to say, quote, The first is that in this head-to-head data, incidence of diagnosed treatment-emergent diabetes was comparable between ZYPREXA and risperidone and also between ZYPREXA and haloperidol.
The second point I want you to walk away with is that incidence of increased random blood glucose is also comparable across these 3 treatment groups.
Do you see that language, sir?
A Yes, sir, I do.
Q Okay. Now, you mentioned earlier that you knew a Dr. Charles Beasley, correct?
A Yes.
Q How did you know Dr. Charles Beasley?
A He's worked as part of the Zyprexa molecule as a clinical research physician.
Q Did you have any dealings with him yourself?
A I don't believe I have ever had any direct interactions with Dr. Beasley.
Q Were you ever informed that in February of 2001, the same month this document was apparently dated, that Dr. Beasley wrote an E-mail in which he noted

that Zyprexa had a statistically significant mean increase on random glucose as compared to Haldol?
MR. BOISE: The question is whether he has heard that before?
MR. SUGGS: Yes.
THE WITNESS: No, sir, I haven't.
QUESTIONS BY MR. SUGGS:
Q Haldol is the same thing as haloperidol that is referred to in this Exhibit 1970, correct?
A Haldol is the branded name for haloperidol which is a generic name.
Q And in this statement that was on the knowledge management database, it's saying that the incidence of diagnosed treatment-emergent diabetes was comparable between Zyprexa and risperidone and also between Zyprexa and haloperidol, correct, or Haldol?
MR. BOISE: Object to the form.
THE WITNESS: What the document is saying is that in this head-to-head data, so it's referring to specific head-to-head data.
We would have to see the sell sheet to know what head-to-head data it's referring to, that the incidence of diagnosed treatment-emergent diabetes was comparable between Zyprexa and risperidone and

also between Zyprexa and haloperidol.
QUESTIONS BY MR. SUGGS:
Q It's your testimony that Dr. Beasley -- well, let me ask you this -- I want to make sure to cover all the bases here. Is it your testimony that neither Dr. Beasley nor anyone else ever told you in February 2001 that analyses of data done by Lilly showed that Zyprexa had a statistically significant mean increase in random glucose as compared to Haldol? Is that a fair statement? No one ever told you about any analysis showing that?
MR. BOISE: Object to the form, foundation.
THE WITNESS: I don't recall anyone ever telling me that in February 2001, no.
QUESTIONS BY MR. BOISE:
Q Do you recall anyone ever telling you that at any other, later time?
A Could you repeat the original question again?
MR. SUGGS: Sure.
Could you read it back to him, please?
(Record read.)
THE WITNESS: No, I don't recall anyone ever telling me that.
QUESTIONS BY MR. SUGGS:
Q Okay. Did anyone -- did Dr. Beasley or anyone else

ever tell you that the increases in blood glucose with Zyprexa were occurring as early as the first week of Zyprexa treatment?
MR. BOISE: Could you read back the question?
MR. SUGGS: Can you read it back?
(Record read.)
THE WITNESS: No, sir, I don't believe so.
MR. SUGGS: I'm going to hand you next what's been previously marked as Plaintiffs' Exhibit 1901. And I'm also going to hand you what we'll have marked as Exhibit 4.
(Deposition Exhibit 4 marked for identification.)
QUESTIONS BY MR. SUGGS:
Q By the way, when you make copies of Exhibit 4 and Exhibit 5, for the record, I would like those to be color copies. I did not notice you wrote a note. Sorry.
For the record, Exhibit 1901 was dated January 14, 2002, according to the database provided to us by Lilly, and Lilly has represented to us in answers to interrogatories in the Alaska litigation that this document, Exhibit 1901, was also in the knowledge management database.
Do you have any basis to dispute that?

A No.
Q If I could direct your attention to Exhibit 1901. It starts off about a third of the page down with a heading of Situation Overview, and it states below that, quote, The competition has been trying to convince our customers that ZYPREXA is not appropriate for many patients because of weight gain and the risk of hyperglycemia and diabetes. For our Lilly counterparts in the Retail Psych market, hyperglycemia, slash, diabetes has become a major obstacle. In October 2000, 60% of the psychiatrists surveyed in market research stated that they believed there was a link between ZYPREXA and hyperglycemia, slash, diabetes. In April 2001, that number increased to 100% of psychiatrists surveyed. You can see that in a short period of time, perceptions can change dramatically.
Do you see that language, sir?
A Yes.
Q Now, at this time in January of 2002 were you still working in U.S. marketing or were you over in Australia at that time?
A I'm sorry. I was in Australia.
Q Okay. Do you have any basis to dispute the statistics that are referred to in that first

paragraph regarding the percentage of psychiatrists who were surveyed believed there was a link between Zyprexa and hyperglycemia?
A No, I do not.
Q Is that, in fact, consistent with what your understanding was?
MR. BOISE: At that time period?
MR. SUGGS: In that time period.
THE WITNESS: I can't speak to the percentages, but I'm certainly aware that there were psychiatrists who had a perception that there was a link, yes.
QUESTIONS BY MR. SUGGS:
Q Would you agree with me, sir, that the longer Zyprexa was on the market the more psychiatrists became concerned about the issue of diabetes with the drug?
MR. BOISE: Object to the form, vague.
THE WITNESS: Yes.
QUESTIONS BY MR. SUGGS:
Q Okay. About the middle of the page there's a paragraph that starts off, "By knowing the facts" -- do you see that?
A Yes.
Q It states, "By knowing the facts, you can more

effectively and efficiently handle any objections raised by physicians BEFORE it becomes an issue. Four Key Message points in bold," and then there are some bullet points below that, correct?
A Yes.
Q The four key points were, quote, Patients treated with ZYPREXA, risperidone, haloperidol, divalproex, and ziprasidone in clinical trials had comparable rates of diabetes and hyperglycemia, even when the data was analyzed in 3 different ways, correct, was one of them?
A Yes.
Q Second one was that there is no direct one to one correlation between weight gain and diabetes, correct?
MR. BOISE: Object to the form.
THE WITNESS: The point actually says, "Although weight gain is one of the risk factors associated with diabetes, it is there is no direct 1:1 correlation. Weight gain can happen independent of diabetes, and diabetes can happen independently of weight gain."
QUESTIONS BY MR. SUGGS:
Q And if we look up above these bullet points, they say "Four Key Message points in bold" and that

language itself is in bold, correct?
A Yes.
Q The four key message points in bold were, No. 1, comparable rates. No. 2, there is no direct one-to-one correlation.
Diabetes is common in the general adult population and is even more common in psychiatric patients, correct?
MR. BOISE: Object to that characterization.
QUESTIONS BY MR. SUGGS:
Q And the third -- or the fourth bolded key factor was -- or key message was, A number of factors affect a person's risk for diabetes.
Those were the bolded key messages being referred to, correct?
MR. BOISE: Object to the form, added a few words.
THE WITNESS: What you described was close to what's bolded there, not exactly.
QUESTIONS BY MR. SUGGS:
Q Okay. Sorry if I added an extra word in there.
MR. BOISE: It was two.
MR. SUGGS: Two extra words.
Q Okay. If I could direct your attention to the second page. There is a heading called "Strategy,"

and the second paragraph under that heading it states in bold language in the first sentence, "Our goal is to continue to drive new patient starts on ZYPREXA, keep patients on therapy longer, and ensure the appropriate dose as utilized," correct?
MR. BOISE: Your question is that what the first sentence says?
MR. SUGGS: Yes.
THE WITNESS: Yes.
QUESTIONS BY MR. SUGGS:
Q Okay. And then towards the bottom of the page it refers to "Explanation of Diabetes Sell Sheet (OL 21620)."
Do you see that?
A Yes, sir.
Q Am I correct that what we marked as Exhibit 4 is the diabetes sell sheet that is being referred to there?
A Yes, that's correct.
Q Okay. And we can tell that by looking at the number on the last page; am I correct?
A Yes, that's correct.
Q It bears the number OL21620, and it says it was -- apparently has a copyright date of 2001, correct?
A Yes.

Q And what this explanation does is it refers to the different parts of the sell sheet and says why they are there and what things mean, correct?
MR. BOISE: Do you have a copy of the sell sheet?
MR. SUGGS: I don't.
MR. BOISE: Okay.
MR. SUGGS: Sorry.
MR. BOISE: I'll peek.
QUESTIONS BY MR. SUGGS:
Q Okay. On the top of page exhibit -- on the top of the first page of Exhibit 4 is a chart that has the title -- or the heading above the chart, it says, "Comparable rates of diabetes and hyperglycemia among psychotropics," correct?
A Yes.
Q And the heading of the -- right below that says, "Patients treated with ZYPREXA had rates of diabetes and hyperglycemia comparable to those in patients treated with risperidone, haloperidol, and divalproex sodium in clinical trials," correct?
A Yes, it states that. And there's also an asterisk which guides the physician toward the study methodologies inside the pamphlet.
Q Okay. And then it notes that -- the second graph

on that page has a heading Baseline to endpoint increase in average glucose levels across comparative studies, correct?
A Yes.
Q And if we look at Exhibit 1901 at the very bottom of page 2, it refers to that second graph and it says, "The second graph measuring baseline-to-endpoint changes in blood glucose presents information from a bulleted point in a previous sales aid, with the addition of the Pfizer study," correct?
A Yes, that's what it says.
Q So apparently this same data had been used in a sales aid or sell sheet before this time, correct?
MR. BOISE: Object to the form, mischaracterizes.
THE WITNESS: What it says to me is that there was a previous sales aid that had a bulleted point; but it does not say that this exact data was necessarily in a previous sales aid. I can't tell from the document.
QUESTIONS BY MR. SUGGS:
Q Okay. Okay. In all of -- both of these charts relate to Message Point No. 1, which was that there are comparable rates in treatment-emergent

diabetes and hyperglycemia, correct?
A These data represent evidence from the clinical trials to support comparable rates of diabetes and hyperglycemia among psychotropic agents, and also support that the two other message points of patients treated with Zyprexa had rates of diabetes and hyperglycemia comparable to those in patients treated with risperidone, haloperidol and divalproex sodium in clinical trials, and also that the baseline to endpoint increase in average glucose levels across the comparative studies.
Q That's a long way of saying that the main message point of No. 1 was comparable rates, correct?
MR. BOISE: Object to the form, restrict your characterization.
QUESTIONS BY MR. SUGGS:
Q If we go back to the first page of Exhibit 1901, the four key message points in bold, was comparable rates, correct?
A The message for the reps to communicate, though, and this is important in terms of how we teach them, is that, yes, comparable rates of diabetes and hyperglycemia among psychotropics is a message point; but it's also important to communicate the supporting data and the remaining comments that is referring these

studies that patients treated with Zyprexa had rates of diabetes and hyperglycemia comparable to those in patients treated with risperidone and haloperidol and divalproex sodium in clinical trials.
I think the context of this message statement in the context of the available clinical trials is important to be comprehensive.
Q According to Exhibit 1901, the second key message point was that there is no direct correlation between weight gain and diabetes, correct?
A I'm sorry. Where are you looking now?
MR. BOISE: Back to --
MR. SUGGS: Looking at Exhibit 1901.
MR. BOISE: Exhibit 1901, which is this document, back to the first page of that document.
THE WITNESS: Okay.
MR. BOISE: Your question is the second point?
QUESTIONS BY MR. SUGGS:
Q The second mean -- what they refer to as the second key message point was that there is no direct one-to-one correlation between weight gain and diabetes, correct?
MR. BOISE: Object to the form of the question.

THE WITNESS: The second message point described in the resource guide is, that although weight gain is one of the risk factors associated with diabetes, there is no direct one-on-one correlation. Weight gain can happen independently of diabetes and diabetes can happen independently of weight gain.
QUESTIONS BY MR. SUGGS:
Q If I could direct your attention to second page of Exhibit 1901. There's a heading on the -- that page about Message Point #2, correct?
MR. BOISE: Do you mean the third page, David?
MR. SUGGS: No, referring to the second page of Exhibit -- I'm sorry. You are right, third page of Exhibit 1901.
THE WITNESS: Yes.
QUESTIONS BY MR. SUGGS:
Q The first paragraph in that section states, quote, Many physicians think there is a logical link between weight gain and diabetes. In market research we see that many of them even use these two words interchangeably. We believe it is essential to weaken this link in order to neutralize the diabetes/hyperglycemia issue.
Do you see that language, sir?
A Yes, sir, I do.

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

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

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

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

Page 119

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 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?

Page 122

MR. BOISE: Object to form. It speaks for itself.
QUESTIONS BY MR. SUGGS:
Q One was a 2001 copyright date, the other one has 2003 copyright; two years' difference, correct?
A Yes, that would be about two years.
Q Okay. And the title on the very first page of the brochure is "Diabetes and patients with mental illness."
MR. BOISE: Put that down so we can both see it. There wasn't another copy provided.
QUESTIONS BY MR. SUGGS:
Q Up in the red at the very top, the heading is "Diabetes and patients with mental illness."
A Yes.
Q On the second page, at least the page that has the next red border at the top, it states, "How do the medications you use compare?" Correct?
A I'm sorry.
Q Can you put it down for a second?
A I'm sorry. I skipped -- okay.
Q Are you now on the same page?
A Yes.
Q The heading is "How do the medications you use compare?" Right below that it says, "Rates of

Page 123

diabetes were comparable for commonly prescribed psychotropics during longer-term clinical trials," correct?
A Yes.
Q And then if I direct your attention to the following page with the red bordered heading at the top, it states, "Incidence and odd ratios of developing diabetes during treatment with antipsychotics"; and right below that it says, "Findings from 5 epidemiological studies show no consistent differences regardless of the agent studied," correct?
A That's what it says, yes.
Q It was expected that sales reps would use these brochures in their sales representations to physicians, correct?
MR. BOISE: Object to the form.
THE WITNESS: I would have to refer to the implementation guide to know exactly what the direction was provided to sales representatives, but this clearly was a promotional tool that could have been part of their sales message to customers, yes.
QUESTIONS BY MR. SUGGS:
Q Okay. And bears the date 2003, as we mentioned

Page 124

before.
In November of 2003, you came back to the U.S. to head up U.S. marketing to take over from Jack Jordan, correct?
A Yes.
Q And also in November of 2003, the American Diabetes Association and the American Psychiatric Association, the American Association of Clinical Endocrinologists and also the North American Association For the Study of Obesity convened a consensus conference to address the issue of diabetes in connection with the use of various antipsychotic drugs, correct?
A Yes, that's correct.
Q Okay. And you were aware that, although that conference was held in November of 2003, in, I believe, it was February of 2004 those four medical associations published their consensus statement, were you not?
A Yes, my recollection is that it was in February of 2004.
Q You would have reviewed that consensus statement when it came out in 2004, would you, correct?
A Yes.
Q Let me hand you a copy of what's been previously

Page 125

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.

THE WITNESS: It's important to note, I'm not a clinical expert and rely on my medical colleagues to answer that question but that's certainly not consistent with our conclusions.
QUESTIONS BY MR. SUGGS:
Q. Okay. It's quite different from your conclusions.
We need to change the tape.
THE VIDEOGRAPHER: Marks the end of Tape No. 2, the deposition of David Noesges at 12:14.
(Lunch recess.)
THE VIDEOGRAPHER: Back on the record. This is the beginning of Tape No. 3 of the deposition of Dave Noesges. We are on the record at 1:10. You may proceed.
QUESTIONS BY MR. SUGGS:
Q. Mr. Noesges, before we took our lunch break we were talking about the consensus statement and I believe the record will show that you testified that the conclusions of the ADA consensus statement that clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia were inconsistent with Lilly's position, correct?
A. Yes, that's correct.
Q. Before October of 2007 did Lilly ever instruct its

sales force to tell physicians that Lilly believed that the rates of diabetes with Zyprexa were higher than with other drugs?
MR. BOISE: Object to the form of the question.
THE WITNESS: No, I don't believe that was ever a specific message that our representatives were instructed to communicate to physicians.
QUESTIONS BY MR. SUGGS:
Q. After October of 2007 were Lilly sales reps -- only a couple of months ago.
Between October of 2007 and the present has Lilly ever instructed its sales force to tell physicians that the rate of diabetes with Zyprexa is higher than with other drugs?
A. No.
Q. I'm going to hand you what's been previously marked as -- well, it's been previously marked in several other depositions; but it does not have a uniform number on it.
I'm going to have to mark it again here as Exhibit 6.
(Deposition Exhibit 6 marked for identification.)
QUESTIONS BY MR. SUGGS:

06-05630 CI

Q This is a March 28, 2007, letter from FDA to Eli Lilly.
Do you recall ever seeing this document before, sir?
A Yes, I have.
Q When did you see it?
THE WITNESS: Barry, can we consult?
MR. BOISE: You can answer that question yes or no.
You can answer the question, time frame.
THE WITNESS: I saw it within the last week.
QUESTIONS BY MR. SUGGS:
Q After you stopped your responsibilities for Zyprexa, correct?
A Yes.
Q Okay. If I can direct your attention to the -- about the middle of the first page of Exhibit 6. There is a heading entitled "Updated Information on Risks of Weight Gain, Hyperglycemia, and Hyperlipidemia."
Do you see that, where I'm at, there?
A Yes, I do.
Q And the paragraph below that, in the middle of the paragraph third line down, there is a sentence that starts off, "In particular" -- do you see where I'm

at there?
A Yes.
MR. BOISE: David, can I have a continuing objection on this being beyond the scope, question concerning this regulatory document?
MR. SUGGS: Sure.
QUESTIONS BY MR. SUGGS:
Q Sentence goes on to state, quote, "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."
Do you see that language, sir?
A Yes, I do.
Q And at the time you were head of U.S. marketing for Zyprexa whose generic name is olanzapine, correct?
MR. BOISE: Object to the form, foundation.
THE WITNESS: Yes, that's correct.
QUESTIONS BY MR. SUGGS:
Q Were you informed in March of 2007 -- I realize you have not seen the document before. You said you just saw it last week.
But did anyone ever tell you that FDA had written to Lilly in March of 2007 and took the

position that the Zyprexa labeling was deficient with regard to information about weight gain, hyperglycemia, and hyperlipidemia?
MR. BOISE: Object to the form.
David, I think there was a disconnect with the witness as to what his position was at this time.
MR. SUGGS: I know what his position was at this time.
MR. BOISE: You said marketing.
MR. SUGGS: Did I misspeak?
MR. BOISE: What was your position in March of 2007?
THE WITNESS: Yes, I'm sorry. I think I did misspeak. I was the executive sales director for our west region at this time frame.
QUESTIONS BY MR. SUGGS:
Q You were the executive sales director for Zyprexa in the western region?
A I was the executive sales director for neuroscience including responsibility for Zyprexa in the western region, yes.
Q And under you, you had how many sales folks who were out selling Zyprexa?
A I had approximately 700 sales representatives.
Q 700 sales representatives.

They would call on, roughly, how many doctors?
A Each of them calls on between a hundred and probably a hundred and ninety doctors.
Q So we are talking thousands, like 70,000 doctors?
Am I doing my math right?
A Yes, I think that's right.
Q Okay. So you had hundreds of sales representatives who were calling on thousands, tens of thousands, of doctors selling Zyprexa?
A Yes.
Q Did anyone tell you in March of 2007 that the FDA had written to the company and said that they believed, they, the FDA believed, that the labeling for Zyprexa was deficient with regard to information about weight gain, hyperglycemia and hyperlipidemia?
MR. BOISE: Object to the form, foundation, mischaracterizes the document.
THE WITNESS: I was aware at this time, it was communicated to -- that we had had communication back from the FDA on our new drug application and that they had asked, as I understood it, for some -- potentially some additional data and also for a dialog with our medical/regulatory colleagues with regard to -- with regard to our new drug

application.
QUESTIONS BY MR. SUGGS:
Q Is that a yes or a no?
MR. BOISE: Object to the form, asked and answered.
QUESTIONS BY MR. SUGGS:
Q Were you aware that the FDA in this communication took the position that the Zyprexa's labeling was deficient with regard to information about weight gain, hyperglycemia and hyperlipidemia?
MR. BOISE: Object to the form, mischaracterizes the document.
THE WITNESS: No, I was not.
QUESTIONS BY MR. SUGGS:
Q Okay. Nobody told you that part of it?
MR. BOISE: Object to the form, foundation.
QUESTIONS BY MR. SUGGS:
Q Correct? You were not aware of that?
A No.
Q If I could direct your attention to the following page.
Do you see how there is a section about two-thirds of the way down called, "Post Marketing Commitments"? It's a bolded heading about two-thirds down.

A Yes.
Q Okay. I want to direct your attention to the paragraph just above that, where the FDA in this letter to Lilly, stated, quote, 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. We do not feel that current labeling for 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 anyone ever tell you in March of 2007 that the FDA had written to the company saying that they believed that the labeling was deficient and that they felt, that they, the FDA felt, the physicians could not make reasonable treatment decisions until they had such information?
MR. BOISE: Object to the form, mischaracterizes the document.
THE WITNESS: No.
QUESTIONS BY MR. SUGGS:

Q Okay. Was the first time that you ever learned that there had been the communication of those positions to the company when you saw this letter for the first time last week?
MR. BOISE: Object to the form, foundation.
THE WITNESS: Yes.
MR. SUGGS: I'm going to hand you what we'll have marked as Exhibit 7.
(Deposition Exhibit 7 marked for identification.)
QUESTIONS BY MR. SUGGS:
Q Which, for the record, is a copy of an October 5, 2007, Dear healthcare provider letter, and you have, I'm assuming, have seen this document before, sir, is that correct?
A Yes, I have.
Q And would you agree with me that this letter to healthcare professionals informs them of a change in Lilly's label?
A Yes. This is a letter to healthcare professionals informing them of a change in our label for Zyprexa and Symbyax.
Q And the change in the label was to add additional language in the warning section regarding hyperglycemia, correct, that was one part of it?

A These label updates included warnings for weight gain, hyperlipidemia, and updated information in the warning for hyperglycemia.
Q Right. So part of it was to update or add additional information on hyperglycemia?
A Yes.
Q And the other part was to add totally new warning sections regarding weight gain and hyperlipidemia, correct?
MR. BOISE: Object to the form.
THE WITNESS: That labeling updates included new warnings for weight gain and hyperlipidemia and again updated information in the warning for hyperglycemia.
QUESTIONS BY MR. SUGGS:
Q Before October of 2007 there had been no language in the warning sections of the labeling regarding either weight gain or hyperlipidemia, correct?
A Weight gain and hyperlipidemia was addressed in the label, but not in the warning section until October 2007.
Q The answer to my question was --
MR. BOISE: Let him finish.
QUESTIONS BY MR. SUGGS:
Q The answer to my question was: No, prior to

Page 138

October 2007 there was no discussion of weight gain or hyperlipidemia in the warning section; isn't that correct, sir?
MR. BOISE: Object to the form.
THE WITNESS: Prior to October 2007 weight gain and hyperlipidemia were addressed in our label, but not in the warning section.
QUESTIONS BY MR. SUGGS:
Q In this new labeling -- by the way, was it your understanding that this label change occurred at the request of the FDA?
MR. BOISE: Object to the form, beyond the scope.
THE WITNESS: I certainly am not a regulatory expert. My understanding of the process is that FDA responded to our -- originally to our new drug application for Symbyax and asked for additional information, and then through a collaborative process and discussion with our medical and regulatory colleagues, we agreed on new label language.
QUESTIONS BY MR. SUGGS:
Q Well, my question, sir: Was it your understanding or did anyone inform you that this label change was at the specific request of FDA?

Page 139

MR. BOISE: Object to the form, foundation, beyond the scope.
THE WITNESS: My understanding is that the FDA asked for additional information and opened a dialog with our medical and regulatory colleagues in response to our new drug application for Symbyax, which ultimately led to a label change.
QUESTIONS BY MR. SUGGS:
Q Did anyone inform you that the FDA said that a label change was necessary in order to protect the public health?
MR. BOISE: Object to the form, foundation.
THE WITNESS: No, I don't recall anyone communicating that to me.
QUESTIONS BY MR. SUGGS:
Q Okay. When did you first learn that this label change had occurred or was going to occur?
MR. BOISE: Which one?
MR. SUGGS: The October 2007 label change.
Q When were you aware that this was going to occur?
A I don't remember exactly, but I would have learned probably several weeks prior to the label change that a change was likely to occur.
Q Who was it that informed you of that?
A The communication would have come from the Zyprexa

Page 140

marketing director.
Q Which was who at that time?
A Mark Nagy.
Q If I could direct your attention to -- by the way, do you know who this label -- strike that.
Do you know who this letter was supposed to go to?
MR. BOISE: Object to the form, vague.
THE WITNESS: Yes. This letter would have gone to all of our -- what we call targeted physicians or physicians who are in our database to whom we are directly communicating or promoting our products to, both psychiatrists and primary care physicians.
QUESTIONS BY MR. SUGGS:
Q So this would not have gone to all healthcare professionals, only some that Lilly chose, correct?
MR. BOISE: Object to the form.
THE WITNESS: I would have to review the database and probably turn to one of our marketing folks to know exactly, but my understanding was it would have gone as broadly as we were able to for those primary care physicians and psychiatrists who are in our database and to whom we could send it to.

Page 141

QUESTIONS BY MR. SUGGS:
Q If I could direct your attention to the third page of the document.
A Okay.
Q Hyperglycemia section of the new changed label, the last sentence in the first paragraph states, quote, 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.
Do you see that language there?
A Yes.
Q Sir, that statement is inconsistent with Lilly's prior positions, correct?
MR. BOISE: Object to the form of the question, foundation.
THE WITNESS: No, that statement is not inconsistent with our prior positions.
QUESTIONS BY MR. SUGGS:
Q In your view that is the same as saying rates are comparable?
MR. BOISE: Object to the form, mischaracterizes testimony.

Page 142

THE WITNESS: No, sir, our comparable rates refers to the rate of diabetes associated with Zyprexa relative to other antipsychotics.

This is referring specifically in our label change to an association between atypical antipsychotics and increasing glucose levels falling on a continuum. And olanzapine appears to have a greater association than some other atypical antipsychotics with that increase in glucose levels.

QUESTIONS BY MR. SUGGS:

Q So you see no inconsistency between the statement in the label that increases in glucose level appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics? You see no contradiction or inconsistency between that and Lilly's comparable rates message, correct?

MR. BOISE: Object to the form of the question, compound, mischaracterizes prior testimony, foundation.

THE WITNESS: No, these are two different statements. The statement in our label change saying that antipsychotic and increases in glucose levels appear to fall on a continuum, and

Page 143

olanzapine appears to have a greater association than some other atypical antipsychotics with these increases in glucose levels is a different statement than Zyprexa has comparable rates of diabetes in our clinical trials relative to other antipsychotic agents.

QUESTIONS BY MR. SUGGS:

Q Sir, do you recall when we looked at the letter from Dr. Breier to healthcare professionals in the summer of 2003, which was Exhibit --

MR. BOISE: Referring to 9201, I think.

MR. SUGGS: Yes.

QUESTIONS BY MR. SUGGS:

Q Exhibit 9201, we saw that in that instance where the letter was saying that the available data do not establish a causal link between diabetes and Zyprexa and that there were -- studies show no consistent or clinically significant differences in the risk of diabetes among the different drugs, that letter was delivered by the sales reps to the physician.

Do you recall that?

MR. BOISE: Object to the form and how you have characterized the letter. You have not read the letter consistent with its language and the

Page 144

question is also compound.

Are you saying do you recall whether this letter was delivered?

QUESTIONS BY MR. SUGGS:

Q Do you recall the evidence that we saw demonstrates that this letter was hand delivered to physicians by the sales reps?

A My recollection is we looked at a document that indicated that it was delivered to the sales representatives.

Q Yeah, okay. Was -- this new label change in October of 2007, was it hand delivered to treating doctors by the sales reps?

A I'm sorry. Could you read back the question, please?

Q Let me restate it.

Were the sales representatives instructed to hand deliver the October 5, 2007, letter announcing the label change?

A Yes.

Q Okay. And were the physicians also directly mailed the label change letter in addition to the hand delivery from sales reps?

A I'm confused now as to which letter we were talking about. Because you had the Alan Breier and we had

Page 145

the dear doctor letter. I want to make sure I'm answering the right questions.

Q Okay. Good point. I want to make sure we are clear about that too.

With respect to the October 5, 2007, letter --

A Yes.

Q -- announcing the new label change --

A Yes.

Q -- were sales reps instructed to hand deliver this letter to treating physicians?

A Yes, sales representatives were instructed to -- the letter was made available to them to deliver to physicians and we also had a direct mailing on this letter to all the clinicians in our database.

Q Okay. Good.

Does Lilly still take the position that the -- that the rates of diabetes between the various antipsychotic drugs are comparable?

MR. BOISE: Object to the form of the question, asked and answered.

THE WITNESS: We no longer have a message that our sales representatives are presenting with regard to comparable rates, but it is, in fact, our position that the clinical data do not show a differential risk of diabetes with Zyprexa relative to the other

antipsychotic agents.
QUESTIONS BY MR. SUGGS:
Q And if a physician asks a sales rep today is there -- strike that.
If a physician were today to ask a sales rep, Are the rates of diabetes higher with Zyprexa than with other antipsychotic drugs, the sales rep would tell him, There is no that evidence to show that; is that correct?
MR. BOISE: Object to the form, incomplete hypothetical.
THE WITNESS: No, the sales representative, under those circumstances, would be instructed to offer the doctor a medical letter from our medical department to answer that question.
QUESTIONS BY MR. SUGGS:
Q Didn't require a medical letter before, did it?
MR. BOISE: Object to the form.
THE WITNESS: We have -- throughout my time working on Zyprexa have met -- have had medical letters available to -- for sales representatives to use to respond to questions about Zyprexa in its relation to weight gain and to diabetes.
QUESTIONS BY MR. SUGGS:
Q I understand that, sir, but we have already seen

before there were some sell sheets, we looked at those brochures, the color documents, where, in fact, the sales reps were provided with materials which they could show and discuss with physicians addressing this issue of whether the rates were comparable or whether there were consistent differences and so forth.
Is it your testimony that sales reps would no longer be permitted to use those brochures?
MR. BOISE: The brochures previously marked as 4 and 5 --
MR. SUGGS: Yes.
MR. BOISE: -- could the sales reps use these brochures today?
MR. SUGGS: Yes.
THE WITNESS: No, sales representatives would not be able to use those brochures today.
QUESTIONS BY MR. SUGGS:
Q And is it your testimony that if a physician asked a sales rep whether the rates of diabetes are comparable between Zyprexa and the other drugs, the sales rep would be instructed to tell the doctor, I cannot discuss that with you, but I will send you a medical letter?
A What the drug sales representatives should do if

they get that question is to indicate to the doctor that they would like to send a medical letter to them, which we think can best answer that question for them.
Q Well, suppose the doctor says, Well, gee, Joe, you know, I remember when you were in my office in 2001 and 2002 and 2003 and you were talking about how there were comparable rates and there were no consistent differences. I want you to tell me right now on the spot, you know, are you saying now that still that Zyprexa has comparable rates of diabetes? What would the sales rep do in that? Would he say, I can't answer and walk out?
MR. BOISE: Objection, incomplete hypothetical, lack of foundation.
THE WITNESS: No, sir, what the doctor would be -- what the sales representative would be instructed to do is to politely indicate to the doctor, Look, I would like to provide you all of the medical information that we have available and the medical letter to answer the question.
QUESTIONS BY MR. SUGGS:
Q Would it be fair to say, then, that the sales reps have now been instructed not to discuss with physicians the issue of whether there are

comparable rates or not and instead are instructed to tell the physician that they will get them a letter from the medical department back in Indianapolis? Is that correct?
MR. BOISE: Object to the form of the question, vague.
THE WITNESS: Our sales representatives are instructed to communicate to the doctors consistent with our current promotional materials. Those materials are developed by our medical and regulatory colleagues in conjunction with our marketing colleagues which represent our current marketing message and represent the current -- current label around Zyprexa both from an efficacy and safety standpoint. That's what their instructions are.
QUESTIONS BY MR. SUGGS:
Q I don't think your question -- your answer is responsive.
Could you please read it back to him?
MR. BOISE: The question and the answer?
MR. SUGGS: No, just my question.
MR. BOISE: Just your question.
(Record read.)
MR. BOISE: He's answered that question.

Page 150

What's the next question?
QUESTIONS BY MR. SUGGS:
Q I don't believe you have answered that, sir.
Are they or are they not instructed not -- strike that.
Have the sales reps been instructed not to discuss the issue of comparable rates with physicians?
MR. BOISE: Object to the form of the question.
QUESTIONS BY MR. SUGGS:
Q Either they have or they haven't?
MR. BOISE: Object to the form of the question.
THE WITNESS: Sir, I answered the question.
We don't communicate to our sales representatives all of the things that they can't communicate to the physicians. I think that would be impractical to do so.
What we do is develop our promotional materials, develop the training tools to indicate to them what they should communicate to customers and how to respond to questions that we would anticipate them getting from doctors.
QUESTIONS BY MR. SUGGS:

Page 151

Q Well, we saw before that one of the questions that they could anticipate getting from doctors was if the doctor had a concern about diabetes, and we saw that the answer that they were supposed to give to address that area of concern was to say that there was no causal relationship and that the rates were comparable.
Have sales reps still received that training or has that changed?
MR. BOISE: Objection, asked and answered.
THE WITNESS: Sir, as I indicated, our marketing message and our sales reps' message evolves over time and that message has changed over time. And we use a number of factors to determine that. One is a medical/regulatory/marketing process to determine how to ensure that our message is consistent with our label as it evolves and also consistent with the regulatory expectations and our good promotional practices.
We also, from a marketing perspective, consistently assess customers' perceptions of the product and how best to position our message and answer their questions to answer their specific concerns.
QUESTIONS BY MR. SUGGS:

Page 152

Q We looked earlier at a document that was a good promotional practice document.
Do you recall that?
A Yes, I recall looking at a portion of good promotional practices as one of the documents.
Q And am I correct that sales reps are supposed to adhere to good promotional practices?
A Yes, that's correct. That's a matter of company policy.
Q Okay. I'm going to hand you -- this is troubling. Can I see that document? Did I hand you two documents before? Just the one.
MR. BOISE: There is something here. Is this it?
MR. SUGGS: That is it, yes.
MR. BOISE: You handed me two documents.
MR. SUGGS: Oh, Barry.
MR. BOISE: David.
MR. SUGGS: What are we up to? Are we up to 8 now?
MR. BOISE: Other than you handed me too many documents.
(Deposition Exhibit 8 marked for identification.)
QUESTIONS BY MR. SUGGS:

Page 153

Q I'm going to hand you what I will have marked here as Exhibit 8, which is a copy of a document entitled "LillyUSA SALES GOOD PROMOTIONAL PRACTICES, UNSOLICITED QUESTIONS ON OFF-LABEL INFORMATION OR UNAPPROVED PRODUCTS."
Do you recognize this document, sir?
A Yes, I do.
Q What is it?
A It is a portion of the company's good promotional practices with an effective date listed here on January 15th, 2004.
Q Okay. This particular portion has to deal with unsolicited questions on off-label information, correct?
A Yes.
Q And it notes -- as part of this document it indicates the scope of this policy, correct?
A Yes.
Q And it says, "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," correct?
A That's correct.
Q And that would include in Alaska, correct?

A Yes, it would.
Q Okay. And then there is a policy statement which says, "It is the policy of Eli Lilly and Company to comply with FDA regulations that prohibit the promotion of any unapproved...product; or indication, dosage form and, slash, or dosing schedule for any marketed product, with any customer by sales and marketing personnel, or other Lilly personnel or representatives in a promotional context."
Was that your understanding of the policy?
A Yes, it is.
Q Although this document is dated as having an effective date of January 15, 2004, was that also the policy of the company before that time?
MR. BOISE: That policy statement?
MR. SUGGS: Yes.
THE WITNESS: I would have to refer to the prior GPP to tell you whether the language is exactly the same or not.
QUESTIONS BY MR. SUGGS:
Q Well, that's not really my question. I realize the language may differ to some extent, but let me phrase the question this way: Prior to January of 2004, you were involved in the marketing and sales of Zyprexa, correct?

A Yes, I was. Although, as we talked about before, between 2001 and 2003 I was not responsible for U.S. promotion of Zyprexa.
Q But, in any event, throughout the time you were involved with Zyprexa, was it the policy of Eli Lilly and Company to comply with FDA regulations that prohibit the promotion of any unapproved new product or indication?
A Yes, it was.
Q Okay. And if I could direct your attention down to the Definitions section.
There is a definition of Off-label Information there.
Do you see that?
A Yes.
Q And the definition of Off-label Information is, quote, Any information about a Lilly product that is not contained in or is not consistent with the package insert labeling approved by the FDA. Examples include, but are not limited to, indications, dosage forms, dosing schedules, combination therapy, and safety information.
Do you see that language, sir?
A Yes, I do.
Q And that would have been a correct definition of

off-label information regardless of whether it was the year 2000, the year 1996, the year 2003, or 2007, correct?
MR. BOISE: Object to the form, foundation, beyond the scope.
THE WITNESS: Yes. Well, I would want to consult the specific language, which could have changed slightly. The concept of what constitutes off-label information would have been consistent.
QUESTIONS BY MR. SUGGS:
Q There's no big changes there.
And then there is a description of the procedure and it says what a sales personal -- sales personnel may do and what they may not do, correct?
A Yes.
Q And it says, "Sales Personnel MAY NOT:," quote, "Proactively discuss, present, or promote information concerning unapproved new products or off-label information about approved products with any customer or health care professional."
Did I read that correctly?
A Yes.
Q And, sir, that was -- sales personnel were prohibited to do that in 2000 and in 2001 and

throughout the times Zyprexa has been on the market, correct?
A Yes, that is correct.
Q Okay. And then below that it says, "However, Sales Personnel MAY: Respond orally to unsolicited requests for pre-approval or off-label product information, but only if all of the conditions below are strictly observed," and then there are listed one, two, three, four, five, six, seven, eight, nine, ten different conditions, all of which must apply before there can be such a discussion, correct?
A Yes, that was a direct -- specific direction in this time frame.
Q Okay. In fact, those same types of limitations were applicable prior to January 2004; isn't that correct?
A Again, we would have to look at the specific good promotional practice to understand exactly what the direction was for sales representatives and how to respond to unsolicited questions.
Q Well, do you have an understand -- I realize you don't have the GPP for the prior period in time right in front of you; but do you believe that the GPP on this issue before January 2004 was more lax

in terms of what it permitted the sales reps to do?
MR. BOISE: Object to the form, vague.
THE WITNESS: No, sir, I do not believe that at any time we would have been, as you described it, lax; however, the specific language and exactly the steps potentially have evolved slightly or changed in response to the regulatory requirements.
QUESTIONS BY MR. SUGGS:
Q Was it your understanding that the restrictions on what sales personnel were allowed to say, permissibly under Lilly policy regarding off-label use, was essentially the same before 2004?
A My understanding is that our promotional efforts were required to be consistent with the good promotional practices, which I understand are developed primarily by our legal and regulatory colleagues, to ensure that our company policies are consistent with the applicable laws and regulations.
Q It's your understanding, as the person who's in charge of marketing and sales for some periods of time before 2004, that the restrictions against dissemination of off-label information were essentially the same as this --
MR. BOISE: Dave --
QUESTIONS BY MR. SUGGS:

Q -- before 2004, weren't they?
MR. BOISE: He's answered the question. Objection, asked and answered.
QUESTIONS BY MR. SUGGS:
Q Can you answer?
A Question was awfully broad. I'm not sure I can answer it any more effectively than I have.
Q Let me just ask this question -- maybe I've phrased it similarly to this, but I want to ask the question this way: Is it your belief that the restrictions on dissemination of off-label information by Lilly personnel before January of 2004 were more lax, more strict, or about the same as reflected in this policy statement?
MR. BOISE: Object to the form of the question, foundation, asked and answered.
THE WITNESS: I don't think I can characterize an answer in that context. What I can tell you is that our good promotional practice we endeavor to be consistent with the laws and regulations at the given time frame with the same vigilance throughout that period to do so.
QUESTIONS BY MR. SUGGS:
Q Okay. And, sir, am I correct if a sales rep gave safety information that was not contained in or was

not consistent with the package insert approved by FDA, that would be off-label information?
MR. BOISE: As defined in this policy?
MR. SUGGS: Yes.
THE WITNESS: Could you read that question back to me, please?
QUESTIONS BY MR. SUGGS:
Q I can restate it.
If, for example, a sales rep gave safety information that was not contained in or was not consistent with the package insert approved by FDA, that would be off-label information, correct?
MR. BOISE: By this policy?
MR. SUGGS: Yes.
THE WITNESS: Again, I'm not an expert on on-label versus off-label. I would always consult with my regulatory colleagues to that, but generally anything -- my understanding of on-label is anything that's not in the package insert labeling would be off-label.
QUESTIONS BY MR. SUGGS:
Q Well, for example, here in the Definitions it says, Any -- off-label information is: "Any information about a Lilly product that is not contained in or is not consistent with a package insert labeling approved

by FDA. Examples include, but are not limited to, indications, dosage forms, dosing schedules, combination therapy, and safety information," correct? That's the definition?
A Yes.
Q Okay. And so if, in fact, a sales rep gave safety information, which is one of the examples here, that was not contained in or was not consistent with the package insert labeling approved by the FDA, that would, by definition, be off-label information, correct?
A Yes, that's correct.
MR. BOISE: Object to the form.
QUESTIONS BY MR. SUGGS:
Q Okay. And similarly this document refers to the indications of the package insert, correct?
A Yes.
Q And the medical dictionary definition of an indication is something that points to or suggests the proper treatment of a disease.
Would you accept that term -- that definition of the term "indication"?
MR. BOISE: Could you source it for us?
MR. SUGGS: Pardon?
MR. BOISE: Did you give us a source? You

targets. Key decisions included: Launch will occur in October 2000, promotion will be handled via the Primary Care, dash, Neuroscience sales sleeve, and funding in 2000 would be incremental to existing brand opex.

Do you see that language, sir?

A I must not be reading from the same portion of the document where you are.

Q Under the first paragraph under the Background section.

A Okay. Sorry.

Q And what were your responsibilities with respect to Zyprexa in October of 2000, sir?

A In October of 2000 I was a neuroscience sales director for the Midwest area responsible for our promotion to psychiatrists.

Q And what area did you cover at that time? What was the Midwest area?

A I don't know that I'll be able to recall all of the states. I was Indianapolis based. I had Illinois, Wisconsin, Tennessee, Minnesota, Kentucky, Ohio. That may be all of the states. I would have to go back and look specifically whether I covered all the geography that I was responsible for.

Q Okay. And if I could direct your attention to the

Challenges section.

A Yes.

Q Midway down on the first page it states, "Most PCPs" -- that refers to primary care physicians, correct?

A Yes.

Q "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 PCP's 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."

Do you see that language, sir?

A Yes, I do.

Q When it says Zyprexa's primary indication was schizophrenia and bipolar, at that time in 2000 those were indeed the only indications for Zyprexa; isn't that correct?

A Yes, that's correct.

Q And then in the paragraph below that it states,

Position: Zyprexa: The safe, proven solution in mood, thought, and behavioral disorders.

Do you see that?

A Yes, I do.

Q And then about the middle of the page -- pardon me, middle of the paragraph it refers to "Mental disorders."

Do you see that in quotes?

A Yes, I do.

Q "'Mental disorders' is intentionally broad and vague, providing latitude to frame the discussion around symptoms and behaviors rather than specific indications."

Do you see that language, sir?

A Yes, sir, I do.

Q And, in fact, as you previously testified, Zyprexa was not indicated for mood, thought, and behavior disorders, correct?

MR. BOISE: Object to the form, mischaracterizes testimony.

THE WITNESS: Zyprexa is indicated at this time frame for schizophrenia and Bipolar I disorder.

QUESTIONS BY MR. SUGGS:

Q But Lilly reps at this time -- after this time

promoted Zyprexa for the treatment of symptoms and behaviors rather than specific indications; is that correct?

MR. BOISE: Object to the form, foundation.

THE WITNESS: No, sir. That is not correct.

QUESTIONS BY MR. SUGGS:

Q Well, let's look at what's been previously marked as between 1926, which for the record bears the date June 2002 at the top of the first page.

And I will represent to you, sir, that the database provided to us by Lilly indicates that this document was actually generated on May 1, 2002, and Lilly has represented to us in answers to interrogatories that this document was in the knowledge management database.

And, sir, do you have any information to dispute those representations?

A No, sir, I have no reason to dispute the date that you provided me.

Q Okay. If I could direct your attention to page 3. In the right-hand column about the middle of the page is bold heading ZYPREXA in Primary Care, and the beginning part of that paragraph states, quote, ZYPREXA was originally launched to the primary care audience by the Sigma sales force in November of

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

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.

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

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?

A Yes, sir, that's correct.
Q And one of the patient profiles was of a character that they transcribed as or named Donna, correct?
A This is going back a long way and the names don't have a particular resonance with me. I would have to look at the profile to regain familiarity with it.
Q If you look at page 7 --
A Okay.
Q -- there is a description there, Patient Profile #1: Donna, correct?
A Yes.
Q And she is described as a single mom in her mid-30s, presents in drab clothing and seems ill at ease.
That's what the brochure says, correct?
MR. BOISE: Object to the form. That's part of what it says.
QUESTIONS BY MR. SUGGS:
Q Do you see the brochure there under the name "Donna"?
A Yes.
Q It says, quote, single mom in her mid-30s presents in drab clothing and seems ill at ease. Below that there is a quote, apparently from the fictional

character Donna, I feel so anxious and irritable lately, end quote.
A Yes, I see that.
Q And below that for the history it says, Reports she has been seeing -- pardon me, sleeping more than usual, has trouble concentrating at work and at home.
Now, sir, Zyprexa was approved, as we have talked about before, for the acute manic phase of Bipolar I disorder, correct?
A Yes, sir.
Q And --
MR. BOISE: In this time frame?
MR. SUGGS: In this time frame.
THE WITNESS: In this time frame, yes.
QUESTIONS BY MR. SUGGS:
Q And, sir, patients who are in the acute manic phase of Bipolar I disorder don't usually report having been sleeping more than usual, do they, sir?
MR. BOISE: Object to the form of the question, beyond the scope, foundation.
THE WITNESS: Sir, you are asking me to make a medical assessment that I would defer to a medical colleague to make.
QUESTIONS BY MR. SUGGS:

Q Well, sir, just as a matter of common sense and as someone who has been in the pharmaceutical industry for, lo, these many years and had responsibility for the marketing of Zyprexa, was it your understanding that acute manic phase patients with Bipolar I disorder have trouble sleeping more than usual?
MR. BOISE: Object to the form of the question.
THE WITNESS: Again, I'm not a clinical expert and would defer to my medical colleagues; but in my experience it would not at all be unusual for a patient in acute manic phase to have difficulty sleeping.
QUESTIONS BY MR. SUGGS:
Q Sir, the difficulty that she describes here in this fictional report is that she has been reporting that she has been sleeping more than usual.
People in the manic phase of Bipolar Disorder I, they hardly sleep at all; isn't that right?
MR. BOISE: Object to the form of the question.
THE WITNESS: Again, you are asking me to make a clinical assessment, but in my experience bipolar disorder is very complex and by definition has --

includes depressive elements and manic elements of the disorder.
QUESTIONS BY MR. SUGGS:
Q Aren't manic patients the patients that are usually bouncing off the walls?
MR. BOISE: Object to the form of the question, beyond the scope.
QUESTIONS BY MR. SUGGS:
Q You don't find them sleeping all day; they are the ones that are bouncing off the walls; isn't that true?
MR. BOISE: Object to the form of question.
THE WITNESS: You are asking me to make a characterization that I would defer to a clinician to make about a patient.
QUESTIONS BY MR. SUGGS:
Q I'm going to show you what's been previously marked as Plaintiff's Exhibit No. 1939.
I'll represent to you, sir, that this document -- strike that.
I'll represent to you, sir, that the database that was provided to us indicates that this document was dated June 11, 2002, and that Lilly has represented to us in the answers to interrogatories in the Alaska litigation that it

was in the knowledge management database.
Do you have any basis to dispute that, sir?
A I can't tell from the document whether it would have been in knowledge management or not.
Q Well, if that's what was represented to us in answers to interrogatories that it was in the knowledge management database, would you dispute that?
A No, sir.
Q Okay. If I could direct your attention to the top of the page. They reference ZYPREXA PCP Patient Types, correct?
A Yes.
Q And it says, "Below are detailed descriptions of our current patients within the detail piece."
And there is a reference to Donna, correct?
A Yes.
Q And as to Donna it says, "Donna, paren, bipolar disorder, current episode mixed, exhibits the 4 core symptoms of mood swings, irritability, sleep disturbances and anxiety, as well as other symptoms including a lack of concentration, mood liability and increased energy, depressed mood, loss of interest, and agitation."
Do you see that language, sir?

A Yes.
Q And they draw a distinction between Donna and another fictional patient type Mark --
A Yes.
Q -- down below, correct?
Mark is described as having bipolar disorder, current episode manic, correct?
A Yes.
Q And as we have talked about before, Zyprexa was indicated in 2002 for the acute manic phase of Bipolar I disorder, which would appear to be Mark, right?
MR. BOISE: Object to the form, compound.
THE WITNESS: Sir, as I look at this document, if you put it in context with the first statement which talks about an acute mania indication including patients with manic or mixed episodes were part of the clinical trials, I think that's referring to those two subtypes of patients for the acute mania.
QUESTIONS BY MR. SUGGS:
Q Sir, the description of Mark is current episode manic, correct?
A Yes.
Q And Donna is not listed as being in the acute manic

phase of Bipolar I disorder, correct?
A Donna is listed at bipolar disorder, current episode mixed; but, again, as a subset, if you look at the entire document of an acute mania indication reflecting mixed episode patients, who were part of that clinical trial.
Q I'm going to show you another document, sir. I'm going to hand you what's been previously marked as Plaintiff's Exhibit 1949. And I'm not sure if you are going to be able to help me with this or not, but the database that was provided to us indicates that this was dated July 8th, 2002, and Lilly has represented to us in answers to interrogatories that it was in the knowledge management database.
Do you have any basis to dispute those representations?
A I don't think I'll ever be able to dispute that anything was in knowledge management, unless it says on there "was not in knowledge management."
Q Well, you know, we ask the questions in interrogatories, Mr. Boise and the other lawyers come back and tell us answers and we have to rely on something so that's what we are relying on.
This appears to be a PowerPoint presentation.
Do you agree with me?

A Yes, perhaps it's PowerPoint.
Q Okay. It refers to -- it's entitled "PCP Discussion Guide."
Do you know what sales reps would use this for or how they would use it?
MR. BOISE: Object to the form.
THE WITNESS: I'm going to have to take a look at this for a minute in order to answer your question.
QUESTIONS BY MR. SUGGS:
Q Okay.
A I'm not able to tell from the Discussion Guide itself whther this was for use for sales representatives or what the specific purpose was.
Q I notice that this document on the first page there, in the lower left-hand side, has a number OL 24615.
Does that help at all in terms of indicating what this document's use was?
A No. I would have to go back and talk to somebody who developed the document, what the specific purpose was.
Q Okay. I'm going to hand you what's been previously marked as Plaintiff's Exhibit 1961 and represent to you, sir, that this -- the database that was

Page 182

provided to us indicates that it was dated September 4, 2002, and that Lilly has represented to us in answers to interrogatories that it was in the knowledge management database.
Again, do you have any basis to dispute that?
A No.
MR. BOISE: David, what was the date that you gave?
MR. SUGGS: September 4, 2002.
MR. BOISE: Thank you.
MR. SUGGS: Sure.
QUESTIONS BY MR. SUGGS:
Q And if I could direct your attention to the first page. It states, The four most common -- well, it says, "4 Most Common AOC Verbatim:" -- we have talked previously that AOC stands for area of concern, correct?
A Yes, that's correct.
Q And is "verbatim" a term of art in the Lilly company?
A I'm not sure I understand what "term of art" means.
Q Well, I know the dictionary definition of the word "verbatim," but I'm not sure that means the same thing in the context of selling Zyprexa.
What did you understand the term "verbatim" to

Page 183

mean in Lilly?
MR. BOISE: In this context?
MR. SUGGS: Yes.
THE WITNESS: In this context, it appears that what the document is describing is four potential things that a healthcare provider might raise as an area of concern to a sales representative.
QUESTIONS BY MR. SUGGS:
Q And is that what a verbatim is, an area of concern?
A No. I would probably have the same verbatim dictionary description you have. I don't know that verbatim is necessarily a good characterization of this. I'm trying to interpret the document.
Q Okay. Well, listed under the 4 Most Common Area of Concern Verbatim heading are four things.
No. 1 is Zyprexa causes diabetes; second, Zyprexa causes weight gain; third, I refer that patient; and fourth, you are not indicated for that patient.
And if we turn the page, the heading there is "Diabetes AOC Verbatim."
A Yes.
Q Below that it says, "The competition will attempt to make this an issue, What do you need to convey to your customers?" And then the answer is you

Page 184

should convey "The 4 C's," correct?
A Yes, that's what the document says.
Q The 4 C's being that diabetes is common, Lilly cares, there are comparable rates of treatment-emergent diabetes across agents, and say it with confidence.
Those were the 4 C's, correct?
A That was your summary of the 4 C's.
Q Is that a good summary of the 4 C's?
A I would defer to the document and I can read it to you if you would like.
Q Well, we'll have this up on the screen and the jury can see it. They have -- the 4 C's that they have bolded there are: COMMON, CARES, COMPARABLE and CONFIDENCE, correct?
A Yes.
Q And then if we turn the page, then there's the Weight AOC Verbatim, and then they suggest there what the sales rep should say if there is a concern about weight, correct?
A Yes.
Q And they say, "Therefore on every call, either in safety section of patient profile or the overall safety spread, say:, quote, Doctor, there is a potential for increased appetite, but it may be

Page 185

manageable with simple behavioral changes - unlike Depakote and Lithium where you have to consider blood monitoring and black box warnings."
Did I read that quote correctly?
A Yes, you did.
Q Is it fair to say that those sales reps were expected to say that if the doctors raised a concern about weight, correct?
MR. BOISE: Object to the form of the question, vague, time frame.
THE WITNESS: In this time frame for these sales representatives, that is in fact the verbatim that is being recommended to them, yes.
QUESTIONS BY MR. SUGGS:
Q And finally on the next page, the area of concern was, quote, You're not indicated AOC Verbatim?
A Yes.
Q And this was -- would be a situation where the doctor would say, But you are not indicated for -- for treating this type of patient, correct?
A Yes.
Q And the doctor -- pardon me, the sales rep was instructed to say, 1, Donna is presenting with symptoms of mood swings, irritability and anxiety and disrupted sleep. What I am suggesting is that

Page 186

Donna may have bipolar disorder because these symptoms may be related to mania instead of depression.

Do you see that language, sir?

A Yes, I do.

MR. BOISE: Your question was do you see that language?

MR. SUGGS: Yes. He said he did.

Q Then it goes on to say, "Zyprexa is indicated for the treatment of acute bipolar mania in patients who display an acute manic or mixed episode."

Do you see that language, sir?

A Yes.

Q And that's what the sales reps were instructed to tell the doctor, correct?

MR. BOISE: Object to the form of the question.

THE WITNESS: Yes, in this time frame these representatives were instructed to tell the doctor that.

QUESTIONS BY MR. SUGGS:

Q Okay. And below that it says, "The MDQ is one tool that may be used to help screen for bipolar disorder in patients like Donna."

And that was a diagnostic tool that was

Page 187

developed by Lilly, correct?

MR. BOISE: Object to the form of the question, foundation, compound.

THE WITNESS: This is a diagnostic tool. I don't believe it's a Lilly developed tool, but I would have to confirm that with my medical colleagues.

QUESTIONS BY MR. SUGGS:

Q Okay. I'm going to direct your attention --

MR. BOISE: Do you want to take five minutes?

THE WITNESS: Yes, short rest room --

THE VIDEOGRAPHER: Mark the end of Tape No. 3. We are off the record at 2:22.

(Recess.)

THE VIDEOGRAPHER: We are back on the record. This is the beginning of Tape No. 4 of the deposition of David Noesges. We are on the record at 2:35.

QUESTIONS BY MR. SUGGS:

Q Mr. Noesges, I'm going to hand you what's been previously marked as Plaintiff's Exhibit 1962.

And for the record I'll represent that the database provided to us by Lilly indicates that this document was dated September 4, 2002, and further that Lilly's represented to us in answers

Page 188

to interrogatories that it was in the knowledge management database.

And, I would assume, sir, based on your prior testimony that you don't have any basis to dispute those representations; is that correct?

A That's correct.

Q Okay. The title on the first page is "Hyperglycemia, slash, Diabetes: Sell Sheet Implementation" and as we discussed previously a sell sheet is a brochure that can be discussed with and shown to a physician, correct?

A This is a promotional material that can be used promotionally by sales representatives with physicians.

Q Okay. This one on the second page -- or this document indicates on the second page, "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!"

Did I read that correctly?

A Yes.

Q And the AOC that is being referred to is the diabetes area of concern, correct?

Page 189

A Yes.

Q On the following page there is directions for handling the diabetes AOC, correct?

A Yes.

Q Below the heading states, "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."

Do you see that language, sir?

A Yes, I do.

Q And that was indeed the policy of Lilly at that time in 2002, was it not?

MR. BOISE: Object to the form of the question.

THE WITNESS: That was the instructions that were being provided to sales representatives through this particular sell sheet implementation guide.

QUESTIONS BY MR. SUGGS:

Q And then it goes on to say, "If it does" -- in other words if it does arise from the doctor, this issue or concern about handling -- strike that.

This document notes that if the doctor does express a concern about diabetes, then the sales rep was to do five things, correct?

Page 190

A Yes.
Q No. 1 was cushion and clarify the AOC; No. 2 was handle by providing the verbatim, correct?
A Yes.
Q We talked about what those verbatims were, correct?
MR. BOISE: Object to the form, vague. What this specific verbatim was at this time period or what a verbatim is?
QUESTIONS BY MR. SUGGS:
Q The prior document that we looked at also had the same date of September 4, 2002, and it lists -- it had the verbatims in it, correct?
A We would have to look at the sell sheet this is referring to, to know exactly what the verbatims were that this document is referring to.
Q But at least we can see with this -- these two documents the representations to us by Lilly are, they are both dated the same day, September 4, 2004; they both appear to be -- have similar appearance in terms of the headings on each page, correct?
A Yes.
Q Those little circles that are there and the style and the font and everything else.
And the first document that we looked at, 1961, has verbatims for the four most common areas of

Page 191

concern, correct?
A Yes.
Q And in Exhibit 1962 on the page 3, that we were looking at, the second thing that the sales rep was to do, if the doctor expressed a concern, was to handle by providing the verbatim, correct?
A Yes.
Q And the third point was -- the sales rep was to do was to check for agreement and if there was no agreement then the sales rep should utilize the sell sheet.
And the sell sheet would be the brochure -- would be a brochure that the sales rep would discuss and present to the physician, correct?
A Yes, that is correct.
Q Okay. And then it says Point 4 was to restate the verbatim by utilizing the diabetes sell sheet; 5, check for agreement and get back to Donna, correct? That's what it says?
A Yes.
Q Donna was the fictional patient that we talked about before, correct?
A Donna was in the patient profile that we discussed before.
Q Okay. And then if you turn to the following page

Page 192

the heading is "What are the facts to convey and where do you find them within the sell sheet?"
And then they are laid out there, three different points that are in the sell sheet, correct?
A Yes, that's correct.
Q And the first point it's emphasized that patients with mental illness are two to four times more likely to develop diabetes, correct?
A That statement is bolded in the first step -- first item.
Q The second item it notes, "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)," correct?
A Correct.
Q And the third thing was: "When you look at various agents to treat patients with mental illness, the rate of treatment-emergent diabetes is comparable across agents," correct?
MR. BOISE: You are asking that's what the statement says?
QUESTIONS BY MR. SUGGS:
Q That's what the statement says.

Page 193

A Yes, that's what the statement says.
Q This is another iteration or example of the comparable rates message back in the 2002 time period, correct?
MR. BOISE: Object to the form, vague.
THE WITNESS: This is a third point in this guideline for a sell sheet which says, "When you look at various agents to treat patients with mental illness, the rate of treatment-emergent diabetes is comparable across agents."
QUESTIONS BY MR. SUGGS:
Q Okay. I would like to show you another section of the Lilly Good Promotional Practice guidelines and we'll mark this as Exhibit 9.
(Deposition Exhibit 9 marked for identification.)
QUESTIONS BY MR. SUGGS:
Q And for the record the title of this Good Promotional Practice says, quote, Definition of a Sales Call and Call Notes.
And you are familiar with call notes, are you not, sir?
A Yes, sir, I am.
Q It indicates that the scope of this promotional practice is to apply to "all sales personnel and

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?

Page 198

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.

Page 199

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.

Page 200

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

Page 201

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?

Page 202

MR. BOISE: I believe so, yeah.
QUESTIONS BY MR. SUGGS:
Q Margaret Williams had three of the call notes on this page, and we have been -- it's been represented to us that Ms. Williams is apparently deceased. And then there's also reference to a Thea Jung down at the bottom.
Do you know if she is still a sales rep?
A I don't know.
Q If I could direct your attention to the bottom call note by Thea Jung. In the text of the Action -- or I guess it's actually the text of the Reaction section it states, "Did full Z detail with/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.'"
Do you see that, sir?
A Yes, sir, I do.
Q And, sir, that indicates that, in fact, this doctor, after hearing the presentation by the Lilly sales rep, thought Zyprexa was for something other than bipolar or schizophrenia, correct?

Page 203

MR. BOISE: Object to the form of the question.
THE WITNESS: No, sir, it doesn't indicate that to me at all. Again, it's difficult. These are shorthand notes; but if you are asking me to interpret this, the rep seems to be reflecting that the doctor was excited to hear that it could be applicable for her practice for what she described -- or he or she described as complicated mood disorder. It does not refer at all to the sales representative having suggested that.
QUESTIONS BY MR. SUGGS:
Q Well, it says, "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, quote, complicated mood, end quote," correct?
A Yes, that's what the document says.
Q It goes on to say, "Said she's looking forward to trying it." In the Follow-Up section it says, "Dr. T doesn't quite seem clear on the patient 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" all "the anti-depressants (he used Paxil as his example). I

Page 204

gave him the Donna patient type and tried to explain it's not in either."
Did I read that correctly?
A Yes, you read that correctly.
Q I would like to show you another call note or collection of call notes, which we'll mark as soon as -- I forgot to put a sticker on that.
(Deposition Exhibit 11 marked for identification.)
QUESTIONS BY MR. SUGGS:
Q I'm handing you what we have marked as Exhibit 11. This is another collection of --
MR. BOISE: Did you hand me one, David?
MR. SUGGS: I'm sorry.
MR. BOISE: That's okay.
QUESTIONS BY MR. SUGGS:
Q -- of call notes.
This is another collection of call notes from those that were produced to us in the Alaska litigation. I would like to draw your attention to --
MR. BOISE: What you have handed me was a package of 13 pages.
MR. SUGGS: I have not counted the pages, yes, 13 pages.

Page 205

Q I would like to direct your attention to the first call note on the first page, which appears to be call notes of Margaret Williams, regarding her meeting with Dr. Kendrick Blais, Fairbanks, Alaska, and the notes say, quote, Doc initially said any pats 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 patients and how ZYP reduces hostility, agitation, improves cognition. Then went over ZYP in bipolar mania.
Do you see that language, sir?
A Yes, sir, I do.
Q That indicates that this doctor was under the impression that this category of elderly patients with hostility and agitation was different than the schizophrenics and different than bipolar mania, correct?
MR. BOISE: Object to the form of the question.
THE WITNESS: Again, these are shorthand notes. It's difficult to tell what was noted here, but the rep seems to be indicating that the doctor describing just, as in here, some impressions

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.

Page 210

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

Page 211

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.

Page 212

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

Page 213

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

Page 214

medical colleagues to help me interpret this, but it is certainly my understanding of mood disorders, that bipolar disorder would be a complicated mood disorder.

And, as I've both interacted with Lilly physicians and with a large number of clinicians, there seems to be a common agreement that bipolar disorder would be a complex -- or complicated mood disorder.

Q Is there any question in your mind that the reference to complicated mood disorder in this document refers to bipolar disorder?

MR. SUGGS: Objection.

THE WITNESS: That's clearly how I would interpret the document. Just by reading a little bit further it says, "ZYPREXA will continue to revolutionize the way complicated mood disorders are treated by primary care physicians."

And then the following statement is, "Just as Prozac revolutionized the treatment of depression in the late 80s and throughout the 90s, so too will ZYPREXA forever change the way primary care physicians view and treat bipolar disorder."

The connection there seems pretty clear to me.

Q Direct your attention to what's been previously

Page 215

marked as Plaintiffs' 1961.

A This other document?

Q It's the other document. In particular, I'm referring to page 4 of that document.

Can you read for the jury what Item 4 says on this page?

A Yes. Item 4 says, "The MDQ is one tool that may be used to help screen for bipolar disorder in patients like Donna."

Q Do you know what a screening tool is?

A Yes, I do.

Q Is it something different than a diagnostic tool?

A Again, it's -- I would rely on my medical colleagues in terms of an expert interpretation, but my understanding is a screening tool is a tool to aid in diagnosis but cannot make a diagnosis in and of itself.

Q So it's your understanding that MDQ is not a diagnostic tool?

A Yes, that's correct.

I think I may have previously described it as a diagnostic tool. If that's the case, then I misspoke. At least in my understanding, it would just be used by a clinician to help screen for -- in this case, for bipolar disorder, but they

Page 216

couldn't make a diagnosis from it.

Q If there was any questions about what Zyprexa is indicated for expressed by a physician, does this page also refer to what a sales rep was to say in this time frame, directing to Item 3?

A Yes, in this time frame, you know, the front page talks about four potential common areas of concern a physician would have. In this one would be, Physician being concerned that you are not indicated.

And then I think what this verbatim is designed to do is to help the rep clarify that, in fact, we are talking about Donna who has a complex set of symptoms, but then goes on to say that Doctor, just to be clear, "What I am suggesting is that Donna may have bipolar disorder because these symptoms may be related to mania instead of depression."

And then in the third bullet point, just to be as clear as we can, reinforces that "Zyprexa is indicated for the treatment of the acute bipolar mania in patients who display an acute manic or mixed episode."

MR. BOISE: Thank you. Those are my questions.

Page 217

MR. SUGGS: Let me take a look at one thing. I have no further questions.

MR. BOISE: Okay. Thank you.

THE VIDEOGRAPHER: Marks the end of the deposition of Dave Noesges, Tape 4 of 4. We are off the record at 3:16.

AND FURTHER DEPONENT SAITH NOT.

_____

DAVID THOMAS NOESGES

STATE OF INDIANA
COUNTY OF HAMILTON

I, Carolyn L. Smith, a Notary Public in and for said county and state, do hereby certify that the deponent herein was by me first duly sworn to tell the truth, the whole truth, and nothing but the truth in the aforementioned matter;

That the foregoing deposition was taken on behalf of the Plaintiff; that said deposition was taken at the time and place heretofore mentioned between 9:31 a.m. and 4:16 p.m.;

That said deposition was taken down in stenograph notes and afterwards reduced to typewriting under my direction; and that the typewritten transcript is a true record of the testimony given by said deponent;

And thereafter presented to said witness for signature; that this certificate does not purport to acknowledge or verify the signature hereto of the deponent.

I do further certify that I am a disinterested person in this cause of action; that I am not a relative of the attorneys for any of the parties.

IN WITNESS WHEREOF, I have hereunto set my hand

and affixed my notarial seal this ________ day of
______________, 2008.

____
Carolyn L. Smith, Notary Public

My commission expires:
July 1, 2015

Job No. 40357

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PAGE LINE CHANGE

HYPERGLYCEMIA/DIABETES DATA ON DEMAND RESOURCE GUIDE

Table of Contents

Situation Overview

The competition has been trying to convince our customers that ZYPREXA is not appropriate for many patients because of weight gain and the risk of hyperglycemia and diabetes. For our Lilly counterparts in the Retail Psych market, hyperglycemia/diabetes has become a major obstacle. In October 2000, 60% of psychiatrists surveyed in market research stated that they believed there was a link between ZYPREXA and hyperglycemia/diabetes. In April 2001, that number increased to 100% of psychiatrists surveyed. You can see that in a short period of time, perceptions can change dramatically.

With the launch of Risperdal into primary care, it is expected that these issues will be a key focus in their message. In addition, at the APA this past April, Pfizer and Janssen both sponsored programs to promote the idea that ZYPREXA causes diabetes and weight gain—despite the fact that there is no credible body of data that establishes causality between ZYPREXA and hyperglycemia or diabetes.

By knowing the facts, you can more effectively and efficiently handle any objections raised by physicians BEFORE it becomes an issue. **Four Key Message points in bold:**

- Patients treated with ZYPREXA, risperidone, haloperidol, divalproex, and ziprasidone in clinical trails had **comparable rates** of diabetes and hyperglycemia, even when the data was analyzed in 3 different ways.
- Although weight gain is one of the risk factors associated with diabetes, it is **there is no direct 1:1 correlation**. Weight gain can happen independently of diabetes, and diabetes can happen independently of weight gain.
- Pfizer's own study demonstrated comparable rates of hyperglycemia with ZYPREXA and ziprasidone (a supposedly "weight neutral" product).
- **Diabetes is common in the general adult population and is even more common in** psychiatric patients. Individuals with schizophrenia and bipolar disorder may have upward of a 2-to 4-fold increase in risk.

- **A number of factors affect a person's risk for diabetes**, including those that are intrinsic (such as family history/genetics) and those that are physical (such as weight gain).

- Psychotropic therapy in any individual patient should be evaluated in the context of that patient's overall response and toleration of therapy—the "risks/benefits" equation.

Strategy

First and foremost, striking the right tone with customers is essential. Many customers have stated they are tired of representatives who either "bash the competition" or who deny or minimize the doctors' concerns. We must be proactive with the weight gain issue and only use the diabetes sell sheet when responding to a concern from a physician.

Our goal is to continue to drive new patient starts on ZYPREXA, keep patients on therapy longer, and ensure the appropriate dose is utilized. In order to maximize this effort, we must neutralize the hyperglycemia/diabetes issue, help physicians manage weight gain, and continue to sell the unparalleled efficacy and dependability of Zyprexa.

By neutralizing we mean leveling the playing field, setting the record straight with a "comparable rates" message, and convincing physicians that ZYPREXA has the best safety and efficacy profile of any atypical antipsychotic. In order to do so, we must:

- Explain to doctors that **diabetes is a disease which Lilly takes very seriously. We have been a pioneer in this field for the last 50+ years and have studied the issue of hyperglycemia/diabetes extensively.**

- Admit up front that all antipsychotic medications can increase blood glucose levels.

- Admit that ZYPREXA can cause weight gain, but that does NOT mean it will cause diabetes. There is no 1:1 relationship between weight gain and diabetes.

- Explain that patients with severe mental illness are at higher risk for developing diabetes than the general population.

- Be patient focused.

Explanation of Diabetes Sell Sheet (OL 21620)

Message Point #1

On the first page, the top graph is a comparison of the incidence of treatment-emergent diabetes in longer head-to-head trials. The physician will have data that compares ZYPREXA with other antipsychotics as well as a mood stabilizer. **Summary: All agents had comparable rates in treatment emergent diabetes and hyperglycemia.**

The second graph measuring baseline-to-endpoint changes in blood glucose presents information from a bulleted point in a previous sales aid, with the addition of the Pfizer study. This data

demonstrates that all agents except clozapine had mean blood glucose values within the normal range. The Pfizer study was added for 2 reasons: (1) to show a comparison vs ziprasidone (a supposedly "weight neutral" product, yet comparable rates of hyperglycemia were still found), and (2) to show that whether fasting (Pfizer) or random (Lilly) blood sugars were taken, the results were the same. **Summary: All agents (except clozapine) showed similar changes in Random Glucose Levels, and ZYPREXA vs. ziprasidone showed similar changes in Fasting Glucose Levels.**

The third graph measuring an individual patient's likelihood of experiencing random glucose elevations was also derived from a bulleted point in the previous diabetes piece. This information graphically illustrates the thresholds that were used to determine normal plasma glucose, elevated plasma glucose, and diabetes. **Summary: Individuals taking ZYPREXA were no more likely to experience glucose elevations than patients on haloperidol or risperidone, despite their initial glucose level. Therefore, a patient with a high blood glucose level at baseline was no more likely to show an increase than a patient who had a low glucose level at baseline.**

Message Point #2

Many physicians think there is a logical link between weight gain and diabetes. In market research we see that many of them even use these two words interchangeably. We believe it is essential to weaken this link in order to neutralize the diabetes/hyperglycemia issue.

The pie chart on the left demonstrates that patients who had an episode of hyperglycemia did not experience substantial weight gain. The right side looks at the patients who did see substantial weight gain and skows that an overwhelming number experienced no glycemic abnormalities. **Summary: Weight gain and hyperglycemia does not exhibit a 1:1 correlation. In the rare case that patients experienced hyperglycemia, the majority (79%) did not experience weight gain. Additionally, 96% percent of patients who had substantial weight gain did not experience any glycemic abnormalities.**

Message Point #3 and #4

These points are the same as in the previous diabetes sell sheet. Diabetes is a common illness in the general adult population, and is more common in patients with psychiatric illness. It also examines various intrinsic and variable risk factors for diabetes.

Summary

Eli Lilly and Company has a proud history in innovative diabetes research. The relationship between ZYPREXA and diabetes/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 this marketplace.

Question/Answer

How can ZYPREXA show comparable rates of hyperglycemia to other agents when it causes more weight gain, and significant weight gain is a risk factor for diabetes?

Obesity is one of many risk factors for diabetes. Clearly, there is not a 1:1 correlation between weight gain and diabetes. In other words, weight gain can happen independent of diabetes and diabetes can happen independent of weight gain. The single most important risk factor in clinical trials may be persistent and severe mental illness. Additionally, other factors like lifestyle and family history all play an important role.

Your data looks good, but it is not what I am seeing in my daily practice. I have seen a higher incidence of hyperglycemia/diabetes in my ZYPREXA-treated patients. How do you explain this difference?

Doctor, your clinical experience is extremely important. However, your experience seems to be different from large-scale clinical studies.

There may be a couple of reasons why this may be the case. First, some physicians were more selectively assessing ZYPREXA patients for hyperglycemia or diabetes. When they began to assess patients on other medications as well, they began to uncover additional cases.

Secondly, other physicians have realized their perceptions have been influenced by the fact that they have significantly more patients on ZYPREXA.

Another possibility may be that your patient population may be different. For example, you may be treating a more severely mentally ill population and using more ZYPREXA than other physicians.

Does ZYPREXA affect risk factors other than weight gain?

That's an excellent question, since there are many factors that impact a person's chance of developing diabetes. Some of these are intrinsic and can not be impacted by lifestyle or any agent (such as genetic risk, age, gender, etc.). In terms of variable risk factors like prolactin levels, ZYPREXA does not appear to have any effect that might raise glucose levels. Regarding various lifestyle factors (lack of exercise, excessive alcohol intake, etc.), these may improve to the degree that a patient experiences efficacy from ZYPREXA, potentially improving their risk profile.

Is there a direct effect of ZYPREXA on diabetes?

We've gone back and looked for evidence both preclinically and in our clinical comparison with other antipsychotics and mood stabilizers to determine whether or not ZYPREXA directly interferes with insulin release or insulin activity. We have not found a direct effect. Specifically:

- We have examined our longer-term preclinical animal studies and have not found any changes in insulin release or changes to the pancreas.
- We also looked to determine if there were higher rates of diabetes vs comparator drugs in clinical studies. If there was a ZYPREXA-specific effect, you would expect to find much higher rates of diabetes with ZYPREXA, probably in the first weeks or months of therapy. In fact, our head-to-head clinical trials show comparable rates of diabetes or hyperglycemia to haloperidol or risperidone. While this data can not rule out a class effect, it is evidence against a ZYPREXA-specific effect.
- We are continuing to investigate these questions quite carefully.

Does ZYPREXA cause Type I diabetes?

No. Most treatment-emergent diabetes reported with ZYPREXA and other psychotropics is Type II. We do know that there are patients, independent of the agent they are taking (and even some patients not taking any agent at all), who develop Type I diabetes. In our controlled clinical trials, rates of developing Type I diabetes are not higher with ZYPREXA than with haloperidol or risperidone. Even in pre-clinical animal data, there is no evidence to suggest that ZYPREXA causes Type I diabetes.

Scientific Background (review to extent necessary)

General Overview: Basic Biology

The human body needs fuel in order to function. As we eat, our body breaks down some of the food into sugars, one of which is glucose, the body's main fuel. After glucose is created, it must be transported to the cells, where it is oxidized (burned) to supply energy and allow the body to function. (Most cells can also use alternate energy sources, such as lipids or proteins, but generally use glucose first.) The blood carries glucose to individual cells. As glucose enters the bloodstream, a person's blood glucose level begins to rise, then gradually returns to the normal range as glucose passes into the cells.

It is important to realize that there are daily fluctuations in blood glucose levels, as well as a great deal of inter- and intra-person variability. For example, a measurement of fasting blood sugars (obtained by assessing blood glucose levels 8-12 hours after the last food intake) results in "ideal" plasma levels that may range from 70-100 mg/dl. Nondiabetic individuals usually have fasting glucose levels below 125mg/dl.

The body has a very complex system that makes glucose available to cells to produce energy, and generally this system keeps blood glucose levels within a normal range. When the body senses an increase in glucose, it sends a signal to the beta cells of the pancreas to make insulin. Insulin is a hormone that lowers the blood glucose by acting as a key to unlock the body's cells, thus allowing glucose to pass from the bloodstream into the cells. Once the pancreas releases insulin into the blood, the blood glucose level begins to fall back to normal as the insulin allows glucose to pass from blood into the cell. The body's cells then utilize the glucose for fuel, creating energy for the body.

When the system fails. . .

If the body doesn't make enough insulin or if the insulin doesn't function properly, the sugar cannot gain access to the cells. Instead, the glucose stays in the blood, causing the blood sugar level to be high, potentially signaling diabetes.

Just because a person's blood sugar levels may be elevated doesn't necessarily mean that person has diabetes. A person has "high blood sugar" or hyperglycemia when his or her blood sugar level has risen and stayed well above the ideal range. It requires consistent elevations over a long period of time to be considered diabetes.

Hyperglycemia vs Diabetes

Hyperglycemia and diabetes are conditions characterized by abnormalities in the body's ability to use glucose.

Hyperglycemia that persists for a short period of time usually does not have an adverse effect on the body. Sometimes, hyperglycemia can cause symptoms such as excessive thirst and urination. If hyperglycemia persists for a long period of time (as in diabetes), it can damage certain organs of the body such as the kidneys, eyes, and nerves. Although many individuals experience hyperglycemia, such as after quickly eating a high calorie meal or when they are ill, usually the elevated glucose is transient and goes away without medical intervention.

Diabetes is a complex metabolic disorder predominantly characterized by blood glucose levels that are consistently higher than normal (hyperglycemia). But diabetes is more than just hyperglycemia; frequently it also entails other metabolic problems, such as elevations in cholesterol and triglycerides.

Other definitions

Fasting plasma glucose (FPG)—collected from a patient who has no caloric intake for at least 8 hours. This is the preferred method for measurement because it eliminates high measurements that may result from a patient's eating pattern.

Random plasma glucose—collected any time of the day independent of when or what the individual last ate. This test has its limitations but depending on the patient's situation, it may be the best alternative.

Impaired glucose tolerance (IGT)—These criteria define a group of patients who are hyperglycemic but do not meet the criteria for a diagnosis of diabetes.

Defining diabetes by blood glucose levels

Measurement	Diabetes	Impaired Glucose Tolerance (IGT)	Normal
Random Glucose	≥200 mg/dl	160-200 mg/dl	<160 mg/dl
Fasting Glucose	≥126 mg/dl	110-126 mg/dl	<110 mg/dl

The role of psychotropics and hyperglycemia/diabetes:

Several psychotropics have been associated with high insulin levels and insulin resistance (eg, chlorpromazine, divalproex). The National Diabetes Data Group listed chlorpromazine, haloperidol, and lithium under drugs that impair glucose tolerance.

Cases of hyperglycemia have been found and noted in clinical trials with atypicals; in fact, hyperglycemia and diabetes are included as adverse events in the package inserts of most typical antipsychotics and mood stabilizers and all currently approved atypical antipsychotics. Also, since obesity is a risk factor for diabetes, clinicians may be anticipating more hyperglycemia risk among patients with substantial weight gain during treatment.

There have been a number of case reports describing new-onset diabetes during treatment with ZYPREXA. Of note, many of the reports of abnormal glucose levels involved patients with other risk factors for developing hyperglycemia including race, obesity before treatment, or personal/family history of diabetes. In particular, of 15 case reports regarding treatment with ZYPREXA, 12 involved patients with a history of obesity.

Beyond case reports in the literature, there have been a number of studies implicating ZYPREXA as having higher rates of hyperglycemia or diabetes. Perhaps the best known is the as-yet unpublished work of Dr. Newcomer, who performed a retrospective study looking at hyperglycemia after an oral glucose load in patients on ZYPREXA, risperidone, haloperidol, or clozapine.

While provoking interesting medical research questions, the data does not have practical application, nor does it draw concrete conclusions. The Newcomer study is limited by a number of factors. First, the database is quite small, including <10 patients per group. Second, the study was designed to focus on cognition and was NOT intended to examine hyperglycemia. As such, it did not control for variables such as patient diet or family history of diabetes. Most importantly, assignments to different drugs were not randomized.

To point out how potentially spurious Dr. Newcomer's findings are, it is instructive to look at a very similar study undertaken by Dr. Prior and colleagues from Alberta, Canada. Dr. Prior conducted a study to investigate whether patients taking clozapine, risperidone, and ZYPREXA have unusual responses to oral glucose challenges. Unfortunately, this study also had a small sample size (n=28) and the patients were not randomly assigned to treatment. However, the results indicated that none of the patients treated with ZYPREXA had abnormal glucose metabolism, 40% of patients treated with risperidone had abnormal results, and 67% of patients treated with clozapine had abnormal results.

ZYPREXA "FREQUENT AREAS OF CONCERN" OR "FAOC"

1. *I do not treat that type of patient.*

   Cushion: *Thanks for sharing that with me.*
   Probe 1: *What concerns do you have in treating a patient like this? (or Donna) (This is a great place to "understand needs." Is the PCP afraid of treating the disease state or afraid of the medications he/she will use?)*
   Probe 2: *If you had safe and effective treatment options, how would that impact your decision on whether you treat a patient like Donna or refer them to a psychiatrist?*
   Important notes: *a. Make sure the PCP recognizes the type of patient we are talking about today, not the psychotic patient or severely ill patient, but the complicated mood patient who has symptoms of irritability, anxiety, poor sleep and mood swings. This is most likely a patient he has seen for a few years and has felt comfortable treating. b. Having confirmed the patient type – it is now time to further understand the needs of the physician – and to satisfy those needs with Zyprexa.*

2. *Zyprexa is an anti-psychotic.*

   Cushion: *That is correct, doctor. When Zyprexa was launched, our initial indication was for schizophrenia.*
   Clarify: *What is it about anti-psychotics that you are concerned about?*
   Address AOC: *The FDA has now classified Zyprexa as a psychotropic (see first line in PI), as it is the only medication indicated to treat* **both** *schizophrenia and bipolar mania. Zyprexa is indicated for both the short term and long term treatment of schizophrenia and acute bipolar mania.* **Address AOC:** *Zyprexa's safety profile is much more favorable than the older typical anti-psychotic agents you may be familiar with. Go to Favorable Safety Page (pg. 6 in Detail Aid) and address the concern.*
   Check for Agreement
   Get Back to Selling
   Note: *The American Psychiatric Association recently updated its Standards of Care for Bipolar Illness and listed Zyprexa as first-line therapy.*

3. *I am concerned about EPS/TD.*
   Cushion: *I understand your concern regarding EPS/TD*
   Clarify: *Can you clarify your concern regarding EPS?*
   Address AOC: (go to Favorable Safety page) ***EPS:*** *Zyprexa has a low risk of EPS, and in a study using the most exacting measurements, the Simpson Angus Scale, Zyprexa's rate of EPS was comparable to placebo across all dose ranges (page 6) (if physician is utilizing/comparing with Risperdal). In a head-to-head study vs. Risperdal, the rate of EPS for Zyprexa was 12.5% vs. 22.3% for Risperdal.* ***TD:*** *Zyprexa has a minimal risk for Tardive Dsykinesia (TD). In a*

clinical trial vs. Haldol, the incidence of TD was .52% with Zyprexa vs. 7.45% with Haldol over a 1-year period.
Check for Agreement *How do you feel about this safety data?*
Get back to Selling

4. *I am worried about sedation.*
   Cushion: *Thanks for sharing with me.*
   Clarify: *For a patient like Donna, who presents with irritability, anxiety, mood swings and disrupted sleep, how do you think somnolence may affect this patient?*
   Address AOC: *The #1 side effect that occurred in clinical trials with Zyprexa was somnolence. It appears to be transient and may benefit some patients. Therefore, it is recommended to take Zyprexa either at bedtime or earlier in the evening. Now, if a patient is drowsy in the morning, remember that Zyprexa has a 6 hour Tpeak (time to peak concentration), so simply instructing your patient to take their tablet earlier in the evening, perhaps at dinner, may alleviate the morning drowsiness.*
   Check for Agreement *How do you feel about this safety data?*
   Get back to Selling

5. *I am concerned about weight gain.*
   Cushion: *Thanks for letting me know your concern.*
   Clarify: *Is this something you have seen in your patients or heard about?*
   Address AOC: *Zyprexa may cause an increase in appetite that can lead to weight gain. The increase in appetite can be manageable, and diet and behavioral modifications can help. Many describe this as carb-craving so discussing this up front with your patients is helpful. You can suggest that patients drink diet soda instead of regular soda, or cut back on the amount of carbohydrates they eat. Some patients adopt a "1-plate rule" when they sit down for dinner. Increasing daily activity may also help manage weight*
   Check for Agreement *How do you manage weight gain that results from other medications? If the physician has further questions, offer to have a medical letter sent to them.*
   Get back to Selling

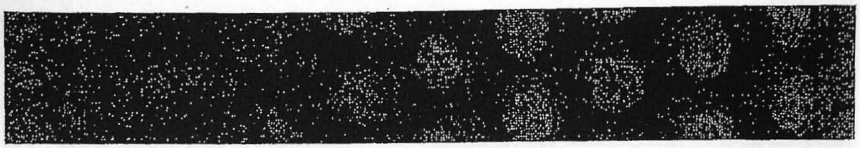
6. *I am concerned about diabetes.*
   Cushion: *Thank you for sharing this concern with me.*
   Clarify: *Is this something you have seen or heard about?*
   a. **Address AOC:** *I understand your concern. The incidence of diabetes is 2-4X more common in mentally ill patients than in the general population. In every study examining this subject, no causal relationship has been established between patients being treated with Zyprexa and the onset of diabetes. The incidence of diagnosed treatment-emergent diabetes with patients taking Zyprexa was comparable to those patients treated with Risperdal, Haldol and Depakote in every clinical study conducted by Lilly or by our competitors. These facts suggest that you should choose a medication based on its efficacy*

in treating complicated mood symptoms, but to be aware of the incidence of diabetes in this population and address it appropriately.

Check for Agreement

Get back to Selling

Important notes: *Confidence and correct tone is very important. We cannot dismiss this objection as a non-issue but rather we need to understand their concerns and address them appropriately.*



Hyperglycemia/Diabetes: Sell Sheet Implementation

For Internal Use Only
Not For Use In Detailing

Lilly
Answers That Matter.

06-05650

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!

For internal use only. Not for use in detailing.

06-05030-2

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!

06-0506301-2

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

For internal use only. Not for use in detailing.

06-05630CI

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.

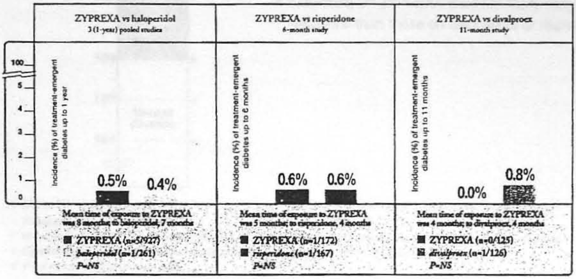
1. While there is a relationship between weight (or specifically obesity) and diabetes, it is not exact and constitutes one of **many** risk factors for diabetes. For example, another is hyperprolactinemia (*Inside cover, "A number of factors..." section 4)*
2. Even among the patients that had substantial 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

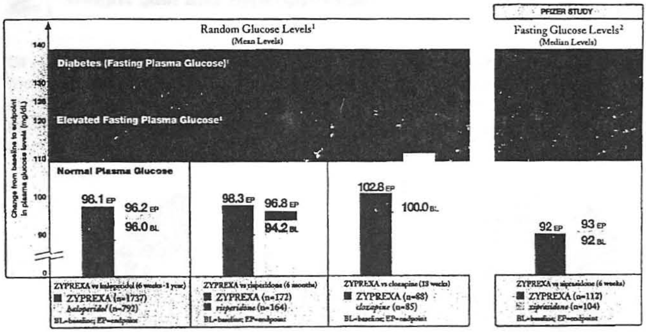
1 Comparable rates of diabetes and hyperglycemia among psychotropics

Patients treated with ZYPREXA had rates of diabetes and hyperglycemia comparable to those in patients treated with risperidone, haloperidol, and divalproex sodium in clinical trials*

Incidence of diagnosed treatment-emergent diabetes in longer head-to-head schizophrenia and bipolar mania trials*



Baseline to endpoint increase in average glucose level across comparative studies*



1. Allison DB, et al. Presented at: 2001 International Congress of Schizophrenia Research, Vancouver, British Columbia.
2. Glick ID, et al. Presented at: 2001 Annual Meeting of the American Psychiatric Association, New Orleans, Louisiana.

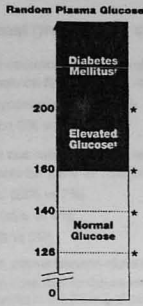
* Please see inside for study methodologies.

† Diabetes (Fasting Plasma Glucose) defined by ADA guidelines as ≥126 mg/dL (2 fasting blood draws).

‡ Elevated Fasting Plasma Glucose defined by ADA guidelines as ≥110 mg/dL (see reference 17).

For safety information on haloperidol, risperidone, clozapine, divalproex, and ziprasidone, see the manufacturers' respective package inserts.

Individual patient likelihood of random glucose elevations[1]



- In head-to-head data measuring random glucose, the likelihood of an individual patient exceeding any of the following thresholds was examined (126 mg/dL, 140 mg/dL, 160 mg/dL, or 200 mg/dL).*
- Individuals on ZYPREXA were not more likely to experience glucose elevations than those on haloperidol or risperidone at any threshold.[1§]

1. Allison DB, et al. Presented at: 2001 International Congress of Schizophrenia Research, Vancouver, British Columbia.

* Thresholds examined in this analysis.

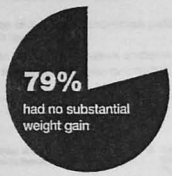
† Diabetes (Random Plasma Glucose) defined by ADA guidelines as ≥200 mg/dL, confirmed with a subsequent fasting or oral plasma glucose test.

‡ Elevated (Random Plasma Glucose) outlined by ADA-supplied information as >160 mg/dL.

§ *P* values ranged from 0.11 to 0.93.

2 Weight gain and hyperglycemia*

Of patients treated with ZYPREXA, the majority (79%) of those who had an episode of hyperglycemia† did not experience substantial weight gain‡ in longer-term comparative studies.



Even among those patients with substantial weight gain,‡ over 96% had no glycemic abnormalities at all.†

* Analysis from Lilly-sponsored head-to-head schizophrenia treatment trials. Please see inside for study methodology.

† Hyperglycemia episodes and glycemic abnormalities defined as random glucose levels ≥160 mg/dL.

‡ Substantial weight gain defined as >10% increase in weight.

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.

See accompanying safety profile and full Prescribing Information for ZYPREXA.

For safety information on haloperidol, risperidone, clozapine, divalproex, and ziprasidone, see the manufacturers' respective package inserts.

Additional prescribing considerations for ZYPREXA

The most common treatment-emergent adverse event associated with ZYPREXA 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

Important for patients changing to ZYPREXA from other antipsychotics and for those on multiple medications, such as diazepam, imipramine, lithium, warfarin, theophylline, and biperiden.

Coadministration of diazepam or ethanol with ZYPREXA may potentiate orthostatic hypotension.

Tardive dyskinesia—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.

* 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.

For safety information on haloperidol, risperidone, quetiapine, thioridazine, and clozapine, see the manufacturers' respective package inserts.

See accompanying full Prescribing Information for ZYPREXA.

References

1. Allison DB, et al. Presented at 2001 International Congress of Schizophrenia Research, Vancouver, British Columbia.
2. Glick ID, Romano SJ, Horne RL, et al. Insulin resistance in ZYPREXA- and ziprasidone-treated patients: results of a double-blind, controlled, 6-week trial. Presented at: 2001 Annual Meeting of the American Psychiatric Association, New Orleans, Louisiana.
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12. American Diabetes Association Screening for type 2 diabetes. *Diabetes Care*. 2000;23 (suppl 1).
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17. American Diabetes Association. Clinical practice recommendations 2000. *Diabetes Care*. 2000;23 (Suppl 1):S1-S116.

Study methodology and limitations

ZYPREXA vs haloperidol, risperidone, clozapine, and divalproex

These results are from randomized clinical trials sponsored by Eli Lilly and Company comparing ZYPREXA vs haloperidol (3 studies, each with an acute double-blind phase of 6 weeks followed by a longer-term double-blind observation allowing total exposure up to 52 weeks); ZYPREXA vs risperidone (1 28-week double-blind study); ZYPREXA vs clozapine (1 18-week double-blind study), and ZYPREXA vs divalproex for acute mania (47-week study). Mean time of exposure to haloperidol was approximately 7 months; to risperidone, approximately 4 months; and to divalproex, approximately 4 months. Patients were 18 to 65 years of age, with a DSM-III-R or DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, or Bipolar I Disorder. Dosage ranges were 2.5 to 25 mg/day for ZYPREXA, 5 to 20 mg/day for haloperidol, 4 to 12 mg/day for risperidone, 200 to 600 mg/day for clozapine, and 500 to 2500 mg/day for divalproex.

The treatment-emergent diagnosis comparison also includes 33 subjects from 1 haloperidol-controlled study receiving ZYPREXA 1 mg/day.

Treatment-emergent diagnosis of diabetes: Diagnosis was based on the clinical discretion/judgment of the investigator. For this analysis, all randomized patients were considered. The ZYPREXA-haloperidol study includes only those patients enrolled in the longer-term trial (up to 52 weeks). ZYPREXA n=927, haloperidol n=261. The patients randomized in the risperidone trial were ZYPREXA n=172, risperidone n=167, and the patients randomized in the divalproex trial were ZYPREXA n=125 and divalproex n=123.

Mean and categorical analysis of plasma glucose: As blood samples were not necessarily fasting, results are considered random plasma glucose. Generally, 2 measurements were obtained prior to initiation of therapy and then with a frequency as specified by protocol. When 2 pretreatment measurements were available, their average was used as the baseline glucose value. All measurements up to and including the day following the last day of treatment were included in these analyses, to a maximum of 52 weeks in the haloperidol-ZYPREXA comparisons, 26 weeks in the risperidone-ZYPREXA comparison, and 18 weeks in the clozapine-ZYPREXA comparison. Patients with a known diagnosis of diabetes or taking antidiabetic medications at baseline were excluded from these analyses. The resulting samples were: haloperidol n=792 vs ZYPREXA n=1737 (from 3 pooled haloperidol-ZYPREXA trials), risperidone n=164 vs ZYPREXA n=172, and clozapine n=85 vs ZYPREXA n=88.

Mean change in glucose: The significance and magnitude of the differences in mean glucose values were assessed using a restricted maximum likelihood-based repeated measures analysis.[16] The following effects were included in the analysis: treatment, time, baseline BMI, mean baseline glucose, age, and study (for the haloperidol comparisons). A 2-tailed *P*-value of <0.05 was considered statistically significant.

Likelihood of exceeding glucose thresholds: An iteratively weighted restricted/residual pseudo likelihood (REPL)-based approach[16] was used to estimate the probability of an "event" of elevated *random* glucose values. Multiple thresholds were used to account for the lack of universally accepted criteria for what constitutes a clinically significant elevation in *random* glucose, in the absence of signs or symptoms of diabetes, with 126, 140, 160 and 200 mg/dL threshold values extrapolated from published suggestions.[17] Analysis with each of these thresholds was performed excluding those patients who had baseline glucose values above that threshold. An "event" was defined as occurrence of one of the following: (a) 2 consecutive glucose measurements at or above threshold, (b) last glucose measurement at or above threshold, or (c) initiation of glycemic medication or glycemic adverse event. Cox proportional hazards regression analyses were implemented to assess the relative hazard of experiencing a glucose measurement that reaches or exceeds the preestablished thresholds.

Limitations: While fasting glucose concentrations with confirmation of elevated values would be a preferable approach to defining potentially clinically significant glucose elevation,[17] these trials were not designed primarily to evaluate glycemic effects. Thus, fasting glucose levels were not determined. To date, fasting glucose results are not available from large randomized prospective comparative trials of ZYPREXA. Secondly, while treatment-emergent diagnosis of diabetes was a prospectively anticipated comparison, the other information reported (mean change in random plasma glucose, likelihood of exceeding a particular glucose threshold, and weight-gain hyperglycemia relationships) are post-hoc analyses of prospectively collected data. Thirdly, these trials are of moderate duration (maximum 1 year) and therefore may not inform about the long-term risks (or lack thereof) of the drugs studied herein. Fourthly, in the studies analyzed, power to detect differences in likelihood of crossing a lower glucose threshold (eg, 126 mg/dL) is greater than at a higher threshold (eg, 200 mg/dL) because of relative infrequency of events at the latter.

ZYPREXA vs ziprasidone

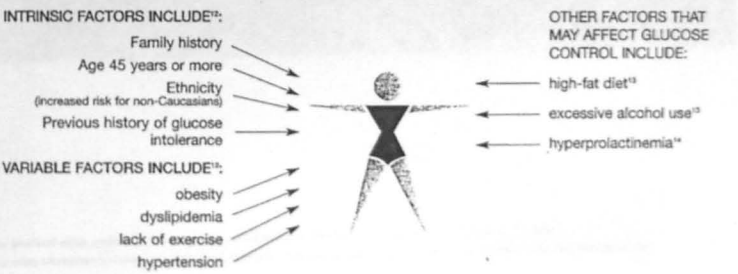
This 6-week, double-blind trial sponsored by Pfizer, Inc. compared ZYPREXA (n=133) to ziprasidone (n=136) for the treatment of schizophrenia or schizoaffective disorder. Dosage was titrated up to 15 mg/day for ZYPREXA and 80 mg BID for ziprasidone. Fasting plasma glucose was measured at baseline and endpoint. Median levels were reported. (Glick et al, American Psychiatric Association, Annual Meeting, 2001.)

3 Diabetes is common

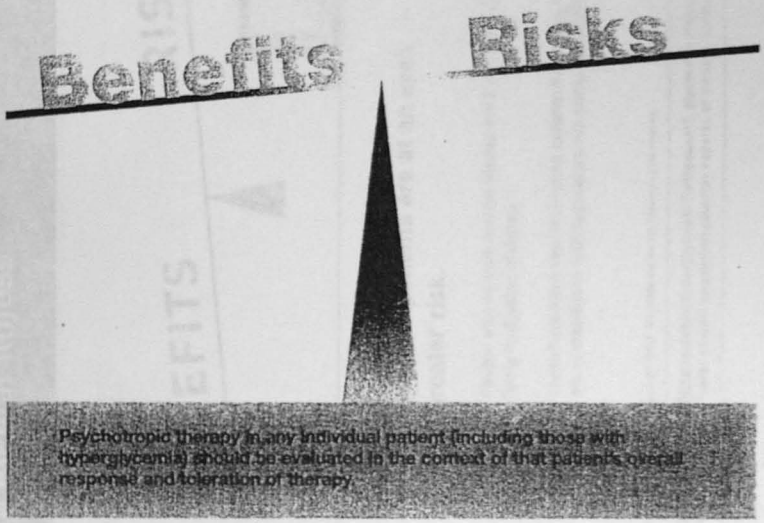
Diabetes is common in the general adult population, and is more common in patients with psychiatric illness

- Approximately 7.8% of the general adult population had diabetes (one-third of which was undiagnosed) as reported in an epidemiologic study of prevalence in the US.[3]
- An additional 6.9% of the general population had fasting blood glucose levels above normal in the same study.[3]
- Prevalence of type 2 diabetes among patients with schizophrenia and bipolar disorder was as high as 2-4 times greater than in the general population in several other studies.[4-7]
- An association between antipsychotics and hyperglycemia has been reported since the 1950s.[8]
- Patients treated with certain mood stabilizers may have disrupted glucose control as compared with the general population.[9-11]

4 A number of factors affect risk for diabetes



Risk/Benefit Analysis



Psychotropic therapy in any individual patient (including those with hyperglycemia) should be evaluated in the context of that patient's overall response and toleration of therapy.

For additional safety profile and other prescribing considerations for ZYPREXA, see inside and full Prescribing Information.

For safety information on haloperidol, risperidone, clozapine, divalproex, and ziprasidone, see the manufacturers' respective package inserts.

zyprexa® Olanzapine

www.ZYPREXA.com

Lilly

06-0563

Diabetes and patients with mental illness

What do you consider when choosing medications?

What benefits do you associate with ZYPREXA® (olanzapine)?

What risks do you associate with it?

EXHIBIT
5
Noesges
8-11-06

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.

Lil
...rs That Matter.

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).

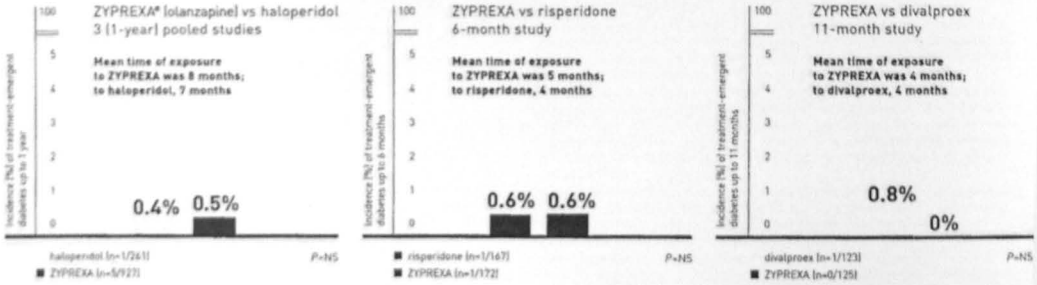
ZYPREXA vs risperidone: One 28-week, double-blind study compared ZYPREXA (5 to 20 mg/day) with risperidone (4 to 12 mg/day).

ZYPREXA vs divalproex: One 47-week, double-blind study compared ZYPREXA (5 to 20 mg/day) with divalproex (500 to 2500 mg/day).

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.
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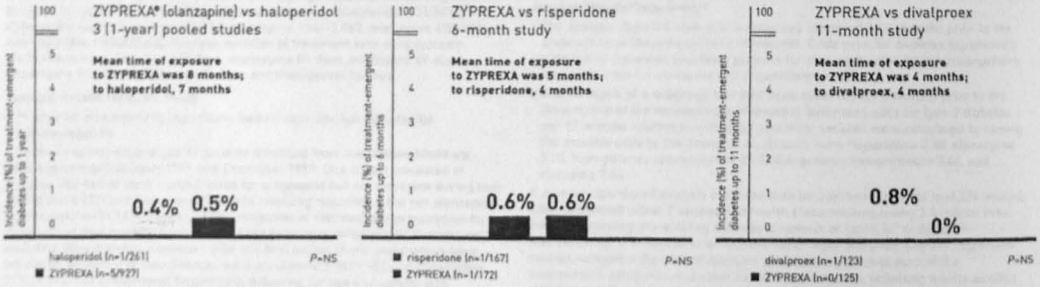

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Answers That Matter.

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 3-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 thioridazine 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 1,378, and low-potency typical antipsychotics 480. Average duration of antipsychotic treatment episodes were: clozapine 8.8 months, olanzapine 5.6 months, risperidone 6.4 months, high-potency typical antipsychotics 6.7 months, and low-potency typical antipsychotics 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.

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 That Matter

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=386), dizziness (11% vs 4%) and tachycardia (4% vs 1%) were reported; these events were not always associated with hypotension.

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17. Foss MC, Paula FJ, Paccoloa GM, et al. Peripheral glucose metabolism in human hyperprolactinaemia. *Clin Endocrinol*. 1995;43:721-726.

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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.

Consider the whole story.

- 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.

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Lilly
Answers That Matter.

Table of Contents

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Introdu

Welcome to the ZY[illegible]yperglycemia/Diabetes Data on Demand Resource Guide. This guide will function as your "go-to" resource when you are faced with an objection surrounding hyperglycemia or diabetes. Since the launch of ZYPREXA four years ago for schizophrenia and almost one year ago for bipolar disorder, we have been very successful in communicating the outstanding efficacy and safety of ZYPREXA to our customers. You have helped thousands of patients with schizophrenia or bipolar disorder achieve either reintegration or balance. Now, with the launch of the new schizophrenia message—including the maintenance of treatment response data—we're taking ZYPREXA to an even higher level.

Our primary focus, as always, is on the outstanding efficacy of ZYPREXA. Clearly, this is the most important facet of an antipsychotic and a mood stabilizer to patients, family members, and the treatment team. Nevertheless, as you are well aware, over the last several years our competition has been relentless in trying to convince our customers that ZYPREXA is not appropriate for many patients because of weight gain. And, more recently, they have focused on a very logical argument: ZYPREXA causes more weight gain; significant weight gain is a risk factor for diabetes, and therefore (they want MDs to think) ZYPREXA causes more hyperglycemia and diabetes.

It is very important to have a good understanding of hyperglycemia and diabetes. This will allow you to be able to properly handle any possible objections you may get, and in the end, spend more time sharing the outstanding efficacy story with your customers. You will learn more about hyperglycemia and diabetes in the Scientific Background beginning on page 11 of this guide.

Market overview

Not every physician has bought into the weight gain/diabetes argument, but there are a growing number of psychiatrists who have. For the most part, their perceptions of ZYPREXA and diabetes have been based on an intuitive argument, but many have either read about case reports in the literature, heard about a patient on ZYPREXA who has developed diabetes, or in some cases, have had a patient on ZYPREXA develop diabetes. In essence, most physicians' perceptions have been based on an argument put forth by our competition buttressed by some anecdotal evidence.

Market research has shown there are two groups of physicians with whom we must be prepared to deal. First, there is a group representing about 60% of psychiatrists who do not view diabetes as a particular concern with antipsychotics. However, this does not mean they have not heard the argument put forth by our competition. In fact, while these physicians may not be concerned enough to let this issue affect their prescribing of ZYPREXA, most of them have heard the argument. If you can get into a deep enough dialogue with them, we've found that many of them do wonder if it might be true. The other 40% of our psychiatrists have specific concerns about ZYPREXA and diabetes, and perhaps half of this group has begun to shy away from ZYPREXA because of their concerns.

Diabetes, after all, is a pretty scary thought for most psychiatrists. First, most are not comfortable with the science around the disease. Though many remember some of their medical school training on the subject, most do not deal with diabetes on a day-to-day basis, so they may not be well versed in the basics, such as risk factors for the disease, diagnostic criteria, or treatments. Second, they are fearful of "causing" a disease that can lead to permanent complications. Even though they may be comfortable assessing the risks of using antipsychotics that may lead to tardive dyskinesia—they've had about 50 years to get used to thinking about that potential side effect. As one psychiatrist said, "We've had to be neurologists, and I don't want to have to become an endocrinologist."

Strategy Overview

Situation overview

We all have been aware of the competitive activity and changing physician perception for some time, and we've been fairly proactive in the marketplace. Along with proactively changing the PI in the second quarter of 2000, we launched a number of efforts to address physician concerns. It is clear that many of you have made some progress utilizing the first hyperglycemia sell sheet with some of your physicians. And there has been a steady DTP effort (CME, Strategy and Consultant Conferences, etc) on the topic. Also, last year, the neuropharm division of the FDA requested all preclinical, clinical, and post-marketing surveillance data from each of the manufacturers of newer antipsychotics. And, in late 2000, the FDA asked Lilly to remove the paragraph in the ZYPREXA PI relating to the relative incidence of treatment-emergent hyperglycemia pending its review of all manufacturers' data.

We anticipate that the FDA will make additional changes to the PIs of many or even all antipsychotics in the next six months to a year. We believe the most likely scenario is that there will be some sort of "class labeling" around hyperglycemia/diabetes.

So, how do we address this issue?

There are a number of "lessons learned" from our experiences selling Redacted ZYPREXA that we need to remember as we address this issue. We've done some good things, and have also made some mistakes as we've dealt with competitive issues such as Redacted Redacted weight gain with ZYPREXA.

- We must be fully aware that "brush fires can turn into forest fires." In essence, although we've handled the competitive attacks on diabetes fairly well to date, we must not be overly confident. We must work to make sure that the 60% of psychiatrists who don't have specific concerns about ZYPREXA remain confident in both the efficacy and safety of our agent.
- We've learned that it's important to be forthcoming—we must not be perceived as "merely denying" a potentially serious side effect, and therefore must address the issue constructively, confidently, and empathetically.
- We must not fight a battle around just one side effect. We must make our first priority discussing the benefits of ZYPREXA with our physicians.
- We must continue to give appropriate tools to the neuroscience sales force, and help provide "air cover" in terms of physician-to-physician communications.
- We must be relentlessly consistent in our alignment and execution across the marketing mix—in the sales force and in our other marketing efforts.
- We must recognize and understand the nature of each customer's concern and tailor our objection handling based on our knowledge of that customer's concern.

Strategy overview

Our strategy for how to deal with this issue is based on a number of things:

- a firm understanding of our customers' perceptions of ZYPREXA and of Lilly;
- an understanding of past, current, and likely future regulatory events;
- an ever-evolving understanding of the truth about ZYPREXA and other psychotropics with respect to hyperglycemia and diabetes; and
- an understanding of the patients our physicians are treating.

So what is the story behind hyperglycemia and ZYPREXA? Our US and Product Team physicians have been working diligently to learn more about the potential for treatment-emergent hyperglycemia and/or diabetes in patients who are treated with ZYPREXA and other agents.

Briefly, diabetes may occur in patients taking antipsychotics and/or mood stabilizers, including ZYPREXA, at rates that are comparable to each other.

This is the key message that we will focus on, and the one that is most relevant to clinicians. After looking at data from pooled clinical trials, we have found that the incidence of treatment-emergent, diagnosed diabetes is comparable between ZYPREXA, haloperidol, and risperidone. We also looked at rates of abnormally elevated blood glucose across these three agents using four different cutoff points, and again found that the likelihood of patients experiencing elevations was not different between these agents *at any threshold examined*. We will go into more detail in the Scientific Background, page 19.

Of note, you will notice that the thrust of our new data on demand for diabetes/hyperglycemia focuses on comparable rates with relevant treatment alternatives in patients with schizophrenia, rather than placebo. One limitation of our placebo data in patients with schizophrenia is that the time of exposure to placebo in our trials is relatively short—on the order of a few weeks—making comparisons of rates challenging. On the other hand, our database comparing ZYPREXA to haloperidol, risperidone, and clozapine is quite robust, having a large number of randomized, prospectively assigned patients followed over a relatively long duration. And perhaps most importantly, these agents (particularly risperidone and haloperidol) are two very relevant alternatives in today's treatment paradigm for patients with schizophrenia and, perhaps to a lesser extent, bipolar mania. You'll note that we do not include data in this sheet on Depakote. This is simply because the data that we have are limited to the three-week HGHQ study, where we did not see differences in glucose levels, but would not have expected to, given the relatively short duration of the trial. In Abbott's 12-week comparative study of ZYPREXA and Depakote, no significant differences in glucose levels were found.

We have also analyzed the large head-to-head database looking at average blood glucose levels for patients taking ZYPREXA and the other comparator agents. Here, we did see some small elevations in patients taking ZYPREXA, but as Dr. Breier discussed in his video shown in the January meetings, these small increases were not clinically relevant. Nevertheless, it is important that we share this information with our customers because it helps build credibility. **We are NOT saying that there are no changes in blood glucose on ZYPREXA, nor are we saying that there are no differences in blood glucose for patients on ZYPREXA as compared with patients on the other agents. The key point is that we do not see differences in rates of diabetes or hyperglycemia across these agents.**

There are, of course, a number of other key messages that are essential to communicate.

- **Diabetes is quite common in the general population, and is higher in patients with psychiatric illness.**

  The incidence of diabetes is on the rise in the United States. In the general population, the incidence of diabetes is 7.8%, with about one third being undiagnosed. In other words, there are people who have diabetes and don't even know it. On top of this, an additional 6.9% have abnormal hyperglycemia, with blood glucose levels falling short of the diagnostic threshold for diabetes. *The incidence of diabetes among patients with schizophrenia and bipolar disorder is 2-4 times higher than the general population.*

  We do not mean to minimize the problem of glucose elevation at all. In fact, to the contrary, it is important our physicians understand that if they were to look carefully at their patient population, they likely would find elevations in glucose. Clearly, hyperglycemia and diabetes are part of a much bigger picture than merely the effects of psychotropic medications. This leads us to the next part of our message.

- **There are a large number of factors that affect risk for diabetes, such as obesity or other potentially stronger risk factors.**

  There are some factors that cannot be changed, such as family history, age, ethnicity, etc. On the other hand, there are a number of factors that are variable. Variable factors include diet and exercise, which can play a role beyond mere weight gain. Although significant weight gain is indeed a risk factor for hyperglycemia and/or diabetes, there are many other factors involved. Even though a patient has some or even all of these risk factors, he/she may not develop diabetes. Conversely, some patients with diabetes have none of these risk factors. Clearly, diabetes is a complex disease with a large number of contributing factors.

  So then, how can ZYPREXA be associated with more weight gain, but still have comparable rates of hyperglycemia? In fact, differences in patterns of weight gain on various agents that we've analyzed did NOT translate into differences in rates of diabetes or hyperglycemia. As Dr. Breier outlined in his video, weight gain is just one part of the picture. In fact, the majority of patients (79%) who did have an episode of hyperglycemia did NOT experience substantial weight gain (ie, increase of 10% or more from baseline). And even among those patients with substantial weight gain, over 95% had no glycemic abnormalities. Further detail is provided in the Scientific Background, page 19.

In essence, our strategy is to set the record straight regarding the incidence of hyperglycemia associated with antipsychotic medications. Specifically:

- Rates of hyperglycemia/diabetes are comparable among patients taking antipsychotic medications
- Diabetes is common in the general adult population and is more common in patients with psychiatric illness
- There are many factors that influence hyperglycemia/diabetes
- Obesity is one risk factor among many that may contribute to hyperglycemia

Market research testing

We have had the opportunity to test the new sell sheet with a number of your key customers. First off, in our testing, physicians had a very consistent takeaway of key message points. And, the message appears to be generally believable. Now, this is not to say that in all cases physicians "changed their minds" on the spot. In almost all cases, however, the dialogue with the physician succeeded in making them think.

If we deliver the right message to the depth required, we can get physicians thinking. And with the "air cover" that is being provided in CME programming and other peer-to-peer programs, it is our intent to reframe this issue over time so that fear of diabetes does not become a reason to avoid starting a patient on ZYPREXA (or on any other psychotropic).

Resources available

At upcoming coaching clinics, you will be working with a new sell sheet. This guide includes photos of the front and back of the sell sheet, as well as a sample script.

In addition, there are a number of other resources that you have at your disposal. Of course there is a medical letter available. And, there are several enduring materials from DTP programs that can also provide good information on this topic for physicians who request it. Specifically, you may want to provide the November 2000 PsychLink (as discussed in the January meetings) to those physicians who request it. We also have updated speaker slides that can be used in peer-to-peer selling efforts.

Critical observations on this new information

First, these data are an enhancement to and consistent with our previous message. Clearly, the information in this sell sheet is more relevant to physicians because it directly discusses comparable rates across certain psychotropic agents. Please note you must discontinue use of the previous sell sheet (OL # 18524) after the upcoming district meeting/coaching clinic.

Second, you must utilize the new sell sheet appropriately with your physicians. Specifically, if you know a physician (or treatment team member) who (a) has a deep-seated and specific objection to using ZYPREXA due to fear of hyperglycemia, and/or (b) brings up a serious hyperglycemia objection at the beginning of your detail, you should address the objection up front in your detail, utilizing the new materials. For other physicians (which will probably be most physicians), you should proceed with the usual "efficacy" message, making sure that you probe carefully during the safety/tolerability section of the detail to uncover an objection. Of course, if you discover one, please handle it appropriately with the new materials.

Additionally, it is critical that you tailor the objection handling to the physician based on a clear understanding of the physician's perceptions. In most instances, you can limit your discussion to the "comparable rates" page. If necessary, though, the second page provides additional information.

Third, our success will be largely dependent on our tone with physicians: we must handle the objection in a confident, non-defensive, forthcoming manner. But we must also answer the objection to the depth required, based on a good understanding of that physician's thoughts and perceptions of the issue. So, of course, active listening is required. Also, the sell sheet is designed so that you can limit your discussion to the "comparable rates" if that will handle the objection. If more is required, you can use the back page as well. In fact, based on our testing with physicians, we've learned that it is **essential** to avoid a "data dump." Therefore, we will practice utilizing this information both in a brief way and a more complete way in the upcoming coaching clinic.

Critical success factors for appropriately dealing with the hyperglycemia/diabetes objection:

1. Focus your sales presentation on the outstanding efficacy of ZYPREXA
2. Have a good understanding of hyperglycemia/diabetes
3. Understand how and when to properly use the hyperglycemia Data on Demand sheet
4. Frame hyperglycemia in the context of the overall safety profile of antipsychotic medications

In closing...

We hope you find this Resource Guide helpful as you prepare yourself to handle any hyperglycemia and/or diabetes objections that your customers may raise. We appreciate your dedication and expertise and are counting on those attributes as we move forward.

We wish you great success in the field!

Scientific Background

This section is designed to give you a brief but fairly thorough understanding of what hyperglycemia is, what diabetes is, and how they differ. Each condition affects the body in different ways. Certain risk factors may predispose one person more than the next. Some of these factors are manageable, some are not. Diabetes has become more common in the general population, and it may be even more common in patients with serious and persistent mental illness.

Once you have an understanding of the disease state, you will then be able to better understand our data on ZYPREXA and diabetes, and how these data compare to other antipsychotics. Obviously, we do not expect you to become diabetes experts. You are sales representatives for ZYPREXA, and your primary mission is to sell ZYPREXA. But unfortunately, for some customers, that may mean you will have to address their concerns about hyperglycemia and diabetes. We hope that we have provided the information to allow you to do that, and then easily transition back to our efficacy message.

General Overview

Basic biology

The human body needs fuel in order to function. As we eat, our body breaks down some of the food into sugars; one of these sugars is glucose, the body's main fuel. After glucose is created, it needs to be transported to the cells in order for the body to function. Glucose is oxidized (burned) in the cells to supply their energy. (Most cells can also use alternate energy sources, such as lipids or proteins, but generally use glucose first.) The blood is responsible for carrying glucose to individual cells. As glucose enters the bloodstream, a person's glucose levels begin to rise, but gradually return to the normal range.

It is important to realize that there are daily fluctuations in blood glucose levels, as well as a great deal of inter- and intra-person variability in blood sugar levels. For example, by one measure of blood sugars (obtained by assessing blood glucose levels 8-12 hours after the last food intake), "ideal" plasma levels may range from 70-100 mg/dl[1] and nondiabetic individuals usually have fasting glucose of below 125 mg/dl.[2]

The body has a very complex system that makes glucose available to cells to produce energy, and generally this system keeps blood glucose levels within a normal range. When the body senses an increase in glucose, it sends a signal to the beta cells of the pancreas to make insulin. Insulin is a hormone that lowers the blood glucose by acting as a key to unlock the body's cells, thus allowing glucose to pass from the bloodstream into the cells. Once the pancreas releases insulin into the blood, the blood glucose level begins to fall back to normal since the insulin allows glucose to pass from blood into the cell. The body's cells then utilize the glucose for fuel, creating energy for the body.

When this system fails...

If the body doesn't make enough insulin or if the insulin doesn't function properly, the sugar cannot gain access to the cells. Instead, the glucose stays in the blood, causing the blood sugar level to be high, potentially signaling diabetes.

Just because a person's blood sugar levels may be elevated doesn't necessarily mean that person has diabetes. A person has "high blood sugar" or hyperglycemia when his or her blood sugar level has risen and stayed well above the ideal range. Consistent elevation over a long period of time makes one more likely to develop diabetes.

Conversely, if blood sugar levels fall below 60-70 mg/dl,[1] this may be an indication of low blood sugar (hypoglycemia). When this happens, people may experience unpleasant symptoms, such as lightheadedness, nausea, drowsiness, or confusion. These symptoms can develop quite suddenly.

Although hypoglycemia is usually easy to treat, serious reactions may result if it is not dealt with quickly, including passing out or having convulsions.

The next section of the Scientific Background will explain in a little more detail the difference between hyperglycemia and diabetes, as well as discuss how each condition can affect the body.

Disease State Overview

Hyperglycemia vs diabetes

Hyperglycemia and diabetes are conditions that center around abnormalities in the body's ability to use glucose. As mentioned, our bodies have a very elaborate mechanism to keep the amount of glucose in the blood within a range that is sufficient to keep body cells energized.

Hyperglycemia that persists for a short period of time usually does not have adverse effects on the body. Sometimes, hyperglycemia can cause symptoms such as excessive thirst and urination. If hyperglycemia persists for a long period of time (as occurs in untreated diabetes mellitus), it can damage certain organs of the body such as the kidneys, eyes, and nerves. Although many individuals experience hyperglycemia, such as after quickly eating a high-calorie meal or when they are ill with the flu, usually the elevated glucose is transient and goes away without medical intervention.

An individual can have episodes of hyperglycemia and not have diabetes or any complications.

Diabetes is a complex metabolic disorder predominantly characterized by blood glucose levels that are consistently higher than normal (hyper-glycemia). But diabetes is more than just hyperglycemia; frequently it also entails other metabolic problems, such as elevations in cholesterol and triglycerides, and symptoms or complications as discussed below. A diagnosis of diabetes is given when the patient meets a certain set of blood glucose criteria, measured by a couple different tests. Let's start by discussing the two types of diabetes, the measurement and evaluation of blood glucose level, and the role of insulin.

Diabetes is more than just hyperglycemia:

- **It is characterized by persistently elevated blood glucose levels above certain thresholds; and**
- **It is also characterized by frequent lipid abnormalities and other complications.**

Types of diabetes

There are two major types of diabetes. Though both include blood sugar elevation, both types have very different causes and presentations, as described below.

Insulin-Dependent Diabetes Mellitus (Type 1 Diabetes) occurs when beta cells of the pancreas do not produce sufficient insulin, typically due to beta cell destruction. Circulating insulin levels are low or undetectable. As such, patients with Type 1 Diabetes require insulin administration for life. While Type 1 Diabetes can occur at any age, it usually presents in children or teens with symptoms such as extreme thirst, frequent urination, and weight loss. In most instances, insulin-dependent diabetes occurs with a background of genetic susceptibility to the disease but is precipitated by altered immune responses and/or environmental stressors. About 10% of all patients with diabetes have insulin-dependent diabetes. As the name of the disorder suggests, most Type 1 Diabetes patients require daily insulin injections in order to live.

Type 1 Diabetes is characterized by *very low or virtually absent* insulin production.

The other 90% of diabetes patients have **non-insulin dependent diabetes mellitus (Type 2 Diabetes)**. Type 2 Diabetes usually occurs in individuals over the age of 40, is often without symptoms in its early stages, and may go undiagnosed for years (average is 7 years). In contrast to insulin-dependent diabetes, non-insulin dependent diabetes is a consequence of the body's cells using insulin inefficiently. Such individuals are not diabetic while blood glucose levels remain normal. The cells are said to be "resistant" to the effects of insulin. When this happens, the body compensates by producing a greater-than-normal amount of insulin. As a result of this compensation, the individual avoids having elevated blood glucose levels even though his or her body's cells have become "insulin resistant." However, the pancreas can only continue this increased insulin secretion for a limited number of years. Eventually the pancreatic beta cells (insulin-secreting cells) lose their ability to maintain adequately high levels of insulin. As the pancreas beta cells fail, insulin levels begin to fall below the supernormal values, and glucose levels begin to rise above normal. As the glucose levels rise above normal and the pancreas is no longer able to compensate by producing more insulin, persistent hyperglycemia develops, and Type 2 Diabetes can be diagnosed when glucose crosses diagnostic thresholds. This high glucose may occur even when measured insulin is in the normal range, because the cells are inefficient in their insulin use.

Type 2 Diabetes is characterized by the body's cells using insulin *inefficiently*.

Type 1 Diabetes vs Type 2 Diabetes

	Type 1 Diabetes	Type 2 Diabetes
Onset	Sudden onset usually before age 30 but may occur at any age	Gradual onset usually after age 40 but increasing incidence in adolescents
Symptoms at onset	Excessive thirst, hunger, and urination; weight loss; fatigue; nausea/vomiting; sweet breath; frequent/recurring infections	Often mild or no symptoms early; blurred vision, frequent urination; cuts/bruises slow to heal; tingling/numbness in hands/feet
Possible causes	Immune mediated, viral, or environmental causes	Not known, but family history and other risk factors are known
Level of insulin deficiency	Absolute insulin deficiency	Inefficient insulin use and insufficient compensatory rise in insulin level

Blood glucose levels

The diagnosis for hyperglycemia or diabetes centers on measurements of blood glucose. The measurements depend on the method of measurement, which can depend on the testing situation. It is extremely important that plasma glucose levels be interpreted within the context of the testing situation. The fasting plasma glucose (FPG) is the preferred method of measurement. The random plasma glucose is also a reliable method, but is not preferred over the fasting plasma glucose due to its limitations, which are described below. The other two tests mentioned below are not as commonly used.

- **Fasting plasma glucose (FPG)** – collected from a patient who has no caloric intake for at least 8 hours. This is the preferred method of evaluating blood glucose levels because it eliminates high measurements that may result from a patient's eating patterns, thereby allowing a more "standardized" comparison to published normal ranges. Once one abnormal result is obtained, this test is repeated before an actual diagnosis of diabetes is made.
- **Random plasma glucose** – collected any time of the day independent of when or what the individual last ate. Unfortunately, this measurement may not accurately reflect normal plasma glucose—if the patient recently ate a meal that he or she doesn't normally eat, such as a McDonald's Big Mac, this particular measurement may not be as reflective of the normal plasma glucose level as compared to a fasting plasma glucose measurement. Clearly, this test has some limitations. However, depending on the patient's situation, it may be the best alternative (patient is unable to fast for 8 hours, etc). This is the measurement that we have in our clinical database.
- **2-hour oral glucose tolerance test (OGTT)** – collected two hours after the patient consumes an oral drink "loaded" with glucose. The OGTT is inconvenient and uses more medical resources, so this method is not recommended for routine diagnosis of diabetes.
- **Hemoglobin A_{1c} test** *(sometimes called "glycosylated hemoglobin")* – abnormally high amounts of hemoglobin A_{1c} are produced when plasma glucose is high. As turnover of hemoglobin A_{1c} is relatively slow, it is used to estimate severity of glucose elevation over several weeks. This measurement thereby gives a more longitudinal view than a single measurement of glucose itself. However, it is not currently recommended for the diagnosis of diabetes, and is more helpful in evaluating glucose control in patients with known diabetes.

Defining diabetes by blood glucose levels

The chart below lists the blood glucose levels that may suggest the presence of hyperglycemia or diabetes.[1]

Measurement	Diabetes	Impaired Glucose Tolerance (IGT)	Normal
Random glucose	≥ 200 mg/dl	160-200 mg/dl	<160 mg/dl
Fasting glucose	≥ 126 mg/dl	110-126 mg/dl	<110 mg/dl

It is important to understand that these numbers are arbitrary, as is blood pressure for example. It is not as though 127 mg/dl is significantly different from 125 mg/dl. However, if a patient has two different levels of blood sugars while fasting on two different occasions and both measurements are over 125 mg/dl, then that person would be diagnosed with diabetes. This is an important point, as the **diagnosis of diabetes requires several fasting measurements above 126 mg/dl**, as will be explained in greater detail later.

Impaired Glucose Tolerance (IGT): These criteria also recognize a group of patients who are hyperglycemic (have fasting glucose that is higher than the normal values of 110 mg/dl), but do not meet the criteria for a diagnosis of diabetes. Patients whose glucose values fall between "normal" and "diabetic" are said to have Impaired Glucose Tolerance (IGT) or Impaired Fasting Glucose (IFG). This is an important classification for several reasons. First, it is important to note that IGT and IFG are not clinical entities but rather risk factors for future diabetes and cardiovascular disease.[4] Patients with IGT do not necessarily progress to diabetes, and some patients with IGT revert to normal with appropriate diet and exercise. Whereas an estimated 16 million Americans have diabetes, an estimated 21 million Americans have IGT. And at least 35-40 % of these will go on to develop diabetes.[5] This means that 7 % of the population, or 1 out of 12 individuals, is at high risk for developing diabetes.[6]

Complications of diabetes and hyperglycemia

Remember, just because a person has hyperglycemia does not mean that he or she necessarily has diabetes. However, patients with diabetes do have hyperglycemia, but they also have other metabolic problems, such as elevated cholesterol and triglycerides. From a diagnostic perspective, though, it's really the severity of hyperglycemia that matters, not levels of fat or protein. Diabetes also begins to negatively affect many parts of the body.

Diabetes can lead to a number of long-term complications. While precise mechanisms remain unknown, glucose elevation appears to play a key role. Controlling hyperglycemia, in other words, keeping the blood glucose as close to normal as possible, can prevent or delay many diabetes complications. The main types of complications brought about by diabetes are listed below.[7]

- **Retinopathy** causes the deterioration of the retina, which can lead to blindness; if detected and treated early, retinopathy can be prevented or delayed. Research indicates that the risk for retinopathy can be reduced through good glucose control.
- **Nephropathy** is a kidney disease that, left unchecked, can lead to kidney failure requiring renal dialysis or kidney transplant.
- **Peripheral neuropathy**, damage to sensory nerves in the extremities, may cause patients to be unaware that they've been cut or have an infection; hence, this kind of neuropathy increases the risk of more serious infections. Peripheral neuropathy often leads to amputations because infections of the feet or legs can become advanced before the patient realizes there's a problem (and because damage to blood vessels impairs healing). Diabetes is the leading cause of nontraumatic amputations in the US.
- **Autonomic neuropathy**, damage to nerves in autonomic systems, impairs the "automatic" functions of the internal organs. Difficulty in emptying the stomach, the bladder, or obtaining or maintaining an erection may result.
- **Other microvascular complications** may include disease of the arteries/veins in the heart, extremities, and brain. A thickening of blood vessel walls and arteriosclerosis, a lipid buildup that clogs arteries, can lead to heart attack and stroke. Of patients with diabetes, 80% will die from a cardiac event.

While the above complications accrue due to long-term effects of hyperglycemia and are usually progressive, there are three other types of acute diabetic complications due to imbalance of glucose and insulin. These potentially severe "metabolic" complications are usually both treatable and preventable.

Scientific Background

- **Hyperosmolar coma** is usually a complication of Type 2 Diabetes. Patients become abnormally drowsy and symptoms can progress to coma. Very high blood glucose and dehydration are responsible for the symptoms. Above a certain plasma glucose level (approximately 180 mg/dl), the kidneys cannot fully prevent glucose from "spilling" into the urine. This glucose pulls more water into the urine by osmotic force. Consequently, increased urination and compensatory increased thirst are common symptoms of hyperglycemia. These symptoms worsen as the blood sugar increases. Patients who are unable to drink enough to keep up with the urinary losses (eg, those who are bedridden) are particularly likely to progress to dehydration and hyperosmolar coma. Hyperosmolar coma is treatable with insulin, fluids, and other supportive measures.
- **Diabetic ketoacidosis** (DKA) is a potentially life-threatening situation. It usually reflects a very severe insulin deficit, so is more common in Type 1 Diabetes. DKA usually presents with gastrointestinal symptoms such as pain or nausea, but can progress to drowsiness and coma. In ketoacidosis, as in diabetic coma, blood sugar is elevated. However, unlike diabetic coma, DKA is characterized by greatly excessive blood levels of ketones. Ketones, derived from the body's fatty acids, are acidic and lower the blood's pH. This upsets electrolyte balance and leads to various potentially serious complications. DKA can be treated with appropriate insulin, fluid, and other supportive measures.
- **Hypoglycemic (insulin) shock** comes from abnormally low plasma glucose, resulting from excessive insulin dosing, or (to a lesser degree) from oral hypoglycemics. Nervous system functioning requires adequate availability of glucose. Patients with low blood sugar may experience headache, irritability, and confusion. In severe cases, this may lead to coma. It is treatable with glucose (for example, from orange juice).

It is becoming increasingly clear that the earlier diabetes is diagnosed and appropriately treated, the better chance the patient will have to delay or prevent its complications. Estimates reflect that the typical patient with Type 2 Diabetes has actually had hyperglycemia for at least 5 years before the diagnosis is made, so it is imperative that efforts to reduce and control glucose levels be made as quickly as possible.

Risk factors

There are several risk factors that either directly cause diabetes or are statistically associated with it. The correlation of a risk factor(s) with development of diabetes is never 100%; usually multiple factors are involved. The greater the number of risk factors present in an individual, the greater the chance the individual will develop diabetes. However, it is important to note that just because a person has some or all of these risk factors, it does NOT mean he/she will develop diabetes. And conversely, some patients with diabetes do not have ANY of these risk factors.

The major risk factors for Type 2 Diabetes include intrinsic factors (factors that a person cannot change) and variable factors (factors that can be managed) [1]

Intrinsic factors include:

- **Family history:** If a person has a parent or sibling who has diabetes, that person's risk of developing Type 2 Diabetes is increased by 40%.
- **Race or ethnic background:** The risk of developing Type 2 Diabetes is 2 to 3 times greater for non-Caucasian Americans.
- **Impaired Glucose Tolerance (IGT) diagnosis:** Those patients with a prior diagnosis of IGT have a greater risk of developing diabetes.
- **Age 45 or greater:** The risk of developing diabetes increases progressively as one ages.
- **Diabetes during pregnancy (gestational diabetes):** Women who become diabetic during pregnancy are 40% more likely later to develop persisting Type 2 Diabetes.

Variable factors include:

- **Dyslipidemia:** Those with abnormal blood cholesterol or trigyceride levels (HDL), or "good" cholesterol levels under 35 mg/dl, and/or a triglyceride level of over 250 mg/dl, have a greater risk of developing Type 2 Diabetes.
- **Hypertension:** Those with high blood pressure have a 20% greater risk of developing Type 2 Diabetes.
- **Obesity (>20% over ideal body weight):** Almost 90% of all people with newly diagnosed Type 2 Diabetes are overweight.[8] In one 20-year study looking at the effects of weight gain over the first 10 years of the incidence of diabetes, the excess incidence of diabetes in those who gained the most weight (over 20 kg) was less than 1% per year more than those who did not have significant weight change. [Ford et al, *Am J Epidemiology*, 146:214-22, 1997.] Obesity increases insulin resistance and contributes to many health problems. Sometimes, losing just 10 pounds can help the body to use insulin better and help bring diabetes under control.
- **Sedentary lifestyle:** Those who exercise or perform some form of increased physical activity 3-4 times per week may decrease their risk of developing Type 2 Diabetes by 40%.

There are a number of other factors that may affect glucose control. For example, excessive alcohol use over a period of many years has been associated with increased risk of Type 2 Diabetes. Also, diets high in fat have been implicated, since those who eat foods high in cholesterol may develop dyslipidemia and increase the risk of developing Type 2 Diabetes. Also, though not as robustly associated with hyperglycemia as the other factors listed above, there is some evidence to suggest that hyperprolactinemia may be associated with elevated glucose levels.

These risk factors are not necessarily causal links, but over time, correlations between one or more of them to diabetes have been observed. For example, weight gain by itself may not contribute to diabetes, but a person who gains weight in the presence of other risk factors may be more likely to get diabetes. In this sense, risk factors help describe the environmental factors that most often work together to produce diabetes. It is prudent that a patient whose history is positive for one or more of these factors be evaluated for the development of diabetes symptoms and/or tested for this condition.

HYPERGLYCEMIA, DIABETES, AND MENTALLY ILL PATIENTS

Now that we have outlined hyperglycemia and diabetes, we need to know how this affects us, our customers, and their patients. Interestingly enough, diabetes is common in patients with serious and persistent mental illness. Below we present data on this subject.

General population data

The number of patients with Type 2 Diabetes in the general population continues to increase at an alarming rate in the US and other developed countries. During the 1990s, the prevalence of Type 2 Diabetes increased by 33% overall, and by 70% among people in their 30s. Currently an estimated 16 million Americans (6 %) have diabetes. As many as one third of the people with the disease, or about 5 million individuals, are undiagnosed.[8] Further, an additional 6.9% of the general population have fasting glucose levels that are above normal, but not high enough to be classified as diabetes.

Serious and Persistent Mental Illness (SPMI) patient data

The rates of Type 2 Diabetes have been reported to be more common in patients with major mood disorders and schizophrenia than the general population, although reasons for this phenomenon remain unclear.

Some studies even show that the rates of diabetes in patients with bipolar disorder or schizophrenia are 2-4 times greater than the general population.[7,10-12]

Commonly, the onset of psychosis precedes the onset of diabetes, but usually the risk of diabetes is determined by factors other than those influencing age at onset and illness chronicity. Studies in the US found comparable rates of diabetes among patients with schizophrenia who were hospitalized or outpatients.[7] Mukherjee and colleagues (1996) had found that approximately one third of young patients with schizophrenia had a positive family history of Type 2 Diabetes.[7]

The relation between bipolar disorder and diabetes is less clear, but these patients seem to be affected in a similar way. As is the case for patients with schizophrenia, the cause of this relationship is unknown. However, Cassidy and colleagues suggest that possible reasons include: a genetic relationship between the disorders, an overlapping disturbance affecting similar regions of the brain, or the effect of psychotropic medications.[13]

Though increased risk is clear in this population, it is not yet clear whether this reflects a biological predisposition in schizophrenia or bipolar disorder or an individual or class effect of antipsychotic drugs. Quite possibly, it is due to a combination of factors.

Ultimately, these analyses support the disproportionately high incidence and rate of hyperglycemia, IGT and diabetes in patients with schizophrenia, including those treated with placebo in clinical trials.

Antipsychotic-induced hyperglycemia/diabetes data

Several psychotropics have been associated with high insulin levels and insulin resistance (eg, chlorpromazine,[14] divalproex[15]). The National Diabetes Data Group listed chlorpromazine, haloperidol, and lithium under drugs that impair glucose tolerance.[1]

Your customers may already have heard the buzz surrounding recent reports suggesting a link between diabetes and clozapine treatment. These reports have stirred up a swarm of speculation suggesting that atypical antipsychotics as a class provoke increased glucose levels or incidence of diabetes at a greater rate than conventional antipsychotics.[16]

Today's clinicians may be unaware that speculation about a link to diabetes similarly implicated conventional antipsychotic drugs, especially phenothiazines, many years ago.

Cases of hyperglycemia have been found and noted in clinical trials with atypicals; in fact, hyperglycemia and diabetes are included as adverse events in the package inserts of most typical antipsychotics and mood stabilizers and all currently approved atypical antipsychotics.[17] Also, since obesity is a risk factor for diabetes; clinicians may be anticipating more hyperglycemia risk among patients with substantial weight gain during treatment.[17,18]

There have been a number of case reports describing new-onset diabetes during treatment with ZYPREXA. Of note, many of the reports of abnormal glucose levels involved patients with other risk factors for developing hyperglycemia including race, obesity before treatment, or personal/family history of diabetes.[16] In particular, of 15 case reports regarding treatment with ZYPREXA, 12 involved patients with a history of obesity.

One factor that may contribute to the higher number of case reports for patients on ZYPREXA as compared with risperidone or other agents could be that physicians may be

more prone to monitor and/or report abnormalities on ZYPREXA due to preconceptions about effects on glucose.

Beyond case reports in the literature, there have been a number of studies implicating ZYPREXA as having higher rates of hyperglycemia or diabetes. Perhaps the best known is the unpublished (so far) work of Dr. Newcomer, who performed a retrospective study looking at hyperglycemia after an oral glucose load in patients on ZYPREXA, risperidone, haloperidol, and clozapine.

While provoking interesting medical research questions, the data has no practical application nor does it make concrete conclusions. Unfortunately, used and misrepresented by Janssen in a number of CME programs and physician programs, Newcomer's data is generating undue concerns and misinformation.

The Newcomer study was restricted by a number of factors. First, the data are quite limited, including <10 patients per group. Second, the study was designed to focus on cognition and was NOT intended to examine hyperglycemia. As such, it did not control for variables such as patient diet or family history of diabetes. Most importantly, assignment to the different drugs was not randomized. Further, these data are not interpretable because of the methodology used to look at glucose levels: instead of a standard, 2-hour glucose test, Dr. Newcomer looked at values at 15, 45, and 75 minutes. Lastly, the glucose levels he used did not meet the criteria for diabetes.

To point out how potentially spurious Dr. Newcomer's findings are, it is instructive to look at a very similar study undertaken by Dr. Prior and colleagues, from Alberta, Canada. Dr. Prior conducted a study to investigate whether patients taking clozapine, risperidone, and ZYPREXA have unusual responses to oral glucose challenges. Unfortunately, this study also had a small sample size, which did not allow proper statistical evaluation (n=28). Like the Newcomer study, patients were not randomly assigned to treatment. However, the results indicated that none of the patients treated with ZYPREXA had abnormal glucose metabolism, 40% of patients treated with risperidone had abnormal results, and 67% of patients treated with clozapine had abnormal results.

Clearly, more robust methodology must be employed to understand the relative incidence of hyperglycemia in patients treated with these various agents. For now, the best available data regarding ZYPREXA comes from Lilly's extensive clinical trial database.

Data from our clinical trial database

The main point of the new sell sheet is this:

> **Patients treated with ZYPREXA had rates of diabetes and hyperglycemia comparable to those in patients treated with risperidone and haloperidol in clinical trials.**

To demonstrate this, we included 2 graphs in the sell sheet that illustrate the incidence of diagnosed treatment-emergent diabetes in longer head-to-head schizophrenia trials. These are actual cases. The first graph depicts 3 pooled 1-year studies of ZYPREXA vs haloperidol, which includes the largest head-to-head study conducted between these two agents. The incidence of treatment-emergent diabetes for patients treated with ZYPREXA was less than 1%, 0.5% to be exact. This amounts to 5 patients out of 927 (mean ZYPREXA exposure = 8 months). The incidence for haloperidol was 0.4% (1 patient out of 261, with a mean haloperidol exposure = 7 months). These data demonstrate that the two agents had comparable rates of diabetes.

The second graph depicts a 6-month study of ZYPREXA vs risperidone in patients with schizophrenia (ie, the Tran study), which again is the largest head-to-head study between these 2 agents. The incidence of treatment-emergent diabetes was 0.6% for both. This corresponds to 1 patient treated with ZYPREXA out of 172 vs 1 risperidone patient out of 167 (mean exposure to

ZYPREXA = 5 months and to risperidone = 4 months). Again, the important point here is that both agents had the same rate of diabetes.

Another way to help address physicians' concerns was to analyze what happened to the patients' random blood glucose levels on ZYPREXA and other agents. During the clinical trials, we saw a relatively small elevation in glucose, on the order of 3.2 mg/dl to 4.6 mg/dl for patients treated with ZYPREXA. (These elevations were examined using a "least squares mean" estimate, which corrrects for baseline variable and dropouts.) To put this in perspective, the average random glucose level at baseline for patients treated with ZYPREXA in these trials was 95 mg/dl to 100 mg/dl. During market research, we found that most physicians were comfortable with this information, and recognized that these elevations in glucose levels were not clinically significant.

Now, we know that the average random blood glucose elevation with ZYPREXA was relatively small, but how did this compare to other agents? We found that there was a non-significant difference compared with risperidone (ZYPREXA was 1.5 mg/dl above haloperidol). The increase with ZYPREXA was 4.3 mg/dl **above** that on haloperidol and 10.1 mg/dl **below** that found with clozapine. Again, most physicians we spoke with during market research felt comfortable with the fact that indeed these agents are comparable. Some were even pleasantly surprised.

To determine the likelihood of a patient experiencing random blood glucose elevations, we looked at elevations above 4 different thresholds based on random blood glucose measurements—elevations above 126, 140, 160, and 200 mg/dl. The data show that there were comparable estimated rates of hyperglycemia across all treatments studied, with a total of 2850 patients included in the analysis. What this re-emphasized to physicians was that, regardless of the level of increase in blood glucose, all agents showed similar effects.

These data were positively received by most of the physicians we spoke with during market research. However, some brought up the fact that they associate weight gain with increased risk for hyperglycemia. Clearly, we must understand and be able to explain why ZYPREXA contributes to more weight gain than, for example, risperidone and haloperidol and yet rates of hyperglycemia are comparable.

What we are trying to communicate is this: in the context of these studies, substantial weight gain (>10% from baseline weight), was associated in most comparisons with some increase in risk of a glycemic event. However, the magnitude of this excess risk was consistently less than 1%, not enough to lead to clinically significant between-treatment differences in categorical risk. This likely reflects (a) weight gain did not occur exclusively within the ZYPREXA group; (b) even among those with substantial weight gain, the great majority did not have a glycemic event in the course of these observations; and (c) as there are many known (and probably unknown) factors beside weight impacting glucose regulation, glycemic events also occurred in the group without substantial weight increase.

So, the majority of patients (79%) who did have an episode of hyperglycemia (random glucose elevations above 150 mg/dl), did NOT experience substantial weight gain. Furthermore, of those patients who did experience substantial weight gain, over 95% had no glycemic abnormalities at all. So, while obesity is a risk factor for diabetes, differences in weight across the various treatment groups did not result in different rates of diabetes or hyperglycemia across these agents.

The dataset and analysis that we are presenting are far bigger than any other clinical trial on the topic. However, like all analyses, there are some limitations. Keep in mind that the clinical trial database was designed to study the efficacy of ZYPREXA for psychiatric disorders and NOT to look specifically at glycemic effects. Therefore, these studies did not require fasting blood samples (which probably would have been hard to obtain in long-term schizophrenia trials, even if we had so intended).

As discussed earlier, random plasma glucose is not the usual tool for diagnosing diabetes, and some elevations may be "false positives." The Lilly investigators dealt with this by defining cases by any of 3 criteria: elevation of 2 consecutive levels above the threshold; elevation of the last level above the threshold; or prescribing of an antidiabetic medication. They also sought to characterize effects at a variety of thresholds. Of course, the higher the threshold the fewer the number of cases, and the lower the power to detect differences. For example, in the ZYPREXA-risperidone trial at the 200 threshold, there were just 2 cases on ZYPREXA and one on risperidone. There may or may not prove to be significant differences in risk of crossing glucose in extremely large databases. However, it is reassuring that there were not significant differences in this very large dataset, suggesting that it is unlikely an individual physician would observe a statistically or clinically significant difference in practice.

Finally, despite the fact that we cannot completely answer what happens to patients' glycemic levels over the long term (the maximum duration of these trials was 1 year), this analysis is based on a randomized data set that is bigger and longer than any other results available to date.

But what about Depakote and lithium?

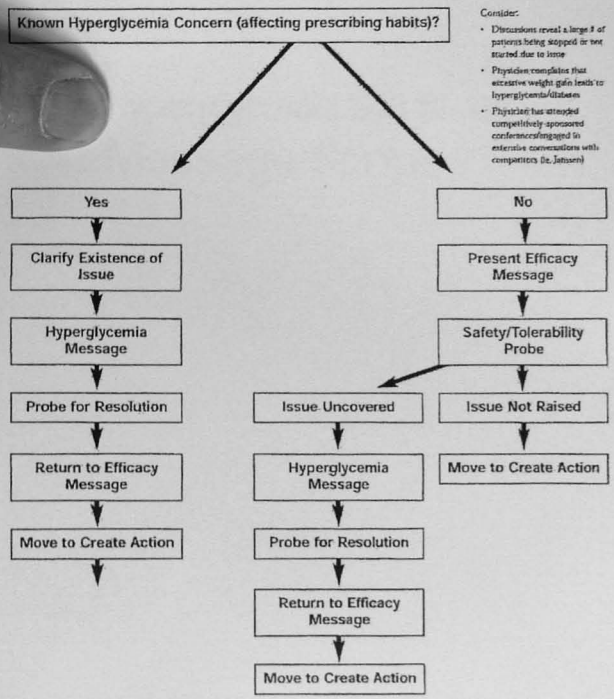
We do not have longer term head-to-head data comparing hyperglycemia rates of ZYPREXA vs Depakote or lithium. However, there have been case reports of patients treated with Depakote who have experienced changes in glucose control, mainly as a factor of weight gain.[18] Likewise, lithium also has been associated with changes in glucose regulation, again, mainly as a factor of weight gain.[19] Lithium's effects on glucose metabolism have been reported as early as the late 1960s, with some studies finding increases in fasting glucose shortly after administration of lithium.[21]

In the 3-week HGHQ study comparing ZYPREXA with Depakote, we did not see significant differences in glucose levels. Of course, one would not expect to see differences given the relatively short duration of the trial. Nevertheless, in Abbott's 12-week comparative study of ZYPREXA and Depakote, no significant difference in glucose levels was reported.

We have given you a tremendous amount of information on diabetes and hyperglycemia, and the incidence of these two conditions with ZYPREXA and our major competitors. We hope that you will be able to take this information and use it in the manner that we will outline in the next sections of this Resource Guide.

MESSAGE ALGORITHM

When and High-level Implementation Hows



Hyperglycemia Sell Sheet
Message Script

MESSAGE SCRIPT

First, clarify the objection:

Doctor, help me understand your concern. Also, please help me understand the basis for your concern. If we can effectively address this concern, can I share some new information with you on the largest head-to-head study ever done between two mood stabilizers…or some new information about how ZYPREXA offers patients a better chance to achieve REINTEGRATION and stay there?

High Ground Opener

I understand that this is an issue of potential concern, and there is certainly a lot of noise from pharmaceutical firms on this issue. This question deserves some dialogue and to have large/controlled data brought to bear. Lilly wants to continue to be forthcoming in addressing this topic. This new information I have today is important in that it comes from the large, randomized, double-blind, controlled data within Lilly's clinical database.

There are two main points that I want you to walk away with. The first is that in this head-to-head data, incidence of diagnosed treatment-emergent diabetes was comparable between ZYPREXA and risperidone and also between ZYPREXA and haloperidol. The second point I want you to walk away with is that incidence of increased random blood glucose is also comparable across these 3 treatment groups. Let's take a closer look at this information.

Core Message

The first graph is from 3 year-long studies of ZYPREXA vs haloperidol with over 2,000 patients, which includes, in fact, the largest head-to-head study ever done between these two agents. The incidence of treatment-emergent diabetes, that is, diabetes diagnosed during the clinical trial, was less than 1% for each agent. Notice that the same holds true in a six-month study comparing ZYPREXA to risperidone, which, again, was the largest head-to-head study between these two agents. In this case, the incidence of treatment-emergent diabetes was 0.6% for both ZYPREXA and risperidone.

PROBE: Are you surprised by this? Any comments or questions? (wait for the answer)

Another way to look at this is to compare what happened to the patients' random blood glucose levels on ZYPREXA with these other treatments. On ZYPREXA, across all patients, we see a relatively small elevation in glucose, on the order of 3.2 mg/dl to 4.6 mg/dl. To put this in perspective, the average random glucose level at baseline for patients treated with ZYPREXA in these trials was 95 mg/dl to 100 mg/dl.

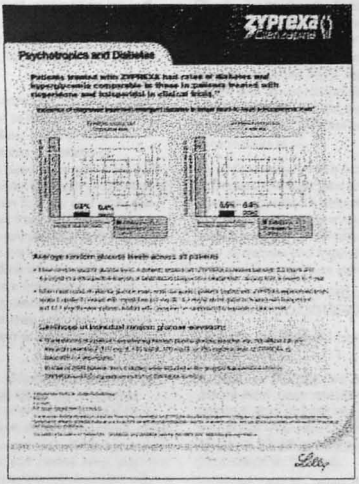
PROBE: Do you consider this to be clinically significant?

When looking at how this small increase might compare with changes seen on other agents, we found that changes on ZYPREXA were very similar to changes on risperidone (a difference of >2 mg/dl). Also, the small increase of ZYPREXA was 4.3 mg/dl **above** that on haloperidol, and it was 10.1 mg/dl **below** that on clozapine.

We found comparable rates of diabetes, and saw some small increases in average random glucose levels. We delved deeper into the relative rates of hyperglycemia between these agents. To do this, we looked at the likelihood of blood glucose elevations above four different thresholds based on random blood glucose measurements—elevations above 126, 140, 160, and 200 mg/dl. What the data shows is that across treatment groups, there were again comparable rates of hyperglycemia at each of these thresholds.

PROBE: Do you find this surprising? Or comforting? How does this data affect the way you think about this issue? (wait for answer)

IF THIS ADDRESSES THE MD's QUESTIONS, collect the chip for a concern answered and get back to a sense of joint discovery with the efficacy-oriented discussion.



Notes

For your information ONLY; not for use in detailing.

Zyprexa Olanzapine

If physician still has concerns based on weight gain, (ie, "but ZYPREXA has more weight gain, and I know weight gain can cause diabetes") then continue on.

Considering the contributing factors to incidence of diabetes, we ought to look at the general population as a baseline. In the general population, the incidence of diabetes or abnormally elevated blood glucose is about 15%. Now, other studies show that with the persistently mentally ill population that you deal with, that rate may be anywhere from 2 to 4 times higher. So, in your practice, you should not be surprised to find patients who are having elevations in blood glucose regardless of choice of agent. Clearly, while there are comparable rates of diabetes and hyperglycemia in patients taking these various medications, Lilly does not want to minimize the extent or seriousness of this common illness.

Now, there are a lot of factors, independent of treatment choice, that affect risk of diabetes. There are a number of intrinsic factors such as family history, age, and ethnic background. Other factors that may be more controllable by a patient include exercise, diet, and obesity. Also, excessive alcohol use, hyperprolactinemia, and diets high in lipids have been implicated in higher levels of blood glucose. Clearly, this is not as simple as saying the presence of one factor means a patient will get diabetes. In fact, you may have patients who have all of these risk factors and do not develop diabetes, and conversely you may have patients diagnosed with diabetes who have none of these risk factors.

PROBE: Any questions? What are your thoughts? How does this information, in the context of the overall efficacy of ZYPREXA, impact your selection of a mood stabilizer? (Wait for answer.)

(If needed—eg, the physician is looking for an explanation of how ZYPREXA can have more weight gain and yet have comparable rates of diabetes/hyperglycemia)

Clearly, obesity is a risk factor for diabetes, but it is one of many that may increase a patient's risk for diabetes. The majority of patients—in fact about 79%—who did have an episode of hyperglycemia, did NOT experience substantial weight gain in our clinical studies. Furthermore, of those patients who did experience substantial weight gain, over 95% had no glycemic abnormalities at all.

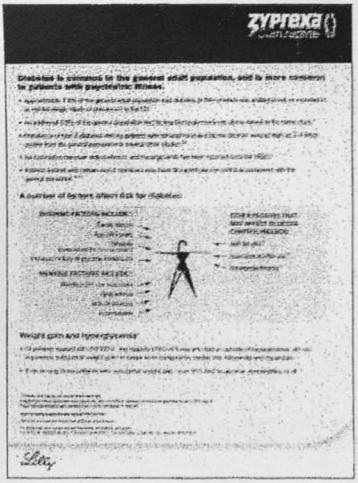
So while obesity is a risk factor for diabetes, differences in weight gain across the various treatment groups did not result in different rates of diabetes or hyperglycemia across these agents. In fact, large controlled data demonstrate that rates of diabetes and hyperglycemia are comparable across these agents.

Frame in terms of efficacy, GET BACK TO JOINT DISCOVERY!

Does this information I have provided address your concern?

If "Yes"— Doctor, we have just talked about how your choices are comparable in one respect. Now, let me show you how ZYPREXA stands alone in its broad-spectrum efficacy. (Get back to selling)

If "No"—Probe deeper to expose where concern still exists.



Notes

ZYPREXA Olanzapine

Q&A

During your sales calls, you may encounter other kinds of questions surrounding hyperglycemia and/or diabetes. Use the verbatims below as answers, then, as always, refocus on your Selling Message.

How can you be comparable in rates of hyperglycemia to other agents when you cause more weight gain, and significant weight gain is a risk factor for diabetes?

In fact, we have examined Lilly's large database of prospectively, randomly assigned patients in longer-term trials. In these trials, weight gain was not found exclusively on ZYPREXA treated patients, although it is no doubt more common in ZYPREXA treated patients.

Clearly, obesity is a risk factor for diabetes, but it is one of many that may increase a patient's risk for diabetes. The majority of patients—in fact about 79%—who did have an episode of hyperglycemia, defined as random glucose levels above 160 mg/dl, did NOT experience substantial weight gain (defined as an increase of 10% or more from baseline).

Furthermore, of those patients who did experience substantial weight gain, over 95% had no glycemic abnormalities at all (again, defined as random glucose levels above 160 mg/dl).

So while obesity is a risk factor for diabetes, differences in weight gain across the various therapies in our head-to-head database did not result in different rates of diabetes or hyperglycemia.

How do you explain the Newcomer data?

The data from the Newcomer study raise a question pertaining to relative impact of the various agents on hyperglycemia. It is not consistent with other data presented in the work described here. When reviewing the study, several limitations became apparent:

- It was a retrospective study designed to look at cognition, not hyperglycemia.
- The study was grossly underpowered (about 8 patients in each group).
- The original study was not controlled—there was no distinction made due to intrinsic risk factors (family history, gender, etc), nor was the patients' behavior monitored (diet, exercise, etc). Most importantly, assignment to the different drugs was not random.
- These findings are not readily interpretable because standard 2-hour glucose levels were not taken. You cannot rely on glucose levels taken before 90 minutes (Dr. Newcomer took levels at 15, 45, and 75 minutes).
- The glucose levels in the study (even with all other limitations) do not meet the criteria for diabetes.

Does ZYPREXA affect risk factors other than weight gain?

That's an excellent question, since there are many factors that impact a person's chance of developing diabetes. Some of these are intrinsic and cannot be impacted by lifestyle or any agent (such as genetic risk, age, gender, etc). In terms of the variable factors like prolactin, ZYPREXA does not appear to have an effect that might increase the risk of diabetes. In addition, we have not seen any effects of ZYPREXA on other factors such as hypertension or dyslipidemia. Regarding various lifestyle factors (lack of exercise, excessive alcohol intake, etc), these factors may improve to the degree that a patient experiences efficacy from ZYPREXA, potentially improving their risk profile.

What does Lilly's database say about the rates of diabetes with other agents (such as Seroquel, Depakote, Clozaril, or Zeldox)?

- The one other large head-to-head, long-term database we have beyond risperidone and haloperidol is versus clozapine. Those data demonstrate that ZYPREXA is much safer in this respect vs clozapine.
- In terms of other mood stabilizers, although the HGHQ head-to-head data vs Depakote has the limitation of being relatively short-term, there was no significant difference in changes in average random glucose levels and none of the 251 patients on either drug developed treatment-emergent hyperglycemia or diabetes.
- In addition, we know from case reports that hyperglycemia and/or diabetes has been reported with virtually all psychotropics (including lithium, quetiapine, risperidone, and clozapine).
- Lastly, it is too early to tell what the true efficacy or side effect profile of ziprasidone may be.

I know that the structure of ZYPREXA is close to that of clozapine. How is it that clozapine has this problem and ZYPREXA does not?

- It is correct that the two compounds are structurally similar. ZYPREXA was derived from clozapine, but with changes in the molecule which were specifically designed to preserve efficacy and remove toxicity.
- In regards to hyperglycemia, as with agranulocytosis, it looks like the changes worked.

Is there a direct effect of ZYPREXA on diabetes?

We've gone back through and looked for evidence both preclinically and in our clinical comparison trials--with other antipsychotics and mood stabilizers to determine whether or not ZYPREXA directly interferes with insulin release or insulin activity and have not found a direct effect. Specifically:

- We have examined our longer-term preclinical animal studies and have not found any changes in insulin release or changes to the pancreas.
- We also looked to determine if there were higher rates of diabetes versus comparator drugs in clinical studies. If there was a direct effect, you would expect to find much higher rates of diabetes with ZYPREXA, probably in the first weeks or months of therapy. In fact, our head-to-head clinical trials show comparable rates of diabetes or hyperglycemia to haloperidol or risperidone.
- We are continuing to investigate these questions quite carefully.

Does ZYPREXA cause Type 1 Diabetes?

We do know that there are patients, independent of the agent they are on (or they may not be on any agent at all) who develop insulin-dependent diabetes. Since diabetes will develop in the general population, the specific question relates to whether ZYPREXA patients develop insulin-dependent diabetes at a rate higher than the general population. In our controlled comparative clinical trials, rates of developing Type 1 Diabetes are not higher on ZYPREXA than on haloperidol or risperidone. We have gone back to our longer-term preclinical animal studies and have not found any changes to insulin release or changes to the pancreas.

How is this different from what you were telling me over the last few months?

It is consistent with what we've been saying. What we're telling you about rates on ZYPREXA has not changed at all. What we have done is expand our analyses comparing rates on ZYPREXA to other antipsychotics, which may be more clinically relevant to you. This new data presents the finding of these various analyses, which conclude that the rates of developing diabetes or hyperglycemia are comparable across agents.

Why do I need to monitor blood when you tell me that no blood monitoring is required with ZYPREXA?

The fact is, you do not have to conduct routine blood monitoring of patients on ZYPREXA. The data suggest that if the right factors are present, hyperglycemia can happen with a patient. Accordingly, just like any other concerns you may have relative to a specific patient, regardless of what agent they're taking, you may need to look further. Fortunately, that's likely to be only a relatively small fraction of patients who are taking ZYPREXA and a number comparable to that found with other agents as well.

How does ZYPREXA affect a person who has diabetes? Glucose intolerance?

As with adding any new medication to the regimen of a patient who has hyperglycemia or diabetes, you may want to check to see what effects the medication may have.

The controlled comparisons that showed comparable rates for blood glucose elevations excluded patients with preexisting diabetes. Lilly is currently conducting analyses of patients with diabetes in clinical trials.

Which patients should I be concerned about?

As you begin to treat any patient, the assessment of their general health is a standard and important step. The risk of hyperglycemia and diabetes are two factors within each patient's scope of overall health that should be considered (along with mental health, lifestyle, etc).

Specific to hyperglycemia and irrespective of disease state and agent used, there may be some people who are inherently at a higher risk relative to other people. They are as follows:

- Clearly, the group of Pima Indians within your practice deserve some special attention since we all know that their risk of developing hyperglycemia is far higher than that of the general (and mental health) population
- Patients who have a number of risk factors (intrinsic and variable)
- Patients who have poor glucose control to begin with
- Patients with extreme weight gain (regardless of source)

MATERIALS AVAILABLE

In addition to the Hyperglycemia Sell Sheet, you may find these other resources helpful when addressing this question with your physicians.

Enduring Materials:

November 2000 PsychLink

January 2001 Provision

Educational Resources:

NTTP educational resources related to healthy lifestyles

Local partners trained in delivering the message of NTTP

Websites:

www.diabetes.org
(official website of the ADA)

www.lillydiabetes.com
(Lilly-sponsored website on diabetes)

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ZYPREXA – Primary Care
Strategy and Implementation Overview

Background: 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 targets. Key decisions included: Launch will occur in October 2000, promotion will handled via the Primary Care – Neuroscience sales sleeve (510 reps), and funding in 2000 would be incremental to existing brand opex.

Current situation: PCPs account for about 18 % of all retail antipsychotic prescriptions. Risperdal holds a 29 share, compared to 18 for Zyprexa. Typical agents, such as Haldol, account for another 40+ percent. Nearly half of all PCP antipsychotic prescriptions go to patients age 65+.

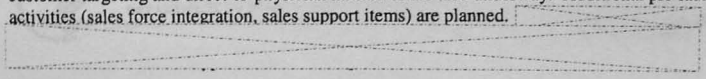
Opportunities: We believe there to be significant unmet medical need among office-based primary care physicians (PCPs). This customer group is huge (>250,000 prescribers, ~ 59,000 are key targets) and its potential in this arena is virtually untapped. By targeting the top deciles, we can maximize return while building a strong clinical foundation. Zyprexa's profile is ideal for primary care (safe, simple, well-tolerated, effective, versatile). Zyprexa would enjoy first mover advantage in this segment, pre-empting Janssen (Risperdal), Abbott (Depakote) and Pfizer (Zeldox). Historically, Zyprexa has closed market share gaps in every segment in which we've actively competed.

Challenges: 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 PCP's 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. Face-to-face sales time with PCPs is very limited. There is some concern that brand image will be diluted.

Position: Zyprexa: The safe, proven solution in mood, thought and behavior disorders
We will emphasize safety to address barriers to adoption, and merchandise the brand's "Four years – Four million patients" base of experience. The word "solution" speaks to unmet medical need, and enables the PCP to take control of clinical situations that previously had led to referrals and/or poor outcomes. "Mental disorders" is intentionally broad and vague, providing latitude to frame the discussion around symptoms and behaviors rather than specific indications. We will position Zyprexa as the incremental next step in the PCP's expanding clinical orbit: e.g., SSRIs => 2nd generation antidepressants => safe, gentle psychotropics.

Strategy: Launch in phases. The launch phase, with its compressed timeline, will focus on a limited # of physicians (10-20K), a clear but lightly tested message, and strong emphases on sales training, peer-to-peer programs (psychiatrists training PCPs) and tight integration with the Neuroscience sales organization. In 2001, the customer list will expand (based on an ROI threshold), materials will be updated to reflect customer feedback (both external and internal), and segment-specific clinical research (outcomes, health economics) will be designed to strengthen Zyprexa's long-term presence in the PCP segment. The Zyprexa-PCP strategy is designed to fit within the brand vision of broad spectrum efficacy.

Implementation: Market research, message development, medical support and the creation of a training calendar is in progress. Logistical details surrounding a proposed single-site launch meeting, sampling considerations, the communications plan, sales metrics and incentives, customer targeting and direct-to-physician initiatives are also underway. Additional pre-launch activities (sales force integration, sales support items) are planned.



Mike Bandick, Brand Manager

August 2000

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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-

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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

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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 8 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

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[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)
- Increase dose cautiously in patients predisposed to hypotensive reactions, hepatic impairment, or with potential for slowed metabolism (2.2)
- 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 Appropriate Letter for information concerning for hyperglycemia cautions.]
- 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 [insert appropriate wording here, 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 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-Parkinsonism – 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 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 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: (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.]

*Sections or subsections omitted from the full prescribing information are not listed.

MAR 9 [illegible]7

G. Brophy

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 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 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 (5.2)) 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 2 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, 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.

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 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 (4.2 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) were observed in 6.3% (31/495) of patients exposed to SYMBYAX compared with 0.5% (3/584) 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 with 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 (5.14)]*.

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 6 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

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

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. 8.5%); 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=1135) 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-Parkinsonian

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, prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QT, prolongation warrants restricting the concurrent use of pimozide and fluoxetine. *[See Contraindications (4)]*.

MAR 2 6 2007

G. Brophy

16

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 (7.25) 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 8 2007

G. Brophy

so 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). n the rabbit, there was no evidence of teratogenicity; however, the high-dose combination produced decreases in fetal weight and etarded skeletal ossification in conjunction with maternal toxicity. Similarly, in the rat there was no evidence of teratogenicity; nowever, 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, nigh-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 (7.1)]*. 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.

.2 **Labor and Delivery**

SYMBYAX — The effect of SYMBYAX on labor and delivery in humans is unknown. Parturition in rats was not affected y 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 lanzapine.

Fluoxetine — The effect of fluoxetine on labor and delivery in humans is unknown. Fluoxetine crosses the placenta; herefore, there is a possibility that fluoxetine may have adverse effects on the newborn.

.3 **Nursing Mothers**

SYMBYAX — There are no adequate and well-controlled studies with SYMBYAX in nursing mothers or infants. Studies valuating the individual components of SYMBYAX (olanzapine and fluoxetine) in nursing mothers are described below. It is not nown whether SYMBYAX is excreted in human milk and because of the potential for serious adverse reactions in nursing infants

on 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 (5.2)]*. 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 3-10 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

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 13 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

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)*.

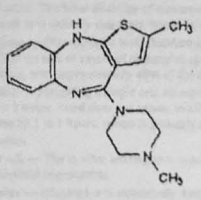
11 DESCRIPTION

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®).

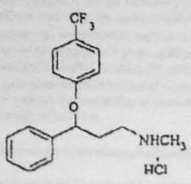
Olanzapine belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44.

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 8 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 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 7.25)]*.

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.

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

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 24 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 cytogenetic 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 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 28 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*
Study 1	SYMBYAX (N=140)	30	-16*
	Olanzapine (N=150)	33	-12
	Placebo (N=151)	31	-10
Study 2	SYMBYAX (N=142)	33	-18*
	Olanzapine (N=169)	33	-14
	Placebo (N=174)	31	-9

*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 3/20 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, 351, 369, respectively,) demonstrated statistically significantly greater reduction in total MADRS scores for SYMBYAX versus fluoxetine (p=0.013, 0.021, 0.105) and or olanzapine alone (p=0.035, 0.003, 0.007) respectively, when analyzed for the samein a 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 (-7.7).

Table 3: MADRS Total Score
Mean Change from Baseline to Endpoint in
Treatment Resistant Depression

MAR 2 9 2007
G. Brophy

27

	Treatment Group	Baseline Mean	Change to Endpoint Mean[1]
Study 1	SYMBYAX (N=92)	30.6	-14.6
	Fluoxetine (N=101)	30.1	-9.0[2]
	Olanzapine (N=102)	30.7	-7.7[2]
Study 2	SYMBYAX (N=10)	29.5	-13.6
	Fluoxetine (N=10)	32.8	-1.3[2]
	Olanzapine (N=9)	25.0	-2.8[2]
Study 3	SYMBYAX (N=163)	30.1	-12.7
	Fluoxetine (N=41)	31.1	-10.0[2]
	Olanzapine (N=42)	31.5	-8.8[2]
Study 4	SYMBYAX (N=91)	29.4	-9.0
	Fluoxetine (N=88)	28.9	-7.0[2]
	Olanzapine (N=90)	28.4	-5.1[2]
Study 5	SYMBYAX (N=101)	29.5	-10.8
	Fluoxetine (N=102)	29.7	-9.4[2]
	Olanzapine (N=95)	29.7	-10.1[2]
Integrated analysis of 5 studies	SYMBYAX (N=462)	29.9	-12.2
	Fluoxetine (N=342)	29.6	-8.5[2]
	Olanzapine (N=342)	29.6	-7.7[2]

[1] Negative number denotes improvement from baseline.
[2] SYMBYAX statistically significant ($p<0.05$) compared to fluoxetine and olanzapine.
[2] 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

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 (5.10) 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 28 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:

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

Eli Lilly and Company
Indianapolis, IN 46285

www.SYMBYAX.com

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/s/

Thomas Laughren
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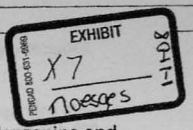


October 5, 2007

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.

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%[a]
		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%[a]
		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%[a]
		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%[a]
		Placebo	9	0%

[a] 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 ≥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

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

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

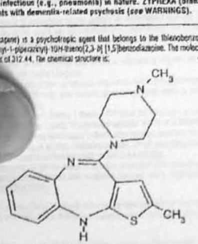
Zyprexa® (olanzapine) is indicated for the short-term and maintenance treatment of schizophrenia. Zyprexa is also indicated as monotherapy or in combination with lithium or valproate for the short-term treatment of acute mixed or manic episodes associated with Bipolar I Disorder and as maintenance treatment 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 psychotropic agent that 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. 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 (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 $5HT_{2A/2C}$, $5HT_6$ (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 48 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 93% 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 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 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 (Childs 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 elderly (>65 years) than in non-elderly subjects (<65 years). Caution should be used in dosing the elderly, especially if there are other factors 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 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 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. Relapse 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 two diagnostic groups: schizophrenia and Bipolar I Disorder (manic or mixed episodes). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam 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 five items comprising 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 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 IM treatment periods; 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.

...putative subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these

...SAGE: Schizophrenia—Oral ZYPREXA is indicated for the treatment of schizophrenia.
...YPREXA was established in short-term (6-week) controlled trials of schizophrenic inpatients (see CLINICAL

...t of oral ZYPREXA at maintaining a treatment response in schizophrenic patients who had been stable on ZYPREXA ...weeks and were then followed for a period of up to 6 months has been demonstrated in a placebo-controlled trial ...EFICACY DATA). Nevertheless, the physician who elects to use ZYPREXA for extended periods should periodically ...g-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).
...te—Acute Monotherapy—Oral ZYPREXA is indicated for the treatment of acute mixed or manic episodes associated ...tolar.

...of ZYPREXA was established in two placebo-controlled trials (one 3-week and one 4-week) with patients meeting ...for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features ...FICACY DATA).
...Monotherapy—The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA after achieving a ...es for an average duration of two weeks was demonstrated in a controlled trial (see CLINICAL EFFICACY DATA). The ...ients to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for ...atient (see DOSAGE AND ADMINISTRATION).
...h Olanzap—The combination of oral ZYPREXA with lithium or valproate is indicated for the short-term treatment of ...manic episodes associated with Bipolar I Disorder.
...y of ZYPREXA IntraMuscular for the treatment of agitation associated with schizophrenia and Bipolar I mania was ...in 3 short-term (24 hours) placebo-controlled trials in agitated inpatients with schizophrenia or Bipolar I Disorder (manic ...isodes) (see CLINICAL EFFICACY DATA).

...DICATIONS: ZYPREXA is contraindicated in patients with a known hypersensitivity to the product.
...ific information about the contraindications of failure or valproate, refer to the CONTRAINDICATIONS section of the package ...these other products.

...S: Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis ...th atypical antipsychotic drugs are at an increased risk of death compared to placebo. ZYPREXA is not approved for the ...of patients with dementia-related psychosis (see BOX WARNING).
...ree controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated ...as significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).
...rovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis—Cerebrovascular adverse ...g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients ...ntia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events ...ts treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of ...with dementia-related psychosis.
...rglycemia—Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been ...d in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical ...otide use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in ...with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the ...ship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, ...iological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated ...e atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and ...ses in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other ...d antipsychotics.
...an increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase I ...Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting ...es) from baseline to the average of the two highest serum concentrations was 12.0 mg/dL.
...matic Monotherapy in Adults—In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with treatment ...ion up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo ...mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with ...ence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse events, patients treated ...anti-diabetic agents, patients with a baseline random glucose level ≥200 mg/dL, and/or a baseline fasting glucose level ...5 mg/dL). These patients had a statistically significantly greater mean increase in HbA_{1c} compared to placebo. In patients with ...line normal fasting glucose levels (<100 mg/dL), 2.2% (N=642) of those treated with olanzapine were found to have high glucose ...ls (≥126 mg/dL) during olanzapine treatment versus 0.4% (N=283) of those treated with placebo. In patients with baseline ...erline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 7.2% (N=178) of those treated with olanzapine were found to have ...h glucose levels (≥126 mg/dL) during olanzapine treatment versus 1.9% (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 ...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 ...nificantly greater mean change in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.99 mg/dL). In patients ...h baseline normal fasting glucose levels (<100 mg/dL), zero out of 124 (0%) of those treated with olanzapine were found to have high ...ose levels (≥126 mg/dL) during olanzapine treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline ...derline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 2 out of 14 (14.3%) of those treated with olanzapine were found ...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 ...ellitus, or having borderline increased blood glucose level (fasting 100–126 mg/dL, non-fasting 140–200 mg/dL). Patients taking ...lanzapine should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, ...mily history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the ...eginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored ...r symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms ...f 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 triglycerides 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, 3.9 mg/dL, and 20.8 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 ...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	29.6%*
		Placebo	462	26.1%
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Olanzapine	457	9.2%*
		Placebo	261	4.4%
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	136	39.3%*
		Placebo	65	29.0%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.6%*
		Placebo	462	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	178	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	36.9%*
		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 2.5 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=2870) (%)	6 Months (N=1536) (%)	12 Months (N=778) (%)	24 Months (N=427) (%)
≥0	27	21	20	22
0-5 (0-11 lb)	57	34	25	22
5-10 (11-22 lb)	15	26	23	22
10-15 (22-33 lb)	2	12	16	18
>15 (>33 lb)	0	5	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 4.8 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; 48.8% 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 11 kg.

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (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.

luation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases sentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or xtrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include toxicity, heat stroke, drug fever, and primary central nervous system pathology.

of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential y, 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious which specific treatments are available. There is no general agreement about specific pharmacological treatment

s antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be The patient should be carefully monitored, since recurrences of NMS have been reported.

a—A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is pon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop ther antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

oping tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can much less commonly, after relatively brief treatment periods at low doses.

wn treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, atment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has n course of the syndrome is unknown.

nsiderations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive ic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is l to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are ppropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment actory clinical response should be sought. The need for continued treatment should be reassessed periodically.

ymptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. atients may require treatment with olanzapine despite the presence of the syndrome.

formation about the warnings of lithium or valproate, refer to the WARNINGS section of the package inserts for these

General—Hemodynamic Effects—Olanzapine may induce orthostatic hypotension associated with dizziness, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic perties. Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in non-agitated patients with which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three ministered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in essure (i.e., decrease ≥30 mmHg) (see DOSAGE AND ADMINISTRATION). Syncope was reported in 0.6% (15/2500) ated patients in phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation cular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine otension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the events amuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and y be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain tropic drugs.

apine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg (se AD ADMINISTRATION). A more gradual titration to the target dose should be considered if hypotension occurs.

cular olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation.

ould be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to ehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, and/or bradycardia might put the patient at increased medical risk.

cessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, ntral nervous system depression (see Drug Interactions). Concomitant administration of intramuscular olanzapine and odiazepine has not been studied and is therefore not recommended. If use of intramuscular olanzapine in combination benzodiazepines is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory commended.

During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were ctors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used atients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's tions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

tinemia—As with other drugs that antagonize dopamine D_2 receptors, olanzapine elevates prolactin levels, and a n persists during chronic administration. Tissue culture experiments indicate that approximately one third of human are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in reviously detected breast cancer of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is ost patients. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia n the olanzapine carcinogenicity studies conducted in mice and rats (see Carcinogenesis). However, neither clinical demiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis available evidence is considered too limited to be conclusive.

e Elevations—In placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of ge) were observed in 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. patients experienced jaundice. In two of these patients, liver enzymes decreased toward normal despite continued n two others, enzymes decreased upon discontinuation of olanzapine. In the remaining two patients, one, seropositive had persistent enzyme elevation for four months after discontinuation, and the other had insufficient follow-up to zymes normalized.

arger premarketing database of about 2400 patients with baseline SGPT ≤90 IU/L, the incidence of SGPT elevation was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver most had transient changes that tended to normalize while olanzapine treatment was continued.

) patients in oral olanzapine clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases.

arketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been postmarketing period.

uld be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic transaminases is recommended in patients with significant hepatic disease (see Laboratory Tests).

Cognitive and Motor Impairment—Somnolence was a commonly reported adverse event associated with olanzapine rring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse event was also omnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

apine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

erature Regulation—Disruption of the body's ability to reduce core body temperature has been attributed to gents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant h anticholinergic activity, or being subject to dehydration.

—Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs cautiously in patients at risk for aspiration pneumonia.

e possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high risk accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent nt management, in order to reduce the risk of overdose.

nts with Concomitant Illness—Clinical experience with olanzapine in patients with certain concomitant systemic enal Impairment and Hepatic Impairment under CLINICAL PHARMACOLOGY, Special Populations) is limited.

exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with olanzapine, olanzapine was associated on, dry mouth, and tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events the basis for discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically static hypertrophy, narrow angle glaucoma, or a history of paralytic ileus.

ebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following rgent adverse events were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater reated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, ia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse events was significantly anzapine 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).

Olanzapine 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 premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients (see Hemodynamic Effects).

For specific information about the precautions of lithium or valproate, refer to the PRECAUTIONS section of the package inserts for these other products.

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe olanzapine:

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.

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 Drug Interactions).

Interference with Cognitive and Motor Performance—Because olanzapine 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 olanzapine therapy does not affect them adversely.

Pregnancy—Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with olanzapine.

Nursing—Patients should be advised not to breast-feed an infant if they are taking olanzapine.

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, since there is a potential for interactions.

Alcohol—Patients should be advised to avoid alcohol while taking olanzapine.

Heat Exposure and Dehydration—Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Phenylketonurics—ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively).

Laboratory Tests—Periodic assessment of transaminases is recommended in patients with significant hepatic disease (see Transaminase Elevations).

Drug Interactions—The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents.

Olanzapine may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Olanzapine—Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 could potentially inhibit olanzapine clearance. 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.

Charcoal—The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

Cimetidine and Antacids—Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Carbamazepine—Carbamazepine therapy (200 mg bid) causes an approximately 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.

Ethanol—Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics.

Fluoxetine—Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended.

Fluvoxamine—Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine Cmax following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

Warfarin—Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics.

Effect of Olanzapine on Other Drugs—In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Lithium—Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium.

Valproate—Studies in vitro 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. In vivo administration of olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam and its active metabolite N-desmethyldiazepam, ethanol, or biperiden. However, the co-administration of either diazepam or ethanol with olanzapine potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

Lorazepam—Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone (see Hemodynamic Effects).

Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenesis—Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily oral dose on a mg/m² basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a mg/m² basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily oral dose on a mg/m² basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily oral dose 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 (2-5 times the maximum recommended human daily oral dose 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 and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the maximum recommended human daily oral dose 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 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 Hyperprolactinemia under PRECAUTIONS, General).

Mutagenesis—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.

Impairment of Fertility—In an oral 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 maximum recommended human daily oral dose 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 maximum recommended human daily oral dose on a mg/m² basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m² basis); therefore olanzapine may produce a delay in ovulation.

Pregnancy—Pregnancy Category C—In oral 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 maximum recommended human daily oral dose on a mg/m² basis, respectively) no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a mg/m² basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a mg/m² basis). In an oral 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 maximum recommended human daily oral dose on a mg/m² basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery—Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery in humans is unknown.

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In a study in lactating, healthy women, olanzapine was secreted in breast milk. Mean infant dose at steady to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving olanzapine should

afety and effectiveness in pediatric patients have not been established.

3 the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (257) were 65 years of age or over. schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in espect to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients ted psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be se presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response ould lead to consideration of a lower starting dose for any geriatric patient (see BOX WARNING, WARNINGS, DWDOSAGE AND ADMINISTRATION).

TIONS. The information below is derived from a clinical trial database for olanzapine consisting of 8651 patients with 1765 patient-years of exposure to oral olanzapine and 722 patients with exposure to intramuscular olanzapine ons database includes: (1) 2500 patients who participated in multiple dose oral olanzapine premarketing trials s and Alzheimer's disease, representing approximately 1122 patient-years of exposure as of February 14, 1995; who participated in oral olanzapine premarketing bipolar mania trials representing approximately 68 patient-years of 81 patients who participated in one intramuscular trial of patients having various psychiatric symptoms in association disease, representing approximately 29 patient-years of exposure; (4) 5788 patients from 88 additional oral olanzapine of December 31, 2001; and (5) 722 patients who participated in intramuscular olanzapine for injection premarketing patients with schizophrenia, Bipolar I Disorder (manic or mixed episodes), or dementia. In addition, information from g 6 week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients d in bipolar mania trials with approximately 22 patient-years of exposure, is included below.

ons and duration of treatment with olanzapine varied greatly and included (in overlapping categories) open-label and ences of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term erse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, ysis, ECGs, chest x-rays, and results of ophthalmoscopic examinations.

ions of the discussion below relating to objective or memoric safety parameters, namely, dose-dependent adverse events, ypes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and s conducted for bipolar mania or agitation. However, this information is also generally applicable to bipolar mania

ents during exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of ossing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing s without first grouping similar types of events into a smaller number of standardized event categories. In the tables s that follow, standard COSTART dictionary terminology has been used initially to classify reported adverse events. frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent t of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while spy following baseline evaluation. The reported events do not include those event terms that were so general as to be . Events listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the events ing treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete g of the safety profile of olanzapine.

ther should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical ly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different ses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating contribution of drug and nondrug factors to the adverse event incidence in the population studied.

of Adverse Events in Short-Term, Placebo-Controlled and Combination Trials—The following findings are based on trials of (1) oral olanzapine for schizophrenia, bipolar mania, a subsequent trial of patients having various psychiatric association with Alzheimer's disease, and premarketing combination trials, and (2) intramuscular olanzapine for injection atients with schizophrenia or bipolar mania.

Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials—Schizophrenia—Overall, difference in the incidence of discontinuation due to adverse events (5% for oral olanzapine vs 4% for placebo). However, tions due to increases in SGPT were considered to be drug related (2% for oral olanzapine vs 0% for placebo) UTIONS).

Mania, Monotherapy—Overall, there was no difference in the incidence of discontinuation due to adverse events (2% for oral vs 2% for placebo).

—Overall, there was no difference in the incidence of discontinuation due to adverse events (0.4% for intramuscular or placebo vs 0% for placebo).

Events Associated with Discontinuation of Treatment in Short-Term Combination Trials—Bipolar Mania Combination e a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to ents were 11% for the combination of oral olanzapine with lithium or valproate compared to 3% for patients who remained or valproate monotherapy. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred n 1 patient were: convulsion (2%), weight gain (1%), and peripheral edema (1%).

ngs Observed Adverse Events in Short-Term, Placebo-Controlled Trials—The most commonly observed adverse events with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo- ients (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)
al hypotension	5	2
ation	9	3
gain	5	1
ss	11	4
ality disorder[1]	8	4
sia	5	1

ality 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)
sis	15	6
outh	22	7
pation	11	5
pain	11	5
ased appetite	6	3
erence	35	13
ness	18	8
ia	8	3

was one adverse event (somnolence) observed at an incidence of 5% or greater among intramuscular olanzapine for treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least of for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24 hour ild period in clinical trials in agitated patients with schizophrenia or bipolar mania was 8% for intramuscular olanzapine for and 3% for placebo.

ose Events Occurring at an Incidence of 2% or More Among Oral Olanzapine-Treated Patients in Short-Term, Placebo-
Table 4 summarizes the incidence, rounded to the nearest percent, of treatment-emergent adverse events that in 2% or more of patients treated with oral olanzapine (doses ≥ 5 mg/day) and with incidence greater than placebo who ded 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=532)	Placebo (N=294)		Olanzapine (N=532)	Placebo (N=294)
Body as a Whole			**Musculoskeletal System**		
Accidental injury	12	8	Extremity pain		
Asthenia	10	9	(other than joint)	5	3
Fever	5	2	Joint pain	5	3
Back pain	5	2	**Nervous System**		
Chest pain	3	1	Somnolence	29	13
Cardiovascular System			Insomnia	12	11
Hypertension	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, constipation, depression, diarrhea, dysmenorrhea (dose/emitter used was for females only [olanzapine, N=207; 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	32	9
Weight gain	26	7
Increased appetite	24	8
Dizziness	14	7
Back pain	9	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=112)
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	5	Dyspnea	3	1
Constipation	8	4	**Skin and Appendages**		
Increased salivation	6	3	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	3	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	7			
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, fever, flatulence, flu syndrome, headache, hostility, hypertonia, libido decreased, libido increased, menstrual disorder (dose/emitter used was for females only [olanzapine, N=126; placebo, N=61]), myalgia, nausea, nervousness, pain, paranoid reaction, personality disorder, rash, rhinitis, sleep disorder, thinking abnormal, vomiting.
[2] Dose/emitter used was for females only (olanzapine, N=126; placebo, N=61).

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ation about the adverse reactions observed with lithium or valproate, refer to the ADVERSE REACTIONS section for these other products.

ncidence of an Incidence of 1% or More Among Intramuscular Olanzapine for Injection-Treated Patients in Short-Term Trials—Table 6 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse s 1% or more of patients tested with intramuscular olanzapine for injection (dose range of 2.5–10 mg/injection) greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with ar mania.

ent-Emergent Adverse Events: Incidence in Short-Term (24-Hour), Placebo-Controlled Clinical Trials of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia or Bipolar Mania†

	Percentage of Patients Reporting Event	
erse Event	Olanzapine (N=415)	Placebo (N=159)
	2	1
System		
	2	0
ension	1	0
	6	3
	4	2
	1	0

t by at least 1% of patients treated with olanzapine for injection, except the following events which s equal to or less than placebo: agitation, anxiety, dry mouth, headache, hypertension, insomnia,

cy of Adverse Events in Short-Term, Placebo-Controlled Trials—Extrapyramidal Symptoms—The following table rcentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of s during acute therapy in a controlled clinical trial comparing oral olanzapine at 3 fixed doses with placebo in the phrenia.

ent-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed ge, 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
15	14	12	14
23	16	19	27

significant differences.
atients with a Simpson-Angus Scale total score ≥3.
atients with a Barnes Akathisia Scale global score ≥2.

the enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by ried adverse events during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses treatment of schizophrenia.

t-Emergent Extrapyramidal Symptoms Assessed by Adverse Events Incidence in a Fixed ge, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia—Acute Phase

	Percentage of Patients Reporting Event			
Placebo (N=98)	Olanzapine 5 ± 2.5 mg/day (N=85)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
	3	3	3
vents†	10	8	14	20
	1	5	11*	10*
s*	4	0	2	1
	1	2	5	1
tal event	16	15	25	32*

ifferently different from placebo.
following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, opisthotonos, torticollis.
following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal sorders, hypokinesia, masked facies, tremor.
following COSTART terms were counted in this category: akathisia, hyperkinesia.
following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, ia dyskinesia.
following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.
he enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by of formal rating scales during controlled clinical trials comparing fixed doses of intramuscular olanzapine for o in agitation. Patients in each dose group could receive up to three injections during the trials (see CLINICAL direct assessments were conducted during the 24 hours following the initial dose of intramuscular olanzapine ere no statistically significant differences when placebo.

Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dose, d Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia*

	Percentage of Patients Reporting Event			
Placebo	Olanzapine IM 2.5 mg (N=48)	Olanzapine IM 5 mg (N=48)	Olanzapine IM 7.5 mg (N=40)	Olanzapine IM 10 mg (N=46)
0	0	0	0	0
0	0	0	0	0
0	0	5	0	0

gnificant differences.
tients with a Simpson-Angus total score ≥3.
tients with a Barnes Akathisia Scale global score ≥2.

e enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by ed adverse events in the same controlled clinical trial comparing fixed doses of intramuscular olanzapine for in agitated patients with schizophrenia. There were no statistically significant differences from placebo

ergent Extrapyramidal Symptoms Assessed by Adverse Events Incidence in a Fixed Dose, l 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=48)	Olanzapine IM 7.5 mg (N=40)	Olanzapine IM 10 mg (N=46)
0	0	0	0	0
0	4	0	0	0
0	0	0	0	0
0	4	2	0	0

ational differences.
following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, opisthotonos, torticollis.
following COSTART terms were counted in this category: akinesia, cogwheel rigidity, hypokinesia, masked facies, tremor.
following COSTART terms were counted in this category: akathisia, hyperkinesia.
following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia.
following COSTART terms were counted in this category: movement disorder, myoclonus,

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Site: Adverse Events—The following table addresses dose relatedness for other adverse events using 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	4	3	6	13
Rhinitis	0	2	0	7
Somnolence	16	20	30	39
Tremor	3	0	5	7

Additional Findings—In a single 8-week, controlled, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=206) 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: 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 >18.27 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: 2.5%; 20 mg/day: 1.8%; 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—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 eosinophil 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 Evaluation 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 (6988 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, abdominal injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, and sudden allergic; *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 embolus.

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:* gallstones, stomatitis, enteritis, esophageal ulcer, gingivitis, 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, hyperkinesia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, and upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hyperproteinemia, 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, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somnolence, stimulant misuse, torpor, 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 psoriatic 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, mydriasis, amblyopia, 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, metritis, 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.

Postmarketing 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 (excluding pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dl, and random triglyceride levels of ≥1000 mg/dl, have been reported.

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JSE AND DEPENDENCE: Controlled Substance Class—Olanzapine is not a controlled substance.

al and Psychological Dependence—In studies prospectively designed to assess abuse and dependence potential, e was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats ed oral doses up to 15 times the maximum recommended human daily oral dose (20 mg) and rhesus monkeys administered s up to 8 times the maximum recommended human daily oral dose on a mg/m² basis.

apine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the ılar, did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible ct on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once d. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

DOSAGE: Human Experience—In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or ental acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, ding the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs usually within normal limits following overdoses.

postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic nts, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal ptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the wing potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular ycardia and one patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic gnant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received rts of fatality in association with overdose of olanzapine alone. In one case of death, the amount of acutely ingested olanzapine was rted to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion 600 mg.

Overdosage Management—The possibility of multiple drug involvement should be considered. In case of acute overdosage, ablish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. Gastric lavage (after bation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The sibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with uced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic nitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension d circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. o not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen potension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until patient recovers.

SAGE AND ADMINISTRATION: Schizophrenia—Usual Dose—Oral olanzapine should be administered on a once-a-day schedule thout regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further sage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements 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 re not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical assessment. The safety of doses above mg/day has not been evaluated in clinical trials.

Dosing in Special Populations—The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine (see CLINICAL ARMACOLOGY; also see Use in Patients with Concomitant Illness and Drug Interactions under PRECAUTIONS). When indicated, se 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 nzapine should remain on it, the effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in izophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a period of up to months has been demonstrated in a placebo-controlled trial (see CLINICAL EFFICACY DATA). Patients should be periodically ssessed 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 meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/ crements 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 ses 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 mg/day, after achieving a responder status for an average duration of two weeks, was demonstrated in a controlled trial e CLINICAL EFFICACY DATA). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the g-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, l 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 ses 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 sh tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the outh. 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 nia—The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose nge 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 nical factors warrant (see CLINICAL EFFICACY DATA). If agitation warranting additional intramuscular doses persists following the tial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for ection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses eater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose ve not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., three doses of 10 mg administered 4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension (see PRECAUTIONS, modynamic Effects). Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic potension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an ditional 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 propriate (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 er clinical factors warrant. A lower dose of 2.5 mg per injection should be considered for patients who otherwise might be bilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine (see CLINICAL ARMACOLOGY; 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 ravenously 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 ution and container permit.

Directions for preparation of ZYPREXA IntraMuscular with Sterile Water for Injection—Dissolve the contents of the vial using 1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution ould appear clear and yellow. ZYPREXA IntraMuscular reconstituted with Sterile Water for Injection should be used immediately thin 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
10	Withdraw total contents of vial
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	4112 LILLY 4112	4115 LILLY 4115	4116 LILLY 4116	4117 LILLY 4117	4415 LILLY 4415	4420 LILLY 4420
NDC Codes: Bottles 30	NDC 0002-4112-30	NDC 0002-4115-30	NDC 0002-4116-30	NDC 0002-4117-30	NDC 0002-4415-30	NDC 0002-4420-30
Blisters-ID* 100	NDC 0002-4112-33	NDC 0002-4115-33	NDC 0002-4116-33	NDC 0002-4117-33	NDC 0002-4415-33	NDC 0002-4420-33
Bottles 1000	NDC 0002-4112-04	NDC 0002-4115-04	NDC 0002-4115-04	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.	4453	4454	4455	4456
Debossed	5	10	15	20
NDC Codes: Dose Pack 30 (Child-Resistant)	NDC 0002-4453-85	NDC 0002-4454-85	NDC 0002-4455-85	NDC 0002-4456-85

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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, SN5 8RU.

ZYPREXA IntraMuscular is available in:
NDC 0002-7597-01 (No. 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 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

PV 5199 AMP

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WARNING

od Antidepressant Drugs—Antidepressants increased the risk acebo of suicidal thinking and behavior (suicidality) in children, nd young adults in short-term studies of major depressive and other psychiatric disorders. Anyone considering the use of y other antidepressant in a child, adolescent, or young adult must sk with the clinical need. Short-term studies did not show an risk of suicidality with antidepressants compared to placebo in age 24; there was a reduction in risk with antidepressants acebo in adults aged 65 and older. Depression and certain other orders are themselves associated with increases in the risk of ts of all ages who are started on antidepressant therapy should be ropriately and observed closely for clinical worsening, suicidality, anges in behavior. Families and caregivers should be advised of ese observation and communication with the prescriber. SYMBYAX d for use in pediatric patients. (See WARNINGS, Clinical Worsening isk, PRECAUTIONS, Information for Patients, and PRECAUTIONS,)

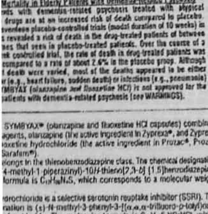
Mortality in Elderly Patients with Dementia-Related Psychosis—nts with dementia-related psychosis treated with atypical drugs are at an increased risk of death compared to placebo. seventeen placebo-controlled trials (modal duration of 10 weeks) in s revealed a risk of death in the drug-treated patients of between mes that seen in placebo-treated patients. Over the course of a ek controlled trial, the rate of death in drug-treated patients was compared to a rate of about 2.6% in the placebo group. Although f death were varied, most of the deaths appeared to be either r (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) YMBYAX (olanzapine and fluoxetine HCl) is not approved for the patients with dementia-related psychosis (see WARNINGS).

SYMBYAX® (olanzapine and fluoxetine HCl capsules) combines agents, olanzapine (the active ingredient in Zyprexa®, and Zyprexa oxetine hydrochloride (the active ingredient in Prozac®, Prozac Sarafem®).

elongs to the thienobenzodiazepine class. The chemical designation 4-methyl-1-piperazinyl)-10H-thieno[2,3-b] [1,5]benzodiazepine. formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight

ydrochloride is a selective serotonin reuptake inhibitor (SSRI). The nation is (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)oxy] ydrochloride. The molecular formula is $C_{17}H_{18}F_3NO \cdot HCl$, which a molecular weight of 345.79.

l structures are:



lanzapine fluoxetine hydrochloride

a yellow crystalline solid, which is practically insoluble in water. drochloride is a white to off-white crystalline solid with a solubility water.

psules are available for oral administration in the following ations:

3 mg/ 25 mg	6 mg/ 25 mg	6 mg/ 50 mg	12 mg/ 25 mg	12 mg/ 50 mg
3	6	6	12	12
25	25	50	25	50

also contains pregelatinized starch, gelatin, dimethicone, titanium lauryl sulfate, edible black ink, red iron oxide, yellow iron oxide, n oxide.

RMACOLOGY: Pharmacodynamics—Although the exact YMBYAX is unknown, it has been proposed that the activation of c neural systems (serotonin, norepinephrine, and dopamine) is its enhanced antidepressant effect. This is supported by animal the olanzapine/fluoxetine combination has been shown to produce ases in norepinephrine and dopamine release in the prefrontal with either component alone, as well as increases in serotonin. a psychotropic agent with high affinity binding to the following nin $5HT_{2A/2C}$, $5HT_6$ (K_i=4, 11, and 5 nM, respectively), dopamine 1 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors nzapine is an antagonist with moderate affinity binding for K_i=57 nM) and muscarinic M_{1-5} (K_i=73, 96, 132, 32, and 48 nM, nzapine binds weakly to $GABA_A$, BZD, and β-adrenergic receptors oxetine is an inhibitor of the serotonin transporter and is a weak orepinephrine and dopamine transporters.

receptors other than dopamine and $5HT_2$ may explain some peutic and side effects of olanzapine. Olanzapine's antagonism of receptors may explain its anticholinergic-like effects. The stamine H_1 receptors by olanzapine may explain the somnolence s drug. The antagonism of α_1-adrenergic receptors by olanzapine orthostatic hypotension observed with this drug. Fluoxetine has nity for muscarinic, α_1-adrenergic, and histamine H_1 receptors. tics—Fluoxetine (administered as a 60-mg single dose or 60 mg caused a small increase in the mean maximum concentration of following a 5-mg dose, an increase in the mean area under the a small decrease in mean apparent clearance of olanzapine study, a similar decrease in apparent clearance of olanzapine of ed following olanzapine doses of 6 or 12 mg with concomitant of 25 mg or more. The decrease in clearance reflects an increase The terminal half-life is not affected, and therefore the time state should not be altered. The overall steady-state plasma olanzapine and fluoxetine when given as the combination in the ranges were comparable with those typically attained with each pies. The small change in olanzapine clearance, observed in both ects the inhibition of a minor metabolic pathway for olanzapine via etine, a potent CYP2D6 inhibitor, and was not deemed clinically re, the pharmacokinetics of the individual components is expected racterize the overall pharmacokinetics of the combination.

Bioavailability—SYMBYAX—Following a single oral 12-mg/50-mg , peak plasma concentrations of olanzapine and fluoxetine occur 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 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 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* PRECAUTIONS, Drugs tightly 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. 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* 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 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* PRECAUTIONS, Drug Interactions).

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.

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 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 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. 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 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, 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 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) 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 to Endpoint Mean[1]
Study 1	SYMBYAX (N=40)	30	-16[a]
	Olanzapine (N=182)	32	-12
	Placebo (N=181)	31	-10
Study 2	SYMBYAX (N=42)	32	-18[a]
	Olanzapine (N=169)	33	-14
	Placebo (N=174)	31	-9

[1] Negative number denotes improvement from baseline.
[a] 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 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,

...tinuing therapy with an MAOI. Since fluoxetine and its major ...y long elimination half-lives, at least 5 weeks [perhaps longer, ...ine has been prescribed chronically and/or at higher doses ...RMACOLOGY, Accumulation and slow elimination)] should ...pping SYMBYAX before starting an MAOI.
...omitant use in patients taking pimozide is contraindicated
...)
...ioridazine should not be administered with SYMBYAX or ...a minimum of 5 weeks after discontinuation of SYMBYAX ...ioridazine).

...Worsening and Suicide Risk—Patients with major depressive ...oth adult and pediatric, may experience worsening of their ...he emergence of suicidal ideation and behavior (suicidality) or ...n behavior, whether or not they are taking antidepressant ...is risk may persist until significant remission occurs. Suicide ...depression and certain other psychiatric disorders, and these ...es are the strongest predictors of suicide. There has been ...oncern, however, that antidepressants may have a role in ...g of depression and the emergence of suicidality in certain ...early phases of treatment. Pooled analyses of short-term ...trials of antidepressant drugs (SSRIs and others) showed that ...se the risk of suicidal thinking and behavior (suicidality) in ...nts, and young adults (ages 18-24) with major depressive ...other psychiatric disorders. Short-term studies did not show ...isk of suicidality with antidepressants compared to placebo in ...24; there was a reduction with antidepressants compared to ...ed 65 and older.

...ses of placebo-controlled trials in children and adolescents ...e compulsive disorder (OCD), or other psychiatric disorders ...24 short-term trials of 9 antidepressant drugs in over ...ooled analyses of placebo-controlled trials in adults with MDD ...disorders included a total of 295 short-term trials (median ...s) of 11 antidepressant drugs in over 77,000 patients. There ...ariation in risk of suicidality among drugs, but a tendency ...in the younger patients for almost all drugs studied. There ...absolute risk of suicidality across the different indications, ...idence in MDD. The risk differences (drug versus placebo), ...ively stable within age strata and across indications. These ...g-placebo differences in the number of cases of suicidality per ...d) are provided in Table 2.

Table 2

...ange	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
...8	14 additional cases
...4	5 additional cases
	Decreases Compared to Placebo
...4	1 fewer case
...	6 fewer cases

...ed in any of the pediatric trials. There were suicides in the ...mber was not sufficient to reach any conclusion about drug ...

...er the suicidality risk extends to longer-term use, i.e., beyond ...ever, there is substantial evidence from placebo-controlled ...adults with depression that the use of antidepressants can ...f depression.

...treated with antidepressants for any indication should ...itately and observed closely for clinical worsening, ...al changes in behavior, especially during the initial few ...of drug therapy, or at times of dose changes, either ...s.

...oms, anxiety, agitation, panic attacks, insomnia, irritability, ...ss, impulsivity, akathisia (psychomotor restlessness), ...have been reported in adult and pediatric patients being ...cants for major depressive disorder as well as for other ...iatric and nonpsychiatric. Although a causal link between ...ymptoms and either the worsening of depression and/or the ...mpulses has not been established, there is concern that ...present precursors to emerging suicidality.

...be given to changing the therapeutic regimen, including ...the medication, in patients whose depression is ...who are experiencing emergent suicidality or symptoms ...s to worsening depression or suicidality, especially if ...vere, abrupt in onset, or were not part of the patient's ...

...en made to discontinue treatment, medication should be ...easible, but with recognition that abrupt discontinuation ...ertain symptoms (see PRECAUTIONS and DOSAGE AND ...ntinuation of Treatment with SYMBYAX, for a description ...ation of SYMBYAX).

...ers of patients being treated with antidepressants ...isorder or other indications, both psychiatric and ...e alerted about the need to monitor patients for the ...irritability, unusual changes in behavior, and the other ...ve, as well as the emergence of suicidality, and to ...mediately to health care providers. Such monitoring ...ervation by families and caregivers. Prescriptions for ...en for the smallest quantity of capsules consistent with ...t, in order to reduce the risk of overdose.
...t SYMBYAX is not approved for use in treating any ...population.

...Bipolar Disorder—A major depressive episode may be ...bipolar disorder. It is generally believed (though not ...als) that treating such an episode with an antidepressant ...elihood of precipitation of a mixed/manic episode in ...sorder. Whether any of the symptoms described above ...n is unknown. However, prior to initiating treatment ...ents with depressive symptoms should be adequately ...hey are at risk for bipolar disorder; such screening ...ychiatric history, including a family history of suicide, ...ssion. It should be noted that SYMBYAX is approved ...epression.

...derly Patients with Dementia-Related Psychosis—...mentia-related psychosis treated with atypical ...an increased risk of death compared to placebo. ...fluoxetine HCl) is not approved for the treatment of ...ted psychosis (see BOX WARNING).
...trolled clinical trials of elderly patients with dementia-...ence of death in olanzapine-treated patients was ...cebo-treated patients (3.5% vs 1.5%, respectively).
...Events (CVAE), Including Stroke, in Elderly Patients ...nsis—Cerebrovascular adverse events (e.g., stroke, ...cluding 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 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 3.6% 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 ≥50 mg/dL	OFC	174	67.3%
		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	36.7%[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 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%[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 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%[a]
		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%[a]
		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%[a]
		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%[a]
		Placebo	9	0%

[a] 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 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.

Weight Gain with Olanzapine Use

...nt Gained ...(lb)	6 Weeks (N=2976) (%)	6 Months (N=1536) (%)	12 Months (N=778) (%)	24 Months (N=422) (%)
≤0	27	21	20	22
...0-11 lb)	57	34	25	22
...(11-22 lb)	15	26	25	22
...(22-33 lb)	2	12	16	18
...(>33 lb)	0	6	14	16

...ing long-term continuation therapy with olanzapine monotherapy (238 median ...f exposure), 56% of olanzapine patients met the criterion for having gained ...r than 7% of their baseline weight. Average weight gain during long-term ...y was 5.4 kg.

...nzapine Monotherapy in Adolescents—The safety and efficacy of olanzapine ...olanzapine and fluoxetine in combination have not been established in ...nts under the age of 18 years. In an analysis of 4 placebo-controlled ...apine monotherapy studies of adolescent patients (ages 13 to 17 years), ...ding those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed ...des) (3 weeks), olanzapine-treated patients gained an average of 4.6 kg, ...was statistically significantly different compared to an average of 0.3 kg in ...bo-treated patients. with a median exposure of 3 weeks, 40.6% of olanzapine-...d patients gained at least 7% of their baseline body weight, which was ...tically significantly different compared to 9.8% of placebo-treated patients, ...a median exposure of 4 weeks. 7.1% of olanzapine-treated patients gained ...ast 15% of their baseline weight, compared to 2.7% of placebo-treated ...nts, with a median exposure of 19 weeks. Clinically significant weight gain ...observed across all baseline Body Mass Index (BMI) categories, but ...changes in weight were greater in adolescents with BMI categories above ...al at baseline. Discontinuation due to weight gain occurred in 1% of ...apine-treated patients, compared to zero placebo-treated patients.

...ring long-term continuation therapy with olanzapine, 65% of olanzapine-...d patients met the criterion for having gained greater than 7% of their ...ine weight. Average weight gain during long-term therapy was 7.4 kg.

...thostatic Hypotension—SYMBYAX may induce orthostatic hypotension ...iated with dizziness, tachycardia, bradycardia, and in some patients, ...pe, especially during the initial dose-titration period.

...the bipolar depression studies, statistically significantly more orthostatic ...es occurred with the SYMBYAX group compared to placebo and olanzapine ...s. Orthostatic systolic blood pressure decrease of at least 30 mm Hg ...red in 7.3% (6/82), 1.4% (5/346), and 1.4% (5/352) of the SYMBYAX, ...apine and placebo groups, respectively. Among the group of controlled ...l studies with SYMBYAX, an orthostatic systolic blood pressure decrease of ...mm Hg occurred in 4% (21/512) of SYMBYAX-treated patients, 5% (10/204) ...xetine-treated patients, 2% (16/644) of olanzapine-treated patients, and 2% ...5) of placebo-treated patients. In this group of studies, the incidence of ...pe in SYMBYAX-treated patients was 0.4% (2/571) compared to placebo ...(1/477).

...clinical pharmacology study of SYMBYAX, three healthy subjects were ...tinued from the trial after experiencing severe, but self-limited, hypotension ...radycardia that occurred 2 to 9 hours following a single 12-mg/50-mg ...of SYMBYAX. Reactions consisting of this combination of hypotension and ...cardia (and also accompanied by sinus pause) have been observed in at ...three other healthy subjects treated with various formulations of olanzapine ...oral, two intramuscular). In controlled clinical studies, the incidence of ...ts with a ≥20 bpm decrease in orthostatic pulse concomitantly with a ...mm Hg decrease in orthostatic systolic blood pressure was 0.4% (2/549) in ...YMBYAX group, 0.2% (1/455) in the placebo group, 0.8% (5/659) in the ...pine group, and 0% (0/241) in the fluoxetine group.

...MBYAX should be used with particular caution in patients with known ...vascular disease (history of myocardial infarction or ischemia, heart failure, ...duction abnormalities), cerebrovascular disease, or conditions that would ...pose patients to hypotension (dehydration, hypovolemia, and treatment ...antihypertensive medications).

...rgic Events and Rash—In SYMBYAX premarketing controlled clinical ...s, the overall incidence of rash or allergic events in SYMBYAX-treated ...s [4.6% (26/571)] was similar to that of placebo [5.2% (25/477)]. The ...ty of the cases of rash and/or urticaria were mild; however, three patients ...tinued (one due to rash, which was moderate in severity, and two due to ...events, one of which included face edema).

...uoxetine US clinical studies, 7% of 10,782 fluoxetine-treated patients ...ped various types of rashes and/or urticaria. Among the cases of rash ...urticaria reported in premarketing clinical studies, almost a third were ...wn from treatment because of the rash and/or systemic signs or symptoms ...ted with the rash. Clinical findings reported in association with rash include ...leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory ...s, lymphadenopathy, proteinuria, and mild transaminase elevation. Most ...s improved promptly with discontinuation of fluoxetine and/or adjunctive ...ent with antihistamines or steroids, and all patients experiencing these ...were reported to recover completely.

...uoxetine premarketing clinical studies, 2 patients are known to have ...ed a serious cutaneous systemic illness. In neither patient was there an ...ocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, ...other, a severe desquamating syndrome that was considered variously ...vasculitis or erythema multiforme. Other patients have had systemic ...mes suggestive of serum sickness.

...the introduction of fluoxetine, systemic events, possibly related to ...is, have developed in patients with rash. Although these events are rare, ...y be serious, involving the lung, kidney, or liver. Death has been reported ...in association with these systemic events.

...hylactoid events, including bronchospasm, angioedema, and urticaria ...d in combination, have been reported.

...onary events, including inflammatory processes of varying histopathology ...fibrosis, have been reported rarely. These events have occurred with ...as the only preceding symptom.

...her these systemic events and rash have a common underlying cause ...due to different etiologies or pathogenic processes is not known. ...more, a specific underlying immunologic basis for these events has ...identified. Upon the appearance of rash or of other possible allergic ...ena for which an alternative etiology cannot be identified, SYMBYAX ...e discontinued.

...onin Syndrome—The development of a potentially life-threatening ...n syndrome may occur with SNRIs and SSRIs, including SYMBYAX ...t, particularly with concomitant use of serotonergic drugs (including ...and with drugs which impair metabolism of serotonin (including MAOIs). ...syndrome symptoms may include mental status changes (e.g., agitation, ...tions, coma), autonomic instability (e.g., tachycardia, labile blood pressure, ...rmia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) ...astrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

...ncomitant use of SYMBYAX with MAOIs intended to treat depression is ...dicated (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors ...and PRECAUTIONS, Drug Interactions).

...comitant treatment of SYMBYAX with a 5-hydroxytryptamine receptor ...riptan) is clinically warranted, careful observation of the patient is advised, ...ly during treatment initiation and dose increases (see PRECAUTIONS, ...ractions).

...ncomitant use of SYMBYAX with serotonin precursors (such as tryptophan) ...ommended (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, 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 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 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) 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.

Thioridazine—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 PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QT_c 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 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.

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 (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.

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).

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. Somnolence led to discontinuation in 2% (10/571) of patients in the premarketing 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.

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).

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 below 130 mmol/L; however, a lowering of serum sodium below the reference range occurred at an incidence of 2% (10/500) of SYMBYAX patients compared with 0.5% (2/380) 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 (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.

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—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 (≥3 times the upper limit of the normal range) were observed in 6.3% (31/496) 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 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.

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 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 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. 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 the premarket testing.

advised when using SYMBYAX in cardiac patients and in patients
s or conditions that could affect hemodynamic responses (see
Orthostatic Hypotension).
with cirrhosis of the liver, the clearances of fluoxetine and its active
norfluoxetine, were decreased, thus increasing the elimination
these substances. A lower dose of the fluoxetine component of
hould be used in patients with cirrhosis. Caution is advised when
YAX in patients with diseases or conditions that could affect its
(see CLINICAL PHARMACOLOGY, Hepatic Impairment and DOSING
ISTRATION, Special Populations).
e and fluoxetine individual pharmacokinetics do not differ significantly
with renal impairment. SYMBYAX dosing adjustment based upon
ment is not routinely required (see CLINICAL PHARMACOLOGY, Renal
).

ion for Patients—Prescribers or other health professionals should
nts, their families, and their caregivers about the benefits and risks
with treatment with SYMBYAX and should counsel them in its
use. A patient Medication Guide about "Antidepressant Medicines,
and other Serious Mental Illness, and Suicidal Thoughts or Actions"
for SYMBYAX. The prescriber or health professional should instruct
eir families, and their caregivers to read the Medication Guide and
st them in understanding its contents. Patients should be given the
to discuss the contents of the Medication Guide and to obtain
any questions they may have. The complete text of the Medication
printed at the end of this document.
should be advised of the following issues and asked to alert their
f these occur while taking SYMBYAX.

Worsening and Suicide Risk—Patients, their families, and their caregivers
encouraged to be alert to the emergence of anxiety, agitation, panic
somnia, irritability, hostility, aggressiveness, impulsivity, akathisia
tor restlessness), hypomania, mania, other unusual changes in
orsening of depression, and suicidal ideation, especially early during
ant treatment and when the dose is adjusted up or down. Families and
of patients should be advised to look for the emergence of such
on a day-to-day basis, since changes may be abrupt. Such symptoms
eported to the patient's prescriber or health professional, especially
evere, abrupt in onset, or were not part of the patient's presenting
Symptoms such as these may be associated with an increased risk for
king and behavior and indicate a need for very close monitoring and
anges in the medication.

cemia—Patients should be advised of the potential risk of
ia-related adverse events. Patients should be monitored regularly for
d glucose control.

ain—Patients should be counseled that SYMBYAX may cause weight
s should have their weight monitored regularly.

Syndrome—Patients should be cautioned about the risk of serotonin
ith the concomitant use of SYMBYAX and triptans, tramadol or other
agents.

Bleeding—Patients should be cautioned about the concomitant use
and NSAIDs, aspirin, or other drugs that affect coagulation since
d use of psychotropic drugs that interfere with serotonin reuptake
ents has been associated with an increased risk of bleeding (see
NS, Abnormal Bleeding).

Patients should be advised to avoid alcohol while taking SYMBYAX.

and Motor Impairment—As with any CNS-active drug, SYMBYAX
tial to impair judgment, thinking, or motor skills. Patients should be
out operating hazardous machinery, including automobiles, until they
ly certain that SYMBYAX therapy does not affect them adversely.

nt Medication—Patients should be advised to inform their physician
ing Prozac®, Prozac Weekly™, Sarafem®, fluoxetine, Zyprexa®, or
®. Patients should also be advised to inform their physicians if they
plan to take any prescription or over-the-counter drugs, including
ments, since there is a potential for interactions.

sure and Dehydration—Patients should be advised regarding
re in avoiding overheating and dehydration.

Patients, if taking SYMBYAX, should be advised not to breast-feed.

Hypotension—Patients should be advised of the risk of orthostatic
specially during the period of initial dose titration and in association
f concomitant drugs that may potentiate the orthostatic effect of
., diazepam or alcohol (see WARNINGS and Drug Interactions).

—Patients should be advised to notify their physician if they
ant or intend to become pregnant during SYMBYAX therapy.
ents should be advised to notify their physician if they develop a
while taking SYMBYAX.

dherence—Patients should be advised to take SYMBYAX exactly
and to continue taking SYMBYAX as prescribed even after their
ns improve. Patients should be advised that they should not alter
imen, or stop taking SYMBYAX, without consulting their physician.
rmation is printed at the end of this insert. Physicians should
nformation with their patients and instruct them to read the
ide before starting therapy with SYMBYAX and each time their
refilled.

ests—Periodic assessment of transaminases is recommended in
gnificant hepatic disease (see Transaminase Elevations).

ions—The risks of using SYMBYAX in combination with other drugs
tensively evaluated in systematic studies. The drug-drug interactions
l components are applicable to SYMBYAX. As with all drugs, the
eraction by a variety of mechanisms (e.g., pharmacodynamic,
c drug inhibition or enhancement, etc.) is a possibility. Caution is
oncomitant administration of SYMBYAX and other CNS-active
d. In evaluating individual cases, consideration should be given
initial doses of the concomitantly administered drugs, using
ation schedules, and monitoring of clinical status (see CLINICAL
GY, Accumulation and slow elimination).

sive agents—Because of the potential for olanzapine to induce
YMBYAX may enhance the effects of certain antihypertensive
RNINGS, Orthostatic Hypotension).

dopa—The olanzapine component of SYMBYAX may antagonize
odopa and dopamine agonists.

es—Multiple doses of olanzapine did not influence the pharma-
epam and its active metabolite N-desmethyldiazepam. However,
ation of diazepam with olanzapine potentiated the orthostatic
erved with olanzapine.
ently administered with fluoxetine, the half-life of diazepam may
some patients (see CLINICAL PHARMACOLOGY, Accumulation
ion). Coadministration of alprazolam and fluoxetine has resulted
razolam plasma concentrations and in further psychomotor
ement due to increased alprazolam levels.
ltiple doses of olanzapine did not influence the pharmacokinetics

—Carbamazepine therapy (200 mg BID) causes an approximate
e clearance of olanzapine. This increase is likely due to the fact
e is a potent inducer of CYP1A2 activity. Higher daily doses of
y 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.

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, the potential for 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).

Theophylline—Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

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. 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 Drugs metabolized by CYP2D6 and CLINICAL PHARMACOLOGY, Accumulation and slow elimination).

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 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 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, olanzapine is unlikely to cause clinically important drug interactions mediated by this enzyme.

Fluoxetine inhibits the activity of CYP2D6, and may make 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, 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, 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 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.

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, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

Drugs tightly 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 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, 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 (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/m² 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/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 and in female 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 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 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 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/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 luteal 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/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 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/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 estrous 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 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) [9 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

of testicular degeneration and atrophy, depletion of epididymal ty in the male progeny. The effects of the high-dose combination oints could not be assessed due to high progeny mortality equate and well-controlled studies with SYMBYAX in pregnant

uld be used during pregnancy only if the potential benefit ial risk to the fetus.

n reproduction studies in rats at doses up to 18 mg/kg/day and s up to 30 mg/kg/day (9 and 30 times the MRHD on a mg/m²), no evidence of teratogenicity was observed. In a rat teratology rptions and increased numbers of nonviable fetuses were se of 18 mg/kg/day (9 times the MRHD on a mg/m² basis). longed at 10 mg/kg/day (5 times the MRHD on a mg/m² basis). In y study, fetal toxicity (manifested as increased resorptions and weight) occurred at a maternally toxic dose of 30 mg/kg/day RHD on a mg/m² basis).

sfer of olanzapine occurs in rat pups.

adequate and well-controlled clinical studies with olanzapine in . Seven pregnancies were observed during premarketing clinical zapine, including two resulting in normal births, one resulting in ue to a cardiovascular defect, three therapeutic abortions, and s abortion.

In embryo fetal development studies in rats and rabbits, there e of teratogenicity following administration of up to 12.5 and espectively (1.5 and 3.6 times the MRHD on a mg/m² basis, oughout organogenesis. However, in rat reproduction studies, an rn pups, a decrease in pup weight, and an increase in pup deaths 7 days postpartum occurred following maternal exposure to 1.5 times the MRHD on a mg/m² basis) during gestation or 0.9 times the MRHD on a mg/m² basis) during gestation and was no evidence of developmental neurotoxicity in the surviving treated with 12 mg/kg/day during gestation. The no-effect dose lity was 5 mg/kg/day (0.6 times the MRHD on a mg/m² basis).

c Effects—Neonates exposed to fluoxetine and other SSRIs or orepinephrine reuptake inhibitors (SNRIs), late in the third developed complications requiring prolonged hospitalization, ort, and tube feeding. Such complications can arise immediately Reported clinical findings have included respiratory distress, , seizures, temperature instability, feeding difficulty, vomiting, ypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, ing. These features are consistent with either a direct toxic effect RIs or, possibly, a drug discontinuation syndrome. It should be ome cases, the clinical picture is consistent with serotonin ONTRAINDICATIONS, Monoamine Oxidase Inhibitors).

ed to SSRIs in late pregnancy may have an increased risk for ary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per the general population and is associated with substantial neonatal ortality. In a retrospective case-control study of 377 women re born with PPHN and 836 women whose infants were born developing PPHN was approximately six-fold higher for infants after the 20th week of gestation compared to infants who had d to antidepressants during pregnancy. There is currently no dence regarding the risk for PPHN following exposure to SSRIs s is the first study that has investigated the potential risk. t include enough cases with exposure to individual SSRIs to RIs posed similar levels of PPHN risk.

pregnant woman with fluoxetine during the third trimester, the carefully consider both the potential risks and benefits of SAGE AND ADMINISTRATION). Physicians should note that in itudinal study of 201 women with a history of major depression ic at the beginning of pregnancy, women who discontinued ication during pregnancy were more likely to experience a relapse n than women who continued antidepressant medication.

ery—*SYMBYAX*—The effect of SYMBYAX on labor and delivery nown. Parturition in rats was not affected by SYMBYAX. be used during labor and delivery only if the potential benefit ial risk.

arturition in rats was not affected by olanzapine. The effect of and delivery in humans is unknown.

e effect of fluoxetine on labor and delivery in humans is e crosses the placenta; therefore, there is a possibility that adverse effects on the newborn.

s—*SYMBYAX*—There are no adequate and well-controlled YAX in nursing mothers or infants. No studies have been ine the excretion of olanzapine or fluoxetine in breast milk treatment. It is recommended that women not breast-feed MBYAX.

a study in lactating, healthy women, olanzapine was excreted n infant dose at steady state was estimated to be 1.8% of the dose.

xetine is excreted in human breast milk. In one breast milk tration of fluoxetine plus norfluoxetine was 70.4 ng/mL. n the mother's plasma was 296.0 ng/mL. No adverse effects eported. In another case, an infant nursed by a mother on crying, sleep disturbance, vomiting, and watery stools. The g levels were 340 ng/mL of fluoxetine and 208 ng/mL of 2nd day of feeding.

afety and effectiveness in the pediatric population have not e BOX WARNING *and* WARNINGS, Clinical Worsening and e considering the use of SYMBYAX in a child or adolescent ential risks with the clinical need.

icant toxicity, including myotoxicity, long-term neurobehavioral icity, and impaired bone development, has been observed of juvenile animals to fluoxetine. Some of these effects relevant exposures.

fluoxetine (3, 10, or 30 mg/kg) was orally administered to ning (Postnatal Day 21) through adulthood (Day 90), male elopment was delayed at all doses, and growth (body weight as decreased during the dosing period in animals receiving the end of the treatment period, serum levels of creatine scle damage) were increased at the intermediate and high muscle and reproductive organ histopathology (skeletal and necrosis, testicular degeneration and necrosis, n and hypospermia) was observed at the high dose. When d after a recovery period (up to 11 weeks after cessation of oral abnormalities (decreased reactivity at all doses and e high dose) and reproductive functional impairment ll doses and impaired fertility at the high dose) were seen; nd epididymal microscopic lesions and decreased sperm und in the high dose group, indicating that the reproductive he end of treatment were irreversible. The reversibility of scle damage was not assessed. Adverse effects similar to 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/m²) 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/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 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 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—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, 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, 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). The bipolar depression column shows the incidence of adverse events with 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
Chest Pain	1	0	0

*Table includes events associated with discontinuation of at least 1% and greater than placebo

Commonly 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 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	1
Twitching	6	2	1
Arthralgia	5	3	1
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, sinusitis, 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 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, 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 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 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: 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

max) at any time during the trial (10 mg/day: 31.2%; 20 mg/day:
y: 61.1%) with significant differences between 10 vs 40 mg/day and
, fatigue (10 mg/day: 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%)
differences between 10 vs 40 and 20 vs 40 mg/day, and dizziness
%, 20 mg/day: 1.6%; 40 mg/day: 6.6%) with significant differences
40 mg, was observed.

Observed in Clinical Studies—*Following is a list of all treatment-*
se events reported at anytime by individuals taking SYMBYAX in
except (1) those listed in the body or footnotes of Tables 7 and
where in labeling, (2) those for which the COSTART terms were
or misleading, (3) those events for which a causal relationship to
was considered remote, and (4) events occurring in only 1 patient
MBYAX and which did not have a substantial probability of being
atening.
classified within body system categories using the following
uent adverse events are defined as those occurring on 1 or more
least 1/100 patients, infrequent adverse events are those occurring
00 patients, and rare events are those occurring in <1/1000 patients.
Whole—Frequent: chills, infection, neck pain, neck rigidity,
ty reaction; *Infrequent:* cellulitis, cyst, hernia, intentional injury,
rdose, malaise, moniliasis, overdose, pelvic pain, suicide attempt;
lerance decreased.
ular System—Frequent: migraine, vasodilatation; *Infrequent:*
bradycardia, cerebral ischemia, electrocardiogram abnormal,
QT-interval prolonged; *Rare:* angina pectoris, atrial arrhythmia, atrial
ndle branch block, congestive heart failure, myocardial infarct,
cular disorder, T-wave inverted.
stem—Frequent: increased salivation, thirst; *Infrequent:* cholelithiasis,
on, esophagitis, gastritis, gastroenteritis, gingivitis, hepatomegaly,
miting, peptic ulcer, periodontal abscess, stomatitis, tooth caries;
s stomatitis, fecal incontinence, gastrointestinal hemorrhage, gum
ntestinal obstruction, liver fatty deposit, pancreatitis.
System—Infrequent: hypothyroidism.
Lymphatic System—Frequent: ecchymosis; *Infrequent:* anemia,
ymphadenopathy; *Rare:* coagulation disorder, leukopenia, purpura,
nia.
d Nutritional—Frequent: generalized edema, weight loss; *Infrequent:*
rance, dehydration, glycosuria, hyperlipemia, hypoglycemia,
obesity; *Rare:* acidosis, bilirubinemia, creatinine increased,
emia, hypoglycemic reaction.
eletal System—Infrequent: arthritis, bone disorder, generalized
mps, tendinous contracture, tenosynovitis; *Rare:* arthrosis, bursitis,
yopathy, osteoporosis, rheumatoid arthritis.
stem—Infrequent: abnormal gait, ataxia, buccoglossal syndrome,
ity, coma, confusion, depersonalization, dysarthria, emotional
a, extrapyramidal syndrome, hostility, hypesthesia, hypokinesia,
, movement disorder, myoclonus, neuralgia, neurosis, vertigo;
in syndrome, aphasia, dystonia, libido increased, subarachnoid
thdrawal syndrome.
System—Frequent: bronchitis, lung disorder; *Infrequent:* apnea,
is, hiccup, hyperventilation, laryngitis, pneumonia, voice alteration,
physema, hemoptysis, laryngismus.
pendages—Infrequent: acne, alopecia, contact dermatitis, dry
ruritis, psoriasis, skin discoloration, vesiculobullous rash; *Rare:*
atitis, maculopapular rash, seborrhea, skin ulcer.
ses—Frequent: abnormal vision, taste perversion, tinnitus;
rmality of accommodation, conjunctivitis, deafness, diplopia, dry
niosis; *Rare:* eye hemorrhage.
ystem—Frequent: breast pain, menorrhagia[1], urinary frequency,
ence, urinary tract infection; *Infrequent:* amenorrhea[1], breast
east neoplasm, cystitis, dysuria, female lactation[1], fibrocystic
ria, hypomenorrhea[1], leukorrhea[1], menopause[1], metrorrhagia[1],
disorder[1], polyuria, urinary retention, urinary urgency, urination
al hemorrhage[1], vaginal moniliasis[1], vaginitis[1]; *Rare:* breast
st engorgement, endometrial disorder[1], gynecomastia[1], kidney
fibroids enlarged[1].
gender.

Observed with Olanzapine or Fluoxetine Monotherapy—The
e events were not observed in SYMBYAX-treated patients during
ical studies but have been reported with olanzapine or fluoxetine
lastic anemia, cholestatic jaundice, diabetic coma, dyskinesia,
monia, erythema multiforme, hepatitis, idiosyncratic hepatitis,
openia, priapism, pulmonary embolism, rhabdomyolysis,
me, serum sickness-like reaction, sudden unexpected death,
vasculitis, venous thromboembolic events (including pulmonary
ep venous thrombosis), violent behaviors. Random cholesterol
ng/dL and random triglyceride levels of ≥1000 mg/dL have

D DEPENDENCE: *Controlled Substance Class*—SYMBYAX is
ubstance.
Psychological Dependence—SYMBYAX, as with fluoxetine and
ot been systematically studied in humans for its potential for
or physical dependence. While the clinical studies did not reveal
r any drug-seeking behavior, these observations were not
is not possible to predict on the basis of this limited experience
h a CNS-active drug will be misused, diverted, and/or abused
onsequently, physicians should carefully evaluate patients for
use and follow such patients closely, observing them for signs
of SYMBYAX (e.g., development of tolerance, incrementation of
g behavior).
and rhesus monkeys designed to assess abuse and dependence
ne alone was shown to have acute depressive CNS effects but
l of abuse or physical dependence at oral doses up to 15 (rat)
mes the MRHD (20 mg) on a mg/m² basis.

MBYAX—During premarketing clinical studies of the olanzapine/
tion, overdose of both fluoxetine and olanzapine were reported
s. Four of the five subjects experienced loss of consciousness
o fatalities occurred.
t introduction of olanzapine in October 1996, adverse event
nbination use of fluoxetine and olanzapine have been reported
mpany. An overdose of combination therapy is defined as
ected ingestion of a dose of olanzapine 20 mg or greater in
dose of fluoxetine 80 mg or greater. As of 1 February 2002,
ation therapy overdose were reported, most of which involved
ces. 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 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.

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)*.

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 3 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 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 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.

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

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

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

FILED IN OPEN COURT
Date: 3-11-08
Clerk: MLD

STATE OF ALASKA)
Plaintiff,)
)
v.)
)
ELI LILLY AND COMPANY)
Defendant)

Case no. 3AN-06-5630CIV

Judge's Rulings
3/12/08
Mark Rindner

DEFENDANT ELI LILLY AND COMPANY'S DEPOSITION COUNTER-DESIGNATIONS FOR TRIAL AND OBJECTIONS TO PLAINTIFF STATE OF ALASKA'S TRIAL DEPOSITION AND EXHIBIT DESIGNATIONS

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 for **Alan Breier, M.D.** The highlighted excerpts are those that must be presented together with the State's affirmative designations to ensure proper context.

Start (Page:Line)	End (Page:Line)	
26:21	28:12	✓
95:6	95:23	✓ include
96:5	96:8	✓
96:11	97:11	✓ need not include
97:14	98:12	✓ Lilly may include
98:15	98:16	✓ as cross.
98:19	100:20	✓
112:3	112:10	✓ include
122:1	122:17	
137:18	139:5	

Start (Page:Line)	End (Page:Line)
140:12	140:14
140:17	140:24
141:3	141:18
160:6	160:15
163:22	164:3
164:6	164:10
164:16	165:13
185:24	186:19
189:23	190:8
201:10	202:2
303:24	303:24
304:1	304:7
357:10	357:11
357:14	357:24
358:1	358:2
358:5	358:10
358:13	358:24
433:2	433:21
451:3	451:12
451:15	451:16
451:19	452:17
457:8	457:9
457:12	458:10

Cross - Neal not included on chart

Cross

Cross

Cross

Cross

Cross

Start (Page:Line)	End (Page:Line)
512:10	512:13
512:16	512:23
526:6	526:9
526:12	526:22

Lilly objects to the following pages and lines of Plaintiff State of Alaska's Trial Deposition Designations for Alan Breier:

O = Overrule

S = Sustain

Start (Page:Line)	End (Page:Line)	Objection	
54:9	64:18	Vague; ambiguous; foundation; prejudicial (Alaska R. Evid. 401, 402, 403, 611)	O
125:23 126:13	126:4 126:15	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action	O
167:15	168:2	Foundation; vague; misstates evidence (Alaska R. Evid. 401, 402, 403, 611)	O
192:10	192:19	Foundation; vague; personal knowledge (Alaska R. Evid. 401, 402, 403, 602, 611)	O
199:18 200:4	200:1 200:11	Compound question; hearsay (admit for notice) (Alaska R. Evid. 401, 402, 611, 802)	O
201:3	201:10	Foundation; vague; personal knowledge (Alaska R. Evid. 401, 402, 403, 602, 611)	O
219:20	221:24	Exhibit itself hearsay; misstates evidence (Alaska R. Evid. 802, 611)	O
282:24	282:23	Hearsay (Alaska R. Evid. 802)	O
287:12	287:23	Hearsay; compound question (Alaska R. Evid. 401,	O

Start (Page:Line)	End (Page:Line)	Objection
		402, 611, 802)
290:13	291:4	Hearsay (Alaska R. Evid. 802)
294:1	294:7	Hearsay (Alaska R. Evid. 802)
295:13	296:8	Hearsay (Alaska R. Evid. 802)
312:8	312:20	Hearsay (Alaska R. Evid. 802)
338:17	339:8	Vague; foundation; compound question; argumentative (Alaska R. Evid. 401, 402, 403, 611)
343:20	344:6	Foundation; personal knowledge (Alaska R. Evid. 401, 402, 602)
347:9	347:15	Vague; foundation; personal knowledge (Alaska R. Evid. 401, 402, 403, 602, 611)
348:18	349:7	Misstates evidence (Alaska R. Evid. 611)
401:16	404:15	Relevance (Alaska R. Evid. 401, 402, 403;) Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
403:15	403:21	Personal knowledge; foundation (Alaska R. Evid. 401, 402, 602)
405:19	406:13	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
406:24	413:15	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
440:15	442:11	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action

Start (Page:Line)	End (Page:Line)	*Objection*
442:19	442:22	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
443:2	444:24	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
445:17	449:13	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
455:3	455:12	Vague; foundation (Alaska R. Evid. 401, 402, 403, 611)
511:8	512:2	Foundation; misstates evidence (Alaska R. Evid. 401, 402, 611); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude Evidence Relating to Defendant's Profits, Net Worth, and the Price of Zyprexa
515:24	516:6	Foundation; misstates evidence (Alaska R. Evid. 401, 402, 611); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude Evidence Relating to Defendant's Profits, Net Worth, and the Price of Zyprexa
518:16	519: 7	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
524:3	524:11	Asked and Answered (Alaska R. Evid. 611); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
525:6	525: 13	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign

Start (Page:Line)	End (Page:Line)	Objection
		Regulatory Action
525:14	526:5	Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action

Lilly also objects to Plaintiff's exhibits for use during the testimony of Alan Breier:

Plaintiff's Exhibit	Objection(s)
Zyprexa Plaintiff's Exhibit No 320	M.I.L. regarding Foreign Regulatory Actions M.I.L. regarding adverse events Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Hearsay (Alaska R. Evid. 801, 802)
Zyprexa Plaintiff's Exhibit No 1110	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: internal planning document regarding internal market research, marketplace perceptions, and planning for proposed sales representative communications Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)
Zyprexa Plaintiff's Exhibit No 1111	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: internal planning document regarding internal market research, marketplace perceptions, and planning for proposed sales representative communications Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)
Zyprexa Plaintiff's Exhibit No 1440	Hearsay; Agree to admit for notice
Zyprexa Plaintiff's Exhibit No 1453	Hearsay; Agree to Admit for Notice

Plaintiff's Exhibit	Objection(s)
Zyprexa Plaintiff's Exhibit No 1605	Not Relevant (Alaska R. Evid. 401, 402) Hearsay (Alaska R. Evid. 801, 802) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Not a Complete Document Foundation (Alaska R. Evid. 901)
Zyprexa Plaintiff's Exhibit No 4051	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: Internal briefing, labeling not discussed Foundation (Alaska R. Evid. 901)
Zyprexa Plaintiff's Exhibit No 4858	Agree to admit subject to M.I.L. regarding adverse events (hearsay - notice)
Zyprexa Plaintiff's Exhibit No 5565	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: Internal communication regarding proposed responses to anticipated questions in Germany. MIL re: Foreign Regulatory Actions Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)
Zyprexa Plaintiff's Exhibit No 7802	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Not a Complete Document Foundation (Alaska R. Evid. 901) Not Authenticated (Alaska R. Evid. 901, 902)
Zyprexa Plaintiff's Exhibit No 9281	Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)
Zyprexa Plaintiff's Exhibit No 10017	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: Internal document discussing Lilly's foreign sales force M.I.L. regarding Foreign Regulatory Actions Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901)

Lilly reserves the right to object to these exhibits, and any others that may be introduced by Plaintiff, under the Alaska Rules of Evidence or any other applicable rule of law,

based on this Court's rulings or the purposes for which Plaintiff seeks to use the exhibits at trial.

Respectfully submitted,

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By: _____

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Dated: March 11, 2008

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

FILED IN OPEN COURT
Date: 3-11-08
Clerk: MTD

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-5630 CIV

DEFENDANT ELI LILLY AND COMPANY'S MOTION FOR RECONSIDERATION OF RULINGS ON OBJECTIONS TO AFFIRMATIVE DEPOSITION DESIGNATIONS OF GARY TOLLEFSON, M.D.

Defendant Eli Lilly and Company ("Lilly") respectfully requests that the Court reconsider its rulings regarding the admissibility of the following excerpt from the deposition of Gary Tollefson, M.D. This designation by the State reflect its allegations that Lilly engaged in off-label promotion—allegations which the Court has deemed irrelevant to, and beyond the scope of, any claim that State asserts. Consistent with the Court's rulings regarding other similar designated testimony in other depositions, Lilly's objections set forth below should be sustained. Relevant pages of the transcripts are attached.

Start (Page:Line)	End (Page:Line)	Objection
124:5 124:21	124:9 125:21	Relevance, vague; foundation; personal knowledge; (Alaska R. Evid. 401, 402, 403, 602, 611). Subject to ruling on Motion for Summary Judgment: off label.

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Dated: March 10, 2008

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of this document has been served via email upon counsel listed below, and by hand delivery and email upon Mary Beth Rivers, Room 532, Tower Two, Captain Cook Hotel.

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Date: March 10, 2008

was spent on the drug; is th

MR. LEHNER: Object t

form.

A. Probably reflecting both. But, specifically, the economics.

[redacted]

MR. LEHNER: Object to the form.

[redacted]

[redacted]

Q. Okay. Did you become aware of efforts to promote Zyprexa to physicians for dementia and depression?

MR. LEHNER: Object to the form.

A. If you're referring to the disease state prioritization table here --

Q. No, I'm not.

A. -- these are clinical candidates.

Q. No, I'm not referring to that [redacted]

MR. LEHNER: Object to the form.

[redacted]

MR. LEHNER: Object to the form.

[redacted]

[redacted]

Page 122

was spent on the d...

MR. LEHNE... form.

A. Probably reflecting both. But, specifically, the economics.

[redacted]

MR. LEHNER: Object to the form.

[redacted]

Page 123

[redacted]

Q. Okay. Did you become aware of efforts to promote Zyprexa to physicians for dementia and depression?

MR. LEHNER: Object to the form.

A. If you're referring to the disease state prioritization table here --

Page 124

Q. No, I'm not.

A. -- these are clinical candidates.

Q. No, I'm not referring to that [redacted]

MR. LEHNER: Object to the form.

[redacted]

MR. LEHNER: Object to the form.

[redacted]

Page 125

[redacted]

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

FILED IN OPEN COURT
Date: 3-11-08
Clerk: MH

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-5630 CIV

DEFENDANT ELI LILLY AND COMPANY'S MOTION FOR RECONSIDERATION OF RULINGS ON OBJECTIONS TO AFFIRMATIVE DEPOSITION DESIGNATIONS OF JACK JORDAN

Defendant Eli Lilly and Company ("Lilly") respectfully requests that the Court reconsider its rulings regarding the admissibility of the following excerpts from the depositions of Jack Jordan. Each of these designations by the State embodies its allegations that Lilly engaged in off-label promotion – allegations which the Court has deemed irrelevant to, and beyond the scope of, any claim that State asserts.

Throughout the Zyprexa litigation, plaintiffs in proceedings in state and federal court, including the State and its counsel, have broadly characterized several different elements of Lilly's marketing strategy and tools as being off-label. The most pervasive allegations, and the ones infusing the testimony below, concern Lilly's marketing Zypexa to primary care physicians. These allegations encompass topics including, but not limited to, Lilly's use of symptom-based promotion, its use of patient profiles (such as "Donna" and "Martha"), and its description of Zyprexa as a mood stabilizer.

Recognizing that testimony of this sort is inadmissible, the Court has sustained Lilly's objections to testimony on these topics in this and other deposition transcripts. *See e.g.*, Jordan Tr. at pp. 243:24 – 244:8 (examining Mr. Jordan on symptom-based promotion); Jordan Tr. at p. 339:6 – 339:11 (examining Mr. Jordan on whether Zyprexa was ever indicated for thought, mood, or behavioral disorders); Jordan Tr. at p. 343:2 – 343:8 (same); Bandick Tr. at p. 496:09 – 497:03 (examining Mr. Bandick on "Donna" patient profile"). Consistent with these rulings, the Court should sustain Lilly's objections to the excerpts below, each of which concerns these very same topics, characterized by the State as off-label.

Start (Page:Line)	**End (Page:Line)**	**Objection**
223:13	223:17	Relevance (testimony is, or is nothing more than a prelude to, off-label testimony).
223:22	223:24	Relevance (testimony is, or is nothing more than a prelude to, off-label testimony).
236:4	236:7	Relevance (testimony is, or is nothing more than a prelude to, off-label testimony).
301:20	302:2	Relevance (testimony is, or is nothing more than the introduction of a document concerning, off-label testimony).
306:1	306:7	Relevance (testimony is, or is nothing more than a prelude to, off-label testimony).
308:18	309:4	Relevance (testimony is off-label testimony).
309:5	309:10	Relevance (testimony is off-label testimony).
309:11	309:21	Relevance (testimony is off-label testimony).
374:24	375:7	Relevance (testimony is off-label testimony).
396:7	397:8	Relevance (testimony is off-label testimony).

Start (Page:Line)	End (Page:Line)	Objection
413:6	413:8	Relevance (testimony is off-label testimony).
421:05	421:13	Relevance (testimony is off-label testimony).
422:16	423:6	Relevance (testimony is off-label testimony).
436:14	436:22	Relevance (testimony is off-label testimony).
437:20	438:7	Relevance (testimony is off-label testimony).

Additionally, consistent with the Court's ruling sustaining Lilly's objection to Zyprexa MDL Plaintiffs' Exhibit No. 3872, the Court should sustain Lily's objections to the following excerpts, the sum and substance of which concern only this excluded document.

342:8	342:9	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
342:11	342:15	Relevance; Probative value outweighed by danger of unfair prejudice; Argumentative; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 611)

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Dated: March 10, 2008

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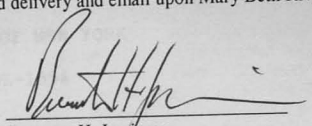
I hereby certify that a true and correct copy of this document has been served via email upon counsel listed below, and by hand delivery and email upon Mary Beth Rivers, Room 532, Tower Two, Captain Cook Hotel.



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Date: March 8, 2008

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

- - -

GOLKOW LITIGATION TECHNOLOGIES
1600 John F. Kennedy Boulevard
Suite 1210
Philadelphia, Pennsylvania 19103
(877) DEPS-USA

Page 222

Lilly, the cover sheet, and then the article would come from a journal.
Q. Anything else? Any other written materials Eli Lilly could prepare for its customers discussing off-label uses of Zyprexa?
A. The medical letters were written materials that, obviously, went out.
Q. Now those medical letters could only be sent out in response to a doctor's query, correct?
A. Yes. That is correct.
Q. Eli Lilly could not prepare medical letters to send out affirmatively to an audience or a group of doctors unless those medical letters were on-label, correct?
MR. GOLD: Objection as to form.
A. Yeah. Yeah. Correct.
Q. Okay. Besides the cover sheet to a medical article, is there anything, any other -- and the medical letters in response to doctors's inquiries, are there any other written documents that

Page 223

Eli Lilly can prepare and disseminate to its customers concerning off-label uses?
MR. GOLD: Objection as to form.
A. Right off the top of my head I can't think of any others.
Q. Thank you, sir.
I've lost it. I apologize.
Here it is.
I'm going to ask you a series of questions, sir, it's going to be the same question about various --
Let me, before I do that, let me ask this: The on-label indication of schizophrenia is a diagnosis, is it not?
A. It is, yes.
Q. It is a defined disease; is it not?
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.

Page 224

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?
MR. GOLD: Objection as to form.
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.
Q. My question to you here, sir, is Eli Lilly during the time -- all these questions until I tell you otherwise are during the time you were either Marketing Director or Brand Leader. Okay? Do you

Page 225

follow me?
A. Yes.
Q. During that time period, did Eli Lilly ever promote Zyprexa for anxiety?
A. That would have been a symptom of bipolar mania and schizophrenia so, but for an indication of anxiety, no.
Q. During the time you were a Brand Leader, did Eli Lilly promote Zyprexa for irritability?
A. That would be a symptom of its approved indications but for an indication variability no.
Q. Are you a doctor?
A. I am not, no.
Q. Do you know the symptoms of schizophrenia?
A. Not all of them but some of them.
Q. Okay. Mr. Fahey's a little irritable today, does he have schizophrenia?
MR. GOLD: Objection. Direct the witness not to answer the question.

Page 234

not?
A. I have, yes.
Q. And I bet you've hit your head before and also had a headache, correct?
A. I have, yes.
Q. So you could have a symptom of a headache but the cause could be different, correct?
A. Yes.
Q. Okay. So my question is: Did Eli Lilly ever promote Zyprexa for symptoms not caused by schizophrenia or bipolar mania?
MR. GOLD: Objection as to form.
A. No. How you communicate diagnoses in mental health is a cluster of symptoms that you get the diagnosis from, so, no.
Q. So no. Is your testimony -- is your testimony that Eli Lilly did not promote Zyprexa for symptoms that were not caused by the patient's schizophrenia or bipolar mania?

Page 235

MR. FAHEY: Objection. Asked and answered.
A. The answer's yes.
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 --
Q. Just so the record --
MR. FAHEY: Let him finish his answer.
Q. Go ahead, finish your answer.
A. Over time it was for

Page 236

different phases of bipolar disorder. But mood stabilizer, again, is just a general term that can cover a number of classes.
Q. Yes, sir. Just so the record is clear, Zyprexa was never indicated for bipolar disorder, was it, sir?
A. No, it wasn't. No.
Q. It was only indicated for bipolar mania only, correct, sir?
MR. FAHEY: Objection. Foundation.
A. During the time I was there, yes.
Q. Okay. Now, back to my question. Let me see if we can approach it a different way if I need to. Was Zyprexa approved by the FDA for anything other than bipolar mania and schizophrenia?
THE WITNESS: During my time?
MR. ALLEN: Yes, sir.
A. Okay. So we're still on my time.
Besides the combination therapy, no, it wasn't.

Page 237

Q. Okay. So the only two FDA-approved indications during your entire time were bipolar mania and schizophrenia, right?
MR. GOLD: Asked and answered three times now.
A. Well, there was maintenance of schizophrenia, too, yes. So --
Q. Either maintenance or acute bipolar mania or schizophrenia are the only two FDA-approved indications during your time?
MR. GOLD: Four times now, asked and answered.
MR. ALLEN: No, he keeps on changing it.
A. Yes.
MR. FAHEY: No. You just changed it. So objection to form.
QUESTIONS BY MR. ALLEN:
Q. Sir, your answer's yes?
A. It is yes.
Q. Thank you very much, sir.
Now, did the FDA ever approve

Page 238

Zyprexa as a mood stabilizer?
A. Did they ever approve it as a mood stabilizer? No.
Q. Did Lilly ever promote Zyprexa as a mood stabilizer?
A. Yes.
Q. So Eli Lilly promoted Zyprexa as a mood stabilizer even though the FDA did not approve Zyprexa as a mood stabilizer, correct?
A. No. I mean, mood stabilizer is just a general term, a class of products of which bipolar mania drugs are a part of the class of mood stabilizers. So it's a class thing, it's not an indication thing, using your language from earlier.
Q. So it is your testimony that Zyprexa was in the class approved by the FDA of mood stabilizing drugs?
MR. GOLD: Misstates his testimony. Objection as to form.
Q. Is it your testimony that the FDA classified Zyprexa as a mood stabilizer?
A. They don't name classes of

Page 239

drugs. They're involved in the indication business.
Q. Okay. So the FDA never approved Zyprexa as a mood stabilizer, did it?
A. The question doesn't make any sense because the FDA doesn't name classes of drugs. I mean, that's -- the field of psychiatry does.
Q. Okay. So let me ask this: Did you ever, you at Eli Lilly ever -- what's Depakote?
A. It's a mood stabilizer approved for bipolar mania.
Q. Is it approved for anything else?
A. I don't know what other indications it's got, I mean -- I think, epilepsy.
Q. What about lithium, what kind of drug is that?
A. It's a mood stabilizer used in bipolar disorder and I don't know what all the indications are.

Page 240

Q. Okay. Did Eli Lilly ever promote -- Did Eli Lilly ever promote Zyprexa for thought disorders?
MR. ALLEN: I think I asked that -- let me strike that question.
QUESTIONS BY MR. ALLEN:
Q. Did Eli Lilly ever promote Zyprexa for the treatment of symptoms unrelated to schizophrenia or bipolar mania?
A. No. It was in the context of those disease states.
Q. Did Eli Lilly ever instruct its sales force when they went to doctor's offices to focus on symptoms and not diagnoses?
MR. GOLD: Objection as to form.
A. We focused on symptoms to discuss the diagnoses.
MR. ALLEN: Objection. Nonresponsive.
MR. FAHEY: No, it's not.
Q. My only question --
MR. ALLEN: See, what we do

Page 241

later is we fight before a judge.
MR. FAHEY: You don't have to put your statement it's not responsive on the record.
MR. ALLEN: It's required by the rule.
MR. FAHEY: No, it's not. They're all reserved other than form.
MR. ALLEN: That's a form objection where I come from, nonresponsive. And your talking is not an objection. So you don't -- so when I object, if I object --
MR. FAHEY: You say it's not responsive. I say it is responsive.
MR. ALLEN: That's an argument that could be made before the court at a later date.
MR. FAHEY: And we will.
MR. ALLEN: Well, then you don't know need to --
MR. FAHEY: You're putting your position on the record, I'll

put mine.
MR. ALLEN: I have to.
MR. FAHEY: No, you don't. I'm saying you don't.
MR. ALLEN: So I don't -- okay.
MR. FAHEY: I'll give you a standing objection that every answer to every witness in the entire MDL, if you think it's nonresponsive later you can make that argument. You don't have to say it every time that somebody says something.
MR. ALLEN: You stipulate to that?
MR. FAHEY: Yes.
MR. ALLEN: And agree on behalf of Eli Lilly?
MR. FAHEY: Yes.
MR. ALLEN: All right.
Q. Now, sir --
MR. FAHEY: Which means you're never going to stay say it again. If you say it again then the

deal's off.
MR. ALLEN: He succeeded there. See, he distracted me. He's not going to do it the rest of the day. He's a talker.
Where was I?
QUESTIONS BY MR. ALLEN:
Q. Oh, symptoms. Did Eli Lilly ever instruct its sales representatives, either in writing or orally, to go to the doctor's office and discuss symptoms and not the diagnosis of schizophrenia or bipolar mania?
MR. GOLD: Objection as to form.
A. The -- I know when we did our primary care research the primary care docs, we learned that you talk about symptoms first and then get into indications when you share the studies. And so as part of the sales process, we would instruct them to talk about symptoms to engage the physician in the indication of bipolar mania.
Q. So you did instruct your

sales representatives to go to the doctors and discuss symptoms and not diagnoses first; is that correct?
A. Within the context of the sales process, describing the patient up front, we would talk about symptoms and then get into indications when we shared the data of the studies, yes.
Q. In fact, you told your sales representatives to focus on symptoms and not diagnoses, did you not?
MR. FAHEY: Objection to form.
A. As part of the sales process, what we learned from market research is that primary care physicians thought symptoms first, and so we would talk to them about symptoms first but always move on to the indications as you'll see in the studies. I'm sure you have those documents.
MR. ALLEN: Objection. Nonresponsive.
MR. FAHEY: Well, there goes the deal. That's a shame. That

lasted about three minutes.
MR. ALLEN: I don't need the deal.
QUESTIONS BY MR. ALLEN:
Q. Hey, Mr. Jordan, you, in fact, at Eli Lilly, prior to the time you launched the primary care physician market knew there was not a specific indication for Lilly representatives to promote in the primary care market, didn't you, sir?
A. As I recall, the early research was they weren't recognizing the disease of bipolar mania in their offices. It was there, but it was unrecognized.
MR. ALLEN: Objection, sir.
Q. My question to you is, you at Eli Lilly knew prior to the primary care physician launch that there was not a specific indication for Lilly representatives to promote in the primary care physician market?
MR. GOLD: Objection as to form.
MR. FAHEY: And asked and

MR. ALLEN: One for your lawyer.

MR. GOLD: Thank you.

QUESTIONS BY MR. ALLEN:

Q. Tell the jury who Jill Lake is.

MR. GOLD: Mr. Allen, give Mr. Jordan an opportunity to read the document.

QUESTIONS BY MR. ALLEN:

Q. Mr. Jordan, I'm not going to ask you about this entire document. I want to ask you about question seven and eight on Page 2.

MR. GOLD: I would like the witness to have an opportunity to read the entire document, otherwise the question you are asking might be out of context.

You presented him with the document. The question appears to be derived from the document. The witness is going to read the entire document before he answers any

questions.

MR. ALLEN: And I object to this proceeding.

MR. FAHEY: Just to remind Mr. Allen that Mr. Woodin, once again, confirmed the best approach would be to give the witness the documents before the deposition as recently as two days ago, but you chose not to do that, sir.

MR. ALLEN: Actually, that's not quite accurate but --

MR. FAHEY: You weren't on the call.

MR. ALLEN: I still say it's not quite accurate for reasons that you could not possibly know.

MR. FAHEY: Okay. Secret, secret issues.

THE WITNESS: Okay.

MR. ALLEN: How long was that?

THE REPORTER: Well, when Mr. Gold said, "Mr. Allen give Mr.

Jordan an opportunity to read the document."

MR. ALLEN: How long was that?

THE REPORTER: That was at 1433, so 2:33 and now it is 1436.

MR. ALLEN: Okay. Four minutes.

QUESTIONS BY MR. ALLEN:

Q. Mr. Jordan, at Eli Lilly did 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.

MR. GOLD: Can you keep your voice up, Mr. Jordan.

THE WITNESS: I'm sorry.

QUESTIONS BY MR. ALLEN:

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

Q. Is question and answer No. 5 redacted?

MR. GOLD: The document speaks for itself. No. 5 is redacted.

MR. ALLEN: Well, I'm entitled also to cross-examine the witness depending on the ruling on it.

Q. Is question and answer No. 5 redacted, sir.

MR. FAHEY: Let me just remind you that I made the offer before this deposition if you had questions about redactions you could bring them up to me before the deposition. The issue came up in Ms. Mehlman's deposition. I said it again there, which was less than a week ago --

MR. ALLEN: No.

MR. FAHEY: -- and you chose not to raise the issue until the middle of the deposition so --

... going to tell
... master there's no
... s an accurate
...tation. A man can't get
...dy for a deposition, read 10,000
documents, and call you to consult
on it. And so we'll take that up later.

MR. FAHEY: The redaction issue in the documents have been around --

QUESTIONS BY MR. ALLEN:

Q. Question and answer No. 5 are not present, are they, sir?

MR. FAHEY: -- over two and-a-half years, Mr. Allen.

QUESTIONS BY MR. ALLEN:

Q. Question and answer No. 5 are not present, are they, sir.

MR. GOLD: Asked and answered.

A. It is not, no.

Q. Question No. 7 is. What is question seven?

A. "Is Zyprexa indicated for depression?"

Q. And the answer is what, sir?

A. It says, "Zyprexa is not indicated for depression. We know Zyprexa improves depressive symptoms in schizophrenic patients" but need to think of it, "but need to think of as a mood stabilizer."

Q. We need to think of it as a mood stabilizer, is that correct? "It" is not there but we need to think of it as a mood stabilizer; is that correct?

A. Yes.

Q. It says, "Zyprexa is not indicated for depression;" is that correct?

A. That's correct. It's not indicated for depression.

Q. And that's accurate, is it not?

A. That is accurate.

Q. Now schizophrenia is a diagnosis. You've already told us that earlier today, right?

A. It is, yes.

Page 306

Q. Now in this question and answer document it says "What if the doctor says," this is question No. 8 following question seven, "what if the doctor says I don't see those types of patients?" Do you see that question?

A. I do.

Q. What is Eli Lilly's response to question No. 8 where it says "what if the doctor says I don't see those types of patients?" Can you read out loud?

MR. GOLD: Mr. Allen, I'm going to object to this line of questioning. I don't think this witness can tell you what Lilly meant by answering this question. Perhaps you should interrogate the author of this document who is indicated on the first page of this exhibit. I don't see how Mr. Jordan can speak for what Eli Lilly meant in answer to that question that appears on this document. He'd be

Page 307

speculating and engaging in total hypothetical conversation with you.

QUESTIONS BY MR. ALLEN:

Q. Sir, can you read out loud the answer to the question reflected in Exhibit No. 5, "what if the doctor says I don't see those types of patients?" What is the answer written on the piece of paper, Exhibit No. 5?

MR. GOLD: I have no objection to that. Go ahead.

THE WITNESS: In question eight?

MR. ALLEN: Yes, sir.

A. Okay. "The doctor's thinking hat he does not see a schizophrenic or ipolar patient."

Q. Let's stop there. The octor is thinking that he does not see chizophrenic or bipolar patients; is that ght?

MR. GOLD: That's what it says, Mr. Allen.

MR. ALLEN: Well, he read it

Page 308

so fast I want the record to be clear.

QUESTIONS BY MR. ALLEN:

Q. Is that correct?

A. That is.

Q. Okay. Continue reading slowly and distinctly so the jury can hear, please.

MR. GOLD: Mr. Allen, when you say "is that correct" do you mean is that what the document says or are you trying to get Mr. Jordan to vouch for what Eli Lilly has presented as the answer to that question? He'll ratify the document says what it says.

QUESTIONS BY MR. ALLEN:

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

Page 309

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."

Q. Question 7 was: "Is Zyprexa indicated for depression?" And the answer to that question indicated in part that "Zyprexa

A. Not that I know of, no.
Q. Would it have been wrong for them to do so?
A. No, it would not have been.
Q. Did Eli Lilly position Zyprexa for behavioral disturbances?
A. Again, I don't know who "Eli Lilly" is but not that I know.
Q. Did Eli Lilly position, to your knowledge, Zyprexa for anxiety disorders?
A. The reason why I'm struggling is we had a lot of planning documents that talked about positioning for a product that doesn't go off until 2011. So it's really hard to say what all plans went into which indications.
Q. Was Zyprexa indicated for thought, mood, and behavioral disorders ever?
A. No. Those are, actually, general terms to talk about the various indications we planned on having.
Q. Okay. So the term thought, mood, and behavioral disorders were various

terms for indications you had planned on having; is that correct?
A. It was an umbrella for current indications as well as future indications, yes.
Q. Wasn't thought, mood -- and, my question, back to my original question, 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 specific indications in the label?
MR. GOLD: Objection as to form.
A. I don't recall that being the case.
(Whereupon, Deposition Exhibit(s) 8 duly received, marked and made a part of the record.)
MR. ALLEN: Okay, sir. I'm going to hand you what's been marked as Jordan Exhibit No. 8, a document I'll provide to counsel. I'll hold it up --
Are you refusing to hold this

up for the jury?
MR. GOLD: He's being directed not to hold it up.
MR. ALLEN: Okay.
(Document displayed to the jury)
MR. ALLEN: We were told --
MR. GOLD: Is this No. 7?
That would be eight. I'm sorry, eight.
QUESTIONS BY MR. ALLEN:
Q. We asked for production in this case, Mr. Jordan, and we were told by your counsel in the production that this document, Exhibit No. 8, came from your files.
MR. FAHEY: His counsel didn't tell him anything. We were involved in the production.
QUESTIONS BY MR. ALLEN:
Q. It was represented by the defense in this case that Exhibit No. 8 came from your files. Do you recognize Exhibit No. 8?

MR. GOLD: Well, it's two questions, sir. Did it come from his files is one question and, No. 2 is does he recognize the exhibit?

MR. ALLEN: No, sir, there's only one question.

QUESTIONS BY MR. ALLEN:

Q. Sir, do you recognize Exhibit No. 8 as coming from your files?

MR. GOLD: No objection.

A. I don't know if it did or didn't. My handwriting's there, so.

Q. Yes, sir. That is your handwriting at the bottom, correct?

A. It is.

Q. Okay. You said in this -- is this a positioning document or a marketing document?

A. I'm not sure exactly what it 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.

question to you was, sir -- listen to my question.

QUESTIONS BY MR. ALLEN:

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?

MR. GOLD: Objection as to form.

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.

Q. You were -- to suggest to this jury that you were anything but right on top of the launch and actively involved -- it was the biggest thing you did in your role as of that time, August of 2000, was the primary care physician launch, wasn't it?

MR. GOLD: Objection as to the form.

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?

MR. GOLD: Objection as to form.

A. No, actually it was not.

position is with regard to a medical product such as Zyprexa? What a position is?

A. A position is, ultimately, how you want your customers to think about your product.

Q. Right. And the position listed in this document is "the safe, proven, solution for mood, thought, and behavioral disorders;" is that correct?

A. That's how Mike wrote it in this document, yes.

Q. The very next sentence says, 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, 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.

MR. FAHEY: Sir --

I object to that as nonresponsive.

QUESTIONS BY MR. ALLEN:

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 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.

Q. Well, at the launch meeting by the time that was ready --

MR. ALLEN: Exhibit No. 12.

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

THE WITNESS: Are we done with this?

Page 394

have with it is that Bullet Point No. 3, this could be an executive summary of the first page of the detail piece. The first page of the detail piece connects with doctors on symptoms and then goes into bipolar disorder. So I don't know what this is an executive summary of.

Q. Yes, sir. The record will reflect at the time of trial what this is an executive summary of.

My question to you was only: Does the Executive Summary, Exhibit 13, third bullet point state: "Sales representatives having most success when their message centers on identifying patient types and treating symptoms instead of focusing on patient diagnosis?"

A. And our strategy on the message was up front to identify patient symptoms, ask the doctors if they had that cluster of symptoms at the patient level, and then share the data around the diagnosis.

So this could be, as much as I know, a summary of that first page of the

Page 395

detail piece.

Q. Did I read the third bullet point correctly or not?

A. You did.

Q. Thank you, sir. Now I'm going to the last page of this document under Recommendations. You see the first bullet point under Recommendations on the last page of this document.

A. Page 13, I only have three pages so.

Q. It's the last page of this exhibit, sir.

A. I know.

Q. Sir, it's not your job to be the lawyer, it's just your job to answer the questions I present to you. Do you understand that?

MR. GOLD: Mr. Jordan is not attempting to be the lawyer. He's just trying to clarify the record that he has Page 13. And even though it is the last page of the exhibit it is not, certainly, not a

13-page document. Go ahead.

QUESTIONS BY MR. ALLEN:

Q. Okay, sir, are you on the last page of Exhibit 13 which is also Page 13?

A. I am.

Q. Of the Sales Rep and District Manager Topline Reaction to the Primary Care Physician Launch. Can you read for the jury out loud the first bullet point under Recommendations?

A. Now, I'm going to assume this is a summary, given, you haven't given it to me, of the first part of the detail piece where they talk about symptoms and then go on to diagnosis as part of the message which is what I saw trained. So in that context: "Continue focusing on patient symptomology and having PCPs identify specific patients rather than on patient diagnosis."

Q. Let's see if I can read this a little slower for the jury. The first bullet point under Recommendations on the last page of Exhibit 13 reads as follows:

Page 397

"Continue focusing on patient symptomatology and having primary care physicians identify specific patients rather than on patient diagnoses." Did I read that correctly?

A. You're reading's correct but I don't know, I don't know that it's represented correctly without seeing everything.

Q. Now remember you talked earlier about this altruistic motivation that you claim Lilly had when it introduced Zyprexa to the primary care physician market?

MR. GOLD: Objection as to form. And it doesn't totally characterize his testimony.

MR. ALLEN: Sir, is it -- let me rephrase the question. I don't think your lawyer had an objection he just had a speech.

MR. GOLD: It is an objection. Go ahead.

QUESTIONS BY MR. ALLEN:

Q. Okay. Sir, do you recall after the launch and periodically over the

A. We never marketed to Martha. We marketed to physicians.
Q. For Martha.
A. With a patient profile of Martha.
MR. GOLD: Objection as to form.
Q. Did Dr. John Buse, by the way --
Well, I'll talk about Dr. Buse in a minute.
What's the next exhibit, sir?
(Whereupon, Deposition Exhibit(s) 16 duly received, marked and made a part of the record.)
MR. ALLEN: I'll hand you Exhibit No. 16. This is an advertisement that has been produced to us.
Exhibit 16, sir. We're moving off of 15. Let me have 15, please.
That was 14. We skipped one

right now we'll come back to.
Exhibit 16, this is an advertisement. I'll hold it up.
(Document displayed to the jury)
Do you recall this advertisement, Antipsychotic Power for Routine Use?
A. I do not, no.
Q. Was Zyprexa an everyday routine drug?
MR. FAHEY: Objection to form.
A. Yeah. It was used in over 4 million patients at that point, yes.
Q. Was Zyprexa intended as a routine drug? It says Antipsychotic Power For Routine Use. Was antipsychotic power in Zyprexa intended for routine use?
A. In schizophrenia, later in bipolar mania, it was used routinely, yes.
Q. Sir, in the inside cover of this advertisement it has a picture of an older woman having a cup of coffee. She

looks nice. She's in a suit, it looks like to me, or maybe a robe. Nice looking lady, isn't it?
MR. GOLD: Do you have a question? Good observation, though. Go ahead.
MR. ALLEN: No, it's a question. Doesn't the second page --
MR. GOLD: Is the woman wearing a robe or -- is that the question?
MR. ALLEN: If you don't interrupt I'll ask the question.
MR. GOLD: Go ahead.
QUESTIONS BY MR. ALLEN:
Q. Doesn't the second page of this exhibit, the advertisement Antipsychotic Power For Routine Use, have a nice picture of an elderly woman?
A. Yes, it does.
Q. Is that Martha?
A. I don't know who she is.
Q. Isn't this attempt to market

to Martha an Antipsychotic Power For Routine Use promotion of Zyprexa off-label?
MR. GOLD: Objection as to form.
A. No.
[redacted]
A. I do, yes.
Q. And Donna was another attempt by Eli Lilly to market off-label, wasn't it, sir?
A. Well, now you're saying "another attempt." This says for positive and negative symptoms, which is schizophrenia.
MR. ALLEN: Objection, nonresponsive, sir.
THE WITNESS: No, you brought it back to this document by saying "another." So you insinuated this one was off-label.
MR. ALLEN: Sir, I'm not -- let me tell you just so you and I are clear. I'm not insinuating this

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.
Q. Yes. It's also taken, this detail piece can be taken to the other customers of Eli Lilly; isn't that right?
A. Well, the only --
Q. Sir, my question is pending.
A. I'm struggling with it because there's always a number at the bottom of these for final approval and I don't see the LY number.
Q. Sir, this was just produced to us by the defense.

A. Okay.
Q. And my question was not anything dealing with an LY number. But 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.
Q. Yes, sir. The fourth page of this document, and in fact, though, in the detail piece it is going to be on the left-hand side of the detail piece.
MR. GOLD: What are you referring to now, Mr. Allen?
MR. FAHEY: You're pointing to the resource guide not the detail piece.
MR. GOLD: You want to give him that document as well?
MR. ALLEN: No. I really don't right now. I think I can ask him questions that are consistent with the resource guide.
MR. GOLD: You're concealing --
MR. ALLEN: It's called impeachment. Yes, it's called impeachment. If he testifies

truthfully we don't even need to go to the resource guide. If he doesn't, we do.
QUESTIONS BY MR. ALLEN:
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.
Q. Okay. I don't see schizophrenia and bipolar mania anywhere in the description of Donna, do you?
A. Well, this is Page 4. Page 2 says Zyprexa is approved for short-term treatment of bipolar mania and short-term treatment and maintenance of schizophrenia.
Q. Yes.
A. So Page 2 has the indications. Page 4 has Donna, yes.
Q. There was no doubt that

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

and look at "Zyprexa utilization by disease state of primary care physicians as of the time of the PCP launch." Are you with me?

A. I am, yes.

Q. And we have a box there. It says, pointing to the graph, it says "schizophrenia, 30 percent," right?

A. Yes.

Q. And "bipolar 7 percent," correct?

A. Yes.

Q. And again, you'd have to agree with me that part of that bipolar prescription would be not bipolar mania, right?

A. Yes.

Q. Okay. But even taking the 30 and the seven, you add it together it's 37 percent, correct? Thirty and seven added together is 37?

A. Yes.

Q. Therefore, Eli Lilly knew, and this document demonstrates, that at the time of the primary care launch 63 percent of

primary care physician's prescriptions of Zyprexa were prescriptions off-label; is that correct?

A. Which I think proves my point. Before we were even there these doctors were using it across the board, and we wanted to grow the bipolar market.

So I think you've just proved my point, that they use products off-label without promotion.

MR. ALLEN: And I object to that as nonresponsive.

QUESTIONS BY MR. ALLEN:

Q. My only question to you was, sir, didn't Eli Lilly know, even prior to the time of the launch of the Viva Zyprexa campaign, that 63 percent of the primary care physician's prescriptions were off-label?

A. Yes. Without promotion they were prescribing off-label and we were focusing on the bipolar mania market.

Q. Sir, I know you're not going to give me any different answer. Can you turn to Page 71 of this about your vision and

strategy for primary care at the time of the launch.

MR. GOLD: Do you have a question?

MR. ALLEN: Yes, sir. I've asked him to turn to the page.

MR. GOLD: He did. He's there.

MR. ALLEN: Then as a courtesy. How do you get a person to turn to the page without saying so?

QUESTIONS BY MR. ALLEN:

Q. Are you at the page Zyprexa Primary Care Vision and Strategy?

A. I am. 71?

Q. Yes. And the vision for the PCP launch was "expand Zyprexa's market by redefining how primary care physicians treat mood, thought, and behavioral disturbances." Did I read that correctly?

A. You did.

Q. Does it say expand Zyprexa's market by having primary care physicians

treat schizophrenia and bipolar mania?

A. Again, a vision is what you want in the long-term. And mood is a part of bipolar mania. Thought is what schizophrenia and behavior disturbances are.

We had an active program in the psychosis associated with Alzheimer's.

Q. Wasn't it your strategic intent at the time of the primary care launch to make Zyprexa an everyday agent in primary care?

MR. GOLD: Objection as to form.

A. Given that our data showed that up to 30 percent of patients who were treated with antidepressants were potentially bipolar patients, that would make it an everyday agent in the bipolar -- I mean in the primary care physician's office.

Q. And, in fact, Zyprexa, Page 72, Strategic Intent says: "Zyprexa can and will become an everyday agent in primary care," correct?

A. Given that antidepressants

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.

Q. Sir, at the time of the primary care physician launch you were informed that your colleagues, Chris Bomba, Suni Keeling, Robert Baker, Patrizia Cavazzoni, and Charles Beasley had gone to an endocrinology advisory board meeting for independent endocrinologists that advised Lilly in the diabetes section. Did you know about that?

MR. GOLD: Objection as to form.

Q. That meeting that Ms. Bomba and Mr. Keeling went to?

A. I don't remember that specific meeting but if you have something to refresh my memory.

Q. Were you informed that when

Dr. Baker, Dr. Beasley, Chris Bomba, Suni Keeling, and Pat Cavazzoni went to this meeting of the endocrinology advisory board, the advisory board informed them that they were very concerned about diabetes and that it was time for Eli Lilly to come clean on the diabetes issue?

A. I don't remember that specific interchange, no.

Q. Do you recall that at the time Dr. Baker, Dr. Beasley, Chris Bomba, and Suni Keeling, and Pat Cavazzoni went to the endocrinology board meeting in October of 2000, the endocrinologists told Eli Lilly that they were skeptical that weight gain seen in the spontaneous event reports was not associated with higher hyperglycemia rates?

MR. GOLD: Objection as the form.

Q. Do you recall that?

A. Given I don't remember the meeting, I don't recall that, no.

Q. Did you recall that the endocrinology board, you were advised in

PCP launch, wanted all the hyperglycemia data turned over to them?

MR. GOLD: Objection as to form.

A. Again, given I don't remember the meeting, I don't recall that being a desire.

Q. And were you advised when Dr. Baker, and Dr. Beasley, and Chris Bomba, and Suni Keeling, and Pat Cavazzoni returned from the endocrine advisory board meeting, they advised Eli Lilly don't get too aggressive and blame the diabetes you are seeing on the schizophrenia. Do you recall that?

MR. GOLD: Objection as to form.

A. I just don't remember that specific meeting.

Q. Do you recall being informed in May of 2002 about Dr. Newcomer's clamp study?

MR. GOLD: Objection as to

form.

A. I, vaguely -- I recall that Dr. Newcomer had done a clamp study.

Q. Do you recall as the brand manager, excuse me, the Brand Leader and the Marketing Director for Zyprexa, being informed in May of 2002, that Dr. Newcomer's clamp study demonstrated increased adiposity. You know what adiposity is, don't you?

A. It's weight gain.

Q. Yes.

A. In fact, I'm sorry, it's fat, basically.

Q. You recall knowing in May of 2002, that Dr. Newcomer's clamp study demonstrated that increased adiposity is strongly associated with decreased insulin action in treated patients with schizophrenia. Treatment-induced increases in adiposity, along with additional disease or treatment effects, may contribute to elevated rates of diabetes mellitus in this population."

MR. GOLD: Objection as to

STOP!

CASE NO. 06-05630CI

Volume No. 14

☒ This is not the last volume of this file, and no documents are to be added. Add new papers to the last volume only.

☐ This case has been consolidated. Add new papers to File No. _____ only.

☐ Venue has been changed to _____. All new filings should be forwarded to the Clerk of Court at that location.

☐ This case has been removed to U.S. District Court, File No. _____. All new filings should be forwarded to U.S. District Court.

☐ Other: _____

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