M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 27, 1996

FROM: Thomas P. Laughren, M.D. TPL
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Zyprexa (olanzapine) for the treatment of psychotic disorders

TO: File NDA 20-592
[**Note:** This overview should be filed with the 9-16-96 submission.]

1.0 BACKGROUND

In our 8-30-96 approvable letter, we requested a safety update, a foreign regulatory update, a world literature update, and a commitment to conduct a relapse prevention study. In the biopharmaceutics area, we identified our preferred dissolution methodology and specifications, and we asked the sponsor to consider a further exploration of the population PK database as an approach to providing additional information regarding drug interactions. We also attached our proposal for labeling. Lilly responded formally to the approvable letter with the 9-16-96 submission.

The review team, up to the level of Team Leader, interacted with the sponsor over a period of several weeks to arrive at the version of labeling [LABOLNPS.AP3] that is included with the approval letter. The sponsor responded initially with an alternative labeling proposal on 9-6-96, including additional modifications on 9-9-96. We responded with a counterproposal that was faxed to Lilly on 9-16-96. The sponsor responded with faxes dated 9-16-96 and 9-17-96, and we held a teleconference with the sponsor on 9-17-96, reaching agreement on most of the disputed issues. Lilly provided language consistent with these agreements in faxes dated 9-18-96 and 9-19-96. Additional faxes dated 9-18-96 and 9-20-96

The sponsor submitted a proposed labeling that was edited and modified by Thomas Laughren, M.D., Greg Dubitsky, M.D., and this reviewer. These modifications were discussed with representatives

addressed remaining issues for pharmacology and a 9-18-96 fax addressed remaining chemistry issues. We faxed a final version of labeling on 9-23-96, and Gary Tollefson, M.D., from Lilly, confirmed late on that same day that this version of labeling, which is included with the approval package, was acceptable to them.

Dr. Paul Andreason reviewed the clinical sections of the 9-16-96 response to the approvable letter, including the safety update, the literature update, and the regulatory status update.

2.0 SAFETY UPDATE

The safety update included reports of deaths, serious adverse events, adverse dropouts, and patients experiencing potentially clinically significant changes in vital signs, laboratory values, and ECGs. This update covered a period from 7-15-95 through 8-14-96 for deaths and serious adverse events and from 7-15-95 through 2-14-96 for all other safety data. The safety update included data for 765 olanzapine patients from the primary database (690 ongoing patients for whom some safety data had already been reviewed in earlier submissions and 75 new patients) and for 148 total patients from the secondary database, including 14 olanzapine patients, and 134 blinded patients.

There were 5 deaths, 1 other serious adverse event, and 3 adverse dropouts, none of which could be reasonably attributed to olanzapine treatment. Dr. Andreason considered only 1 of the patients with potentially clinically significantly laboratory abnormalities to have likely had olanzapine-related changes. That patient had an increase in LFTs, an issue already addressed in labeling.

In summary, none of these reports contained new or unusual findings that would change my view about the approvability of this drug or necessitate further labeling changes.

3.0 WORLD LITERATURE UPDATE

The sponsor's literature update covered the period from the cutoff date for the original NDA submission to 9-4-96, and included 159 clinical and preclinical references. Dr. Andreason reviewed abstracts for all the clinical references and titles for all the preclinical references. These references contained no findings that would adversely affect the conclusions about olanzapine's safety.

Table 1 Studies Included in the Updated Primary Safety Database

4.0 FOREIGN REGULATORY UPDATE

The sponsor warranted in the 9-16-96 submission that Zyprexa is not approved in any countries at the present time, and that no negative regulatory actions have been taken with regard to olanzapine.

5.0 REQUEST FOR RELAPSE PREVENTION TRIAL

The sponsor has committed to conducting a phase 4 study to adequately address the question of long term effectiveness.

6.0 BIOPHARMACEUTICS

The sponsor accepted our proposed dissolution method and specifications.

7.0 LABELING

Lilly proposed numerous changes to the labeling for Zyprexa, many of which we found acceptable, while others were the subject of negotiations with the review team over the roughly 2-week time period described under Background. As noted, we were able to reach agreement at a Team Leader level on labeling. I will comment here on the resolution of labeling issues that required additional data review and discussion:

Suggested Starting Dose/Concerns About Orthostatic Hypotension:

In our labeling proposal, we had emphasized the possibility of orthostatic changes, and recommended a focus by clinicians and patients on initial titration as the period of greatest risk. We also recommended 5 mg as the initial dose, with an increase to 10 mg after several days.

Our view was based partly on theoretical grounds, i.e., olanzapine is a potent α_1 antagonist, and drugs with that property predictably have problems with initial titration. Common sense would lead one to be cautious based solely on this fact. Our recommendations were also based on finding (1) 5.5% of olanzapine vs 1.8% of placebo patients in a pool of 2 studies (HGAD and HGAP) having a potentially clinically significant postural change in systolic blood pressure ($\geq$ 30 mmHg decrease in systolic BP, supine to standing), and (2) spontaneous reports of hypotension in 5.2% of olanzapine patients vs 1.7% of placebo patients for this same pool. These patients also differed in the incidence of dizziness and

Table 2 Studies comprising the secondary safety database (N=148: 134 still blinded)	
Study	Title/Design/Dose Range

tachycardia. In addition, there were 15 instances of syncope in phase 2-3 trials, some of which occurred fairly early in treatment. Phase 1 data were also suggestive of a dose response relationship for syncope during initial titration.

The sponsor argued against a focus on initial titration as a period of risk, and also against a recommendation for 5 mg as a starting dose. They argued that their placebo controlled dose response studies did not show a difference between orthostatic effects between the 5 and 10 mg doses, however, these studies weren't designed to detect this effect, e.g., blood pressure wasn't monitored at a time most likely to reveal an effect. They also argued that olanzapine is 100-fold less potent as an α_1 antagonist than risperidone, and that a 10 mg initial dose was well tolerated in the vast majority of patients receiving this dose in the clinical trials.

Comment: After much discussion, we agreed to precautionary language that did focus on initial titration as a period of concern, and a recommendation for 5 or 10 mg as the starting dose, out of consideration of the possibility of dose dependency for the orthostatic effect. In addition, 5 mg will be the recommended dose for potentially vulnerable patients.

Data from Long-Term Trials Pertinent to Risk of Tardive Dyskinesia:

In our labeling, we had removed from the standard tardive dyskinesia warning Lilly's reference to data from a pool of haloperidol controlled long-term extension trials suggesting a higher rate of emergence of dyskinetic events for haloperidol compared to olanzapine. The pool was based on studies HGAD, E003, and HGAJ. It included 707 olanzapine and 197 haloperidol patients who were free of dyskinesia at entry into the extension phase, and were exposed to olanzapine or haloperidol for a median duration of 237 and 203 days, respectively. Using criteria that seemed reasonable, there did appear to be a greater incidence of dyskinetic symptoms for haloperidol compared to olanzapine, using several approaches.

Lilly objected, arguing that these are valid data that provide important information for prescribers. We acknowledged that, in the past, we have generally not permitted claims of reduced risk of tardive dyskinesia, but that such claims have generally been based either on theoretical considerations or on a lack of new cases in databases that were not adequate for detecting this event. While we further acknowledged that the data are suggestive of a possible difference between olanzapine and haloperidol regarding risk of treatment emergent dyskinesia, nevertheless, we argued that it is

difficult to know their usefulness in predicting the relative risk of tardive dyskinesia for the two drugs at later and possibly more relevant time points. Since the inclusion of such data in labeling would represent an important departure from our usual practice, we indicated that it would be a decision necessitating more work internally and likely consultation with outside experts.
Comment: We agreed to consider expeditiously a supplement that addressed a modification of the tardive dyskinesia statement, and the sponsor agreed to accept our decision not to include these data at this time.

Duration of Prolactin Elevation:

In our labeling proposal, we had noted the finding that prolactin levels are elevated by olanzapine treatment, and that "the elevation persists during chronic administration," since this phrase is in the standard prolactin statement for some antipsychotic drugs.

Lilly objected to this phrase, arguing that, while a modest increase is apparent early in treatment, endpoint analyses reveal no difference between olanzapine and placebo, unlike the data for haloperidol arms in these studies which reveal a persistent elevation for that drug. They wanted to add a sentence to the Hyperprolactinemia statement noting the finding of no difference at endpoint, and to note later in labeling that the elevation is transient. However, we disagreed with their argument that prolactin elevation with olanzapine has been demonstrated to be transient. The LOCF analysis is not the most pertinent, since it carries forward the levels for many placebo patients who dropped out very early. The most relevant analysis is observed cases at week 6, and here, the data show a clear dose response relationship, however, there is insufficient power given the attrition to achieve statistical significance. Furthermore, the data from extension trials revealed that prolactin levels are elevated compared to baseline, albeit to a modest extent and without a placebo control.

Comment: The sponsor agreed to our preference to characterize the effect as persisting, providing we acknowledged that the elevation during longer term treatment was modest. We agreed to this qualification.

Adequate Characterization of Weight Gain Observed with Olanzapine:

In our labeling, we added a Precautions statement describing overall the weight changes observed with olanzapine treatment. Lilly wanted to qualify this statement, by emphasizing that

the effect is most prominent in patients who are underweight at baseline, and they wanted to move the statement to Adverse Reactions.

We agreed with moving this statement to Adverse Reactions. We also agreed to acknowledging in the statement the fact that larger changes are observed in patients with lower BMIs at baseline. However, we noted that the statement must also acknowledge that, despite this differential effect on the basis of BMI, the weight gain was observed generally for olanzapine patients, despite the BMI category. In fact, the longer-term extension data revealed that the effect is even more prominent during longer-term use, with almost half of even the overweight patients taking olanzapine experiencing a $\geq$ 7% increase in body weight compared to baseline. This finding also needs to be incorporated into the revised statement.

Comment: The sponsor agreed to our revised statement, located in the Adverse Reactions section.

Recommended Monitored Regarding Concerns about LFT Increases:

In our labeling, we had recommended baseline transaminases in all patients being considered for treatment, with followup monitoring monthly for any patients having clinically significant baseline abnormalities. Lilly objected, arguing that routine screening of all patients is unnecessary. They proposed alternative language that recommends monitoring only in patients who already have significant hepatic disease. In reconsidering this issue, including an examination of a consult done for Lilly by Hy Zimmerman, we were inclined to agree that requiring baseline LFTs in all patients would be excessive, and in fact, would not be consistent with our labeling for other recently approved drugs with a similar profile of transient, asymptomatic transaminase increase.

Commment: We agreed to a slightly modified version of Lilly's proposed labeling that noted the finding and recommended that caution should be observed in patients with hepatic impairment.

Adequacy of Available Data Pertinent to Long-Term Efficacy of Olanzapine:

In our labeling, we had not permitted Lilly to describe the efficacy findings from patients extended from the short-term phases of their efficacy studies, even though these data were suggestive of an effect. We argued that studies of this design are basically flawed, i.e., the randomization is violated, since only responding patients are continued in the extension phase. They wanted to

distinguish between continuation effects and relapse prevention effects, however, we noted that this basic flaw would apply whether one is focusing on either. We indicated that is was our view that these studies cannot provide definitive data pertinent to the question of long-term efficacy, and to include these data would undermine our current approach to this issue in labeling. Further, we reminded the sponsor that the labeling acknowledges under Dosage and Administration the usual practice of continuing responding patients, so that including this information would not strengthen labeling in any way from the clinician's standpoint.

Comment: We discussed this matter at some length, but in the end, the sponsor agreed with our preference to not include this information in labeling.

8.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has submitted sufficient data to support the conclusion that Zyprexa is effective and acceptably safe in the treatment of psychosis. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling.

cc:
Orig NDA 20-415
HFD-120
HFD-120/TLaughren/PLeber/PAndreason/GDubitsky/SHardeman
HFD-100/RTemple

DOC: MEMOLNPS.AP1

August 30, 1996
Letter from Dr. Robert Temple
Director, FDA Office of Drug Evaluatino
To: Dr. Timothy R.Franson of Eli Lilly

Pg 1

Section 2
Postmarketing

Dr. Temple expresses his concerns that there is NO EVIDENCE to suggest long term effectiveness of Olanzapine.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-592

AUG 30 1996

Eli Lilly and Company
Attention: Timothy R. Franson, M.D.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Franson:

Please refer to your September 22, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) 2.5 mg, 5 mg, 7.5 mg, and 10 mg Tablets.

We acknowledge receipt of your amendments dated:

September 26, 1995	September 27, 1995	September 28, 1995
October 3, 1995	October 19, 1995	October 31, 1995
November 20, 1995	November 27, 1995	December 4, 1995
December 7, 1995	December 15, 1995	January 12, 1996
January 19, 1996	January 29, 1996	February 1, 1996
March 21, 1996	June 4, 1996	June 10, 1996
June 14, 1996	July 22, 1996	July 26, 1996

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to respond to the following requests:

1. Labeling

   Accompanying this letter (Attachment 1) is the Agency's proposal for the labeling of Zyprexa. We believe it presents a fair summary of the information available on the benefits and risks of Zyprexa.

   We have proposed a number of changes to the draft labeling submitted in your original submission. We will be happy to discuss these proposed changes in detail, and to discuss any disagreements you might have with any part of the proposed labeling format or content.

2. Post-marketing Study

   Although the evidence submitted documents the short-term efficacy of Zyprexa in the management of the manifestations of psychosis, there is no evidence bearing directly on the effectiveness of this drug in the maintenance treatment of remitted/partially remitted

psychotic patients. Because it is likely that Zyprexa will be widely used for these purposes, it is critical that appropriate clinical studies be undertaken to evaluate its safety and effectiveness in long-term use. We request that you commit to performing a study of subsequent to approval. Division staff would be happy to discuss this and any other proposals with you. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to Phase 4 commitments must be clearly designated "Phase 4 Commitments."

3. Safety Update

Our assessment of the safety of olanzapine is based on our review of all safety information provided in your original and subsequent submissions, including your safety update (January 12, 1996 amendment). This original review was based on an integrated safety database with a cutoff date of approximately 2-14-95 and on additional serious events and deaths reported up to a cutoff date of approximately 10-31-95. Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you provide a final safety update focusing on deaths, serious adverse events, and dropouts for adverse events. This final safety update can be in the same general format as your 1-12-96 safety update.

4. World Literature Update

Prior to the approval of Zyprexa, we require an updated report on the world's archival literature pertaining to the safety of Zyprexa. This report should include only literature not covered in your previous submissions. We 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 Zyprexa. 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 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.

5. Foreign Regulatory Update/Labeling

We require a review of the status of all Zyprexa 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 Zyprexa is approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for Zyprexa along with English translations when needed.

6. Biopharmaceutics

a. Please adopt the following dissolution methodology and specification for all tablet strengths:

Apparatus:
Media:
Volume:
Speed:
Sampling time:
Specification: not less than

b. We ask that you consider a further exploration of the population PK database as an approach to providing additional information regarding drug interactions.

Please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

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. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact CDR Steven D. Hardeman, R.Ph., Project Manager, at (301) 594-5533.

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

August 30, 1996
Memorandum
From Dr. Paul Leber
Director, FDA Neuropharmacological Drug Products
To: Dr. Robert Temple
Director, FDA Office of Drug Evaluation

Re: concerns about drug trial methodologies

Pg 2
Leber WRONGLY DEFEND the high dropout rates of placebo patients in trials as "reflective" of olanzapine efficacy. This is PROOF of Leber's (and FDA's) IGNORANCE or DISMISSAL of Entire phenomenon of DRUG DISCONTINUATION withdrawal syndromes (rebound vs. withdrawal). At very least, Leber should be acknowledging the fact that high placebo drop-out rates may be partial reflection of patients' return of symptoms, or worsening of symptoms, due to supersensitivity syndrome

pg 3
Leber CORRECTLY concedes that NEGATIVE symptoms that are being "tracked" in these studies may very WELL Have been Parkinsonian symptoms INDUCED by conventional neuroleptic (Haldol). Seems to be understanding that this is NIDS.
[Unfortunately, he is not willing to concede that olanzapine might cause the same condition.]

He regrets not "having the time" to evaluate efficacy data based upon consideration of this fact.
In essence, Leber may be saying: We KNOW that we have argued that olanzapine has superior efficacy in the trials, compared to Haldol === but in retrospect, we cannot draw this conclusion.

*Fortunately, the only claim that appears on LABEL is comparison to placebo.

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 30, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Actions taken and not taken in response to your memorandum of 8/27/96, concerning HFD-120's review of NDA 20-592 Zyprexa® [olanzapine]

TO: File NDA 20-592
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

In your memorandum[1], you offer a number of comments. I have little to say about most of them, but there are a couple to which a response is necessary.

Before doing so, however, I want to acknowledge an oversight.

Dr. Greg Dubitsky had a prominent and important role in the development of the Division's review of the Zyprexa application, a point not obvious from a review of documents in the package originally forwarded to the Office. Greg served as Dr. Andreason's mentor and, as such, is a substantive contributor to that primary review document (e.g., by analogy, if this were an academic manuscript submitted to an archival medical journal, Greg would be the senior coauthor).

Now, I will turn to the substantive points I have about your comments concerning the Zyprexa application.

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[1] I am mindful that the memorandum cited was delivered with a stamp indicating it was intended as a draft. Because the memorandum offered a number of comments and suggestions requiring responses or actions to which the Division has now taken some form of response, the memorandum is functionally much more a preliminary communication that is relevant to the decision making process than a preliminary draft explicating your personal views. In short, there is no practical way I can respond to and/or explain our decisions to act upon and/or not act upon a point conveyed in your memorandum without making reference to it.

1. Dropouts

I'm somewhat surprised by your reaction to the "go open" provision of the HGAP protocol. In fact, in virtually any placebo controlled trial with actively psychotic patients, a high early dropout rate is expected for both "ethical" and "medical" reasons. The use of placebo is considered arguable in the first place. Next, for management reasons (e.g., staff morale, legal risk, etc.), there are few, if any, hospitals in which a study permitting actively psychotic patients to be assigned to placebo is going to continue for even a couple of weeks, let alone 4. Finally, a high early dropout rate attributable to therapeutic failure that differentially affects the placebo group is actually a finding we look for because it documents the assay sensitivity of the population admitted for study. Of course, the censoring biases the between treatment comparisons made at latter time points in the study, but this is the very reason that I consider these studies more as a source of proof of principle of a drug's antipsychotic effects than as a basis to estimate the "effect size" of the drug. Indeed, this is yet another reason that I find drug-drug comparative studies so difficult to assess.

Viewed from my perspective, therefore, HGAP was unusual for the extent it was able to retain subjects until week 4. (If I had the time, I could probably find examples to document this assertion --that is, of antipsychotic trials where dropouts rates at earlier times are very high.) In any case, although 80 % of those randomized in HGAP remained on drug for only the first for 4 weeks, among those who did drop out-- 74, 62 and 56 percent (pbo,1,10) did so for lack of effectiveness--the pattern was consistent with a dose related effect, and, therefore, provides additional proof in principle of Zyprexa's efficacy.

2. Comparisons.

Comparisons are odious. For this reason alone it is sensible to approach any nominal advantage claimed by a sponsor for his product relative to a competitor's with considerable caution, even if the claim seems to rest on evidence adduced in an adequate and well controlled clinical investigation. One concern is that an experimental design for determining whether or not a drug is effective for use may be totally inappropriate for obtaining a fair comparison of the utility and performance of two drugs. Moreover, even if great care is taken to check the conditions under which the experimental comparisons are made, the estimates of the comparative utility adduced in a given experiment may be biased for any number of reasons, many not obvious.

I believe that you share these views, at least insofar as the principle is concerned.

Accordingly, I am surprised at your dismissal of my reservations (discussed in footnote 3 of my August 18 memorandum) about the arguable validity of the instruments used to assess the comparative performance of antipsychotic drugs. Moreover, I find your explanation for doing so unsatisfactory.

You seemingly dismiss, out of hand, my concern that an outcome assessment instrument that is valid as a measure of antipsychotic effect in a drug placebo trial might not reliably measure antipsychotic effect in a drug-drug comparison trial. Perhaps, I failed to develop my argument well enough in my memorandum of August 18, 1996, but the concern cannot be dismissed so easily.

As with a lab test, the performance of an outcome assessment instrument lies as much, if not more, in its specificity as in its sensitivity. The problem in schizophrenia outcome assessment is that some of the so-called "negative" signs and symptoms of that illness are indistinguishable from the pseudoparkinsonian signs and symptoms that are known side effects of antipsychotic drugs like haloperidol. It would be reckless, therefore, to assume that a drug - haloperidol difference detected on an instrument that registers negative symptoms is actually measuring a difference in antipsychotic effectiveness. To be clear, it is in theory possible to look at individual scale items to see to what extent, if any, the difference in total scale scores is attributable to items that might register pseudoparkinsonian signs/symptoms. Unfortunately, we have neither the luxury in time or resources to do this now.

In sum, I believe you cannot dismiss fairly, or with reason, my view that the validity of a measurement must be evaluated in the context of the use to which it is put, or stated conversely, that its validity <u>cannot</u> be judged from its[2] properties examined in isolation. This view is hardly mine alone; in fact, it is the view celebrated in the guidance offered in the American Psychological Association's manual on psychometric test validity.

Accordingly, I believe your implication that my concern about the validity of the assessment instruments can be dismissed on your personal observation

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[2] it refers to the instrument that generates the measurement

that "Although ...a test could respond to some action of a drug other than its antidepressant action, that seems equally true for the comparison with placebo. The answer, I think, is to expect that a difference, to be considered real, will show upon on all (most) of the tests we use to evaluate antipsychotic, antidepressant, etc. findings."

By the way, I agree totally with your view about the value of products that work where others fail. That, however, is a very different comparative matter, one with very different implications for both labeling and advertising.

4. Deaths

On this subject, I have only an observation. I would be very wary of making very much of any extrapolations based on a pooling of data taken from the three drug development cohorts. I have no confidence, let alone a valid means, to know just how comparable they are, and therefore, whether it is appropriate to combine them. In short, any pooled estimate of a common attribute will be of uncertain validity.

Incidentally, as to 'p' values for these or any other post hoc comparisons, I doubt whether or not a correction for multiplicity is or is not made has any effect on their validity. I speak primarily of data conditioned contrasts among groups not formed by randomization. You can calculate a 'p' value for these contrasts, but it has no useful meaning. Such contrasts beg the identity of the null hypothesis being tested in the sense that even if a low 'p' is obtained, the cause of the difference that is too small to be attributed to chance remains uncertain.

Most of the other points covered in your memorandum are about specific issues and I have no comments to offer about them, although Dr. Laughren does in his memorandum. It also addresses issues raised in the course of our meeting. Dr. Laughren also explains why we have not followed certain of your suggestions.

In any event, my comments and observations notwithstanding, the NDA is approvable provided, of course, that Zyprexa is marketed under the draft labeling that is serves as attachment 1 to the approvable action letter now being forwarded.

Paul Leber, M.D. 8/30/96

August 18, 1996
Memorandum
From Dr. Paul Leber
Director, Neuropharm drug products (FDA)
To: Dr. Robert Temple
Director, Office of Drug Evaluations (FDA)

Pg 2

On EFFECTIVENESS:

ADMITS THAT THERE MAY BE NONE ---

"it is only present in principle"

pg3
economics and politics compel approval

pg 4

concerned about non-equieffective doses that have been used in trials.

Pg 5
Concerned about lack of superiority to HALDOL, even when
Patients have been included in the study on BASIS of having FAILED Haldol
In the past

Makes reference to Laughren's past concerns about "small effect size" and the fact
That much larger studies were needed to obtain even slight significance in efficacy

Pg 7
Concedes that it is not possible to address "effect size" .....
That this is NOT a "problem" from a regulatory standpoint

Pg 8

Issues CAUTIONS about safety ====
That even LOW probabilities of risk may be VERY significant in terms
Of REAL population effect, once a drug is used in LARGE numbers

[my Question is: Can we really rely upon safety data in studies that have given average patient
Less than six months of exposure to olanzapine ?]

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 18, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 20-592 Zyprexa® [olanzapine]

TO: File NDA 20-592
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my endorsement of the review team's unanimous recommendation that the NDA for Zyprexa be declared **approvable.**

Introduction

The review team's exposition of the evidence documents that the sponsor's application provides sufficient information to establish, within the meaning of the Act, that olanzapine will be "effective in use" and "safe for use" under the conditions of use recommended in the labeling developed by the Division's review team. In the course of its systematic review of the information and reports provided, the Review team uncovered no finding or issue that could be considered exceptional, disconcerting, or controversial. Accordingly, the NDA has not been presented to the Psychopharmacologic Drug Products Advisory Committee.

Our understanding of the data adduced in the 4 clinical studies deemed by design capable of providing evidence of Zyprexa's effectiveness in use was increased substantially by the analyses conceived of and executed by Dr. Hoberman, the mathematical biostatistician assigned to the review team. His innovative conceptualization of "dropout cohorts" that provide a visual display of the status of dropout's by treatment during each interval over the course of a randomized trial provides an evidence rich basis to assess the impact of censoring on analyses of the " intent to treat" samples upon which primary descriptions of clinical trial results ordinarily rest.

Incidentally, my singling out of Dr. Hoberman's work is in no way intended to

diminish the caliber of work done by other members of the review team. The team's workup was outstanding.

In sum, although I have no reservations about the regulatory decision being recommended to the Office, I do have a number of observations about olanzapine and the sponsor's development program that are of potential importance in regard to the kind of promotional claims that it may or may not be appropriate to allow Lilly to advance for Zyprexa.

Effectiveness (absolute and relative?)

The NDA provides "substantial evidence" that olanzapine is an effective antipsychotic drug product. This conclusion, however, is not intended to convey a judgment that the sponsor's development program has evaluated every important aspect of olanzapine's use in the treatment of psychosis that the agency might like to have available at the time an NDA is approved, or that a prescribing physician would prefer to possess.

The evidence adduced in the sponsor's short term (nominally 6 week long) studies, although it unquestionably provides compelling proof in principle of olanzapine's acute antipsychotic action, does not, because of 1) the highly selected nature of the patients admitted to study, 2) the high incidence of censored observations in the controlled trials, and 3) the indirect means used to assess the product's antipsychotic effects, provide a useful quantitative estimate of how effective[1] (even in the short run) olanzapine actually will be in the population for whom it is likely to be prescribed upon marketing.

The relatively short duration of the controlled clinical trials the sponsor relies upon, as might be anticipated, leaves us largely uninformed both about how effective a "maintenance" treatment olanzapine will be in extended use,

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[1] This acknowledgment is not an implication that some other information gathering strategy on drug performance/use can accomplish what randomized controlled trials of the sort now conducted in commercial drug development cannot. To the contrary, those who use the limitations of the RCT to promote the fatuous notion that observational outcome studies can provide insights that the RCT cannot are deluding themselves. It is a fact that the typical RCT's we rely upon have limited external validity, and that is weakness. It is one, however, that pales in comparison to those of outcome "studies" that have, as a result of their uncontrolled comparisons and limitless undeclared assumptions, neither internal nor external validity.

and how best to administer it (i.e,. dose and regimen) for that use.

These limitations, of course, are hardly unique to the set of trials conducted by Lilly in its development of olanzapine. In fact, as development programs go, Lilly's evaluation of olanzapine is a reasonably good one in light of its primary intent.

Commercial drug development programs are intended to adduce, in the shortest interval possible, the evidence that will allow the approval of an NDA. Accordingly, sponsors do not ordinarily attempt to provide answers in their NDA submissions to every question that may arguably provide useful information about their product.

Moreover, it is not only economic considerations, but the prevailing political environment, one which places great weight on the pace of drug development (i.e., achieving the shortest possible latency between drug discovery and drug availability at the bedside), that undermines the incentive to approach the development of a new drug with the kind of flexibility that allows for the adjustment of development plans to address questions and issues that were unanticipated at the start of a development program (e.g., issues identified during clinical testing)

There is, however, a force at work that operates to increase the volume of clinical testing: marketplace competition. This characteristic of the current health care economy virtually compels those developing new drugs, in particular those that will compete with already marketed products, to advance claims of superiority or advantage. It is this need that drives the conduct of comparative drug trials.

One aspect of this is quite paradoxical. In the midst of an epoch where much attention is being given to efforts to make both the drug development and approval process more efficient (i.e., to reduce the number of studies that, respectively, must be submitted and reviewed, to support NDA approval), sponsors are being driven to conduct more studies and, to boot, ones that are more complicated and difficult to conduct, at least validly. I write, of course, of studies intended to show a product's advantage to an already marketed drug.

Such studies are not only more difficult to design and conduct fairly, but are also more difficult to interpret. Indeed, their assessment requires that attention be given to a number of issues that the "proof of principle"

randomized, controlled effectiveness trials that regulators have long been accustomed to evaluating for assessing effectiveness do not pose.

The typical controlled trial intended to document the advantage of a new drug usually involves some kind of comparison between the new drug and an already marketed product, typically one that dominates the market. Haloperidol, for example, is, if such a thing exists, pretty much the "standard" antipsychotic drug product; accordingly, it is the product against which new antipsychotic products are typically compared. Incidentally, these comparisons need not be performed only in "stand alone" comparison studies, but are often 'piggy-backed" onto the design of the more traditional effectiveness trial.

The review of NDAs, as a consequence, no longer focuses entirely on the relatively simple issue of whether or not the product is, within the meaning of the Act, "effective in use " and "safe for use," but on the much more vexing, perhaps unanswerable question, of whether or not the new drug is better than the standard, if not globally, then on some clinically important domain (ease of use, freedom from one or more untoward effects, etc.).

None of this is wrong, in principle. The comparative performance of a new drug is not only a legitimate question, but an important one. Who would not want to know which of several competing products is most effective and most safe? Who would not want to know that a particular drug, all things considered, gives a "bigger bang for the buck.?" The problem, of course, is that mere wanting is not sufficient. Valid comparisons of drug performance are not readily obtained. Moreover, even comparisons that on face appear compelling and reasonable can prove misleading.

A primary reason is that the information required to determine whether or not a particular comparison is fair and valid is rarely available[2].

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[2] This is an assertion. There are, as yet, no regulatory standards vis a vis comparative claims. I believe, however, that for a drug product comparison to be meaningful, the products involved must be compared at equi-effective doses under conditions that do not give one product an unfair advantage. I also believe that, because equi-effective doses may not be the same from sample to sample, that a valid comparative design must be able to show, from its internal results (not historical expectations), that the drugs compared are being administered at the an equivalent position along their response vs dose curve.

Another problem is that clinical studies, whether conducted by academicians or commercial corporations rarely, if ever, provide a valid estimate of the "effect size" of a product even when the estimate derives from the result of a clinical trial executed with care and competence. If one cannot know reliably what the effect size is, how can one judge the clinical importance of differences in the size of the effect measured among several products?

Moreover, one cannot always be confident as to what an observed between treatment difference adduced on an instrument is due. This concern reflects the oft ignored fact that validity cannot be ascribed to a rating scale in isolation, but to the use for which that scale is employed.[3]

These observations about the problems of comparative inference are not put forward solely for academic reasons. The fact that differences found in clinical trials comparing products have arguable external validity is of major regulatory importance vis a vis drug product labeling and advertising.

Given this background, I will explain why I believe the data adduced in the Zyprexa NDA is, although readily able to support the NDAs approval, insufficient to permit the sponsor to make claims asserting the product's superiority to haloperidol.

In study **HGAD**, a 23 center, study involving some 335 patients randomized to 3 dose ranges of olanzapine (5 +/- 2.5 mg/d, 10 +/- 2.5 mg/d, and 15 +/- 2.5 mg/d), haloperidol (15 +/- 5 mg/d) and placebo, there are no clear findings

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[3] The point made is that the validity of a test cannot be assessed without considering the use to which the test is put. A difference in outcome between drug and placebo assigned patients detected using a multi-item rating instrument may validly reflect a therapeutic effect the instrument was designed to measure. A difference found between two pharmacologically active drugs on the same assessment instrument, however, may not reliably speak to the differential effectiveness of the two products, but to some other consequence of drug action that is detected by the test instrument. The Hamilton Scale for Depression, for example, is sensitive to changes induced by established anti-depressants that have nothing to do with either drug product's therapeutic antidepressant action. Accordingly, caution is required in interpreting the meaning of between treatment differences even when they are detected using instruments that are widely accepted as "valid" for what may seem to be a very closely related use.

that can be claimed to show that olanzapine is more effective than haloperidol, although there are certainly some differences that could be described as "hints" of it. These hints, however, although they are consistent with common expectations predicted by the pharmacology of the two drugs[4] must also be considered in light of the patient sample's prior experience with haloperidol and the doses at which the products are compared. In sum, I would not interpret the results of HGAD as support for a comparative claim, either explicit or implied, because 1) its design is inappropriate,and 2) the sample of patients used is an inappropriate choice.

E003, is a basically failed study; moreover, by design and patient sample selection would, if positive, not prove what the sponsor's wants to show.

Study HGAJ, Lilly's very large[5] randomized trial comparing outcomes over a 6 week period among schizophrenic patients treated with olanzapine and haloperidol (the dose of each drug was permitted to range between 5 mg and 20 mg a day, being adjusted according to the clinical judgment of prescribers) is the second source that the sponsor can argue shows an advantage of olanzapine. The titration design of **HGAJ** makes it ill-suited for evaluating the comparative performance of two drugs, however. Moreover, like other studies in the sponsor's development program, it suffers in that it entered a sample of patients with a history of prior use of haloperidol, a factor, as noted earlier, that makes the study sample inappropriate for comparison purposes.

I am not, however, as concerned as Dr. Laughren is about what he characterizes as the small magnitude of the estimated between treatment difference, nor that fact that a very large study was required to show that the observed difference is unlikely to be due to chance.

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[4] Both the comparative neurotransmitter receptor binding profiles of the products and the electrophysiologic studies of the products would lead many experts to predict that olanzapine would be expected to exhibit less 'neuroleptic' activity than haloperidol. This, in turn, would not only be expected to influence the incidence and kind of ADRs reported, but any effectiveness instruments that are sensitive to the subset of psychotic phenomena (e.g., so-called negative signs/symptoms of Schizophrenia) that overlap with those of pseudoparkinsonism.

[5] 1950 or so subjects in 186 US and European centers: 1312 on randomized to olanzapine, 636 to placebo

The size of a drug's effect is, as my earlier comments indicate, an abstraction, a notion that is not yet fully reified. Importantly, the agency, wisely given the potential difficulties involved in reifying the concept, has steered clear of the issue. I believe we should do so in the arguments about HGAJ.

The allegedly "small" size of the measured difference, in my view, is not its fault, at least from a regulatory perspective. In fact, if I were convinced that differences observed in a study were truly a valid and accurate reflection of a real difference in therapeutic effectiveness of the products compared, I would willingly endorse the presentation of the evidence supporting the conclusion in product labeling, although, as a matter of truth in labeling, I would, if such hypothetical evidence did exist, require the sponsor to include a display of the empirical cumulative distribution of the between product difference in product labeling.

In sum, although I have no reservations at all about concluding, from the evidence adduced and reported, that olanzapine will be effective in use within the meaning of the Act, I would not go further.

Moreover, I believe it is proper to ask that the firm make a commitment to conduct clinical trials that can evaluate in a valid and meaningful manner Zyprexa's performance in extended use as a maintenance treatment.

Evidence of safety for use

Preclinical findings

The full panoply of preclinical tests required to support the approval of an NDA have been performed and reported. Review of the reports submitted has not detected any result that would preclude approval of the NDA, although some findings (e.g., those involving results of in vivo lifetime carcinogenicity testing) warrant description in product labeling.

Clinical findings

No pharmacologically active drug substance is absolutely free of risk. This caveat offered, the evidence adduced in clinical testing that has so far been reported to the Zyprexa NDA is more than sufficient to support the conclusion that olanzapine, within the meaning of the Act, is safe for use under the

directions of use given in the Division's draft labeling.

It bears note that this conclusion is strongly conditioned on the evidence so far adduced. No one should be surprised if, upon marketing, events of all kinds and severity not previously identified are reported in association with olanzapine's use. Moreover, post-marketing experience may easily provide a very different impression of what are or are not the primary considerations of importance to the clinician and patient who, respectively, use and take, Zyprexa. Again, these statements reflect a generic limitation on regulatory inferences of 'safety in use' that derive from limited clinical experience with samples of patients who do not fully reflect the population likely to be treated with a drug upon its approval.

The safety data base reported upon in the Zyprexa NDA, at the time this approvable action is being contemplated, involves approximately 2500 patients. While this is far above the minimum experience required for NDA approval, it is not as robust as it may appear, especially if Zyprexa proves to be, upon marketing, a very popular drug product. Under such conditions, a very low probability of risk, one too small to make it likely that we would see even one case of the event in the NDA, might be sufficient to generate substantial numbers of cases of the event upon marketing.

On the other hand, there are risks that seem certain to be realized; fortunately, they are not likely to be very different from those associated with other antipsychotic drug products that have a similar profile of receptor binding.

Olanzapine's dopamine receptor antagonist actions make it likely that the product will cause prolactin elevation, pseudoparkinsonian signs and symptoms, tardive dyskinesia and the neuroleptic malignant syndrome. It's potent anticholinergic activity may cause some distress and its relatively potent alpha adrenergic antagonism probably will be associated with orthostatic hypotension, syncope, and risks that can arise as a secondary consequence of these latter events.

In any event, the labeling text as proposed alerts the prescriber to these risks. If adopted as proposed and/or recommended (the sponsor still has work to do), the Zyprexa product labeling will be informative and not false or misleading in any particular.

Recommendation:

Issue the draft approvable action letter that is forwarded in the company of this memorandum and action package.

Paul Leber, M.D.
8/18/96