



NDA 22-173

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

We acknowledge receipt on June 13, 2008 of your June 13, 2008 resubmission to your supplemental new drug application for Zyprexa TRADENAME (olanzapine) For Injectable Suspension, 210, 300, and 405 mg/vials.

We consider this a complete, class 2 response to our February 25, 2008 action letter. Therefore, the user fee goal date is December 13, 2008.

If you have any question, call me, at (301) 796-1924.

Sincerely,

{See appended electronic signature page}

Keith Kiedrow, Pharm.D., LCDR USPHS
Senior Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research

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/s/

Keith Kiedrow

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/s/

Keith Kiedrow

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NDA 22-173

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to the meeting between representatives of your group and FDA on May 7, 2008. The purpose of this meeting was to discuss development plans forward following the issued not approvable letter for NDA 22-173.

The official minutes of the meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Keith Kiedrow, Pharm.D., Regulatory Health Project Manager, at (301) 796-1924.

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 (meeting minutes and slides presented by Eli Lilly & Company during meeting)

MEMORANDUM OF MEETING

NDA 22-173; Zyprexa (olanzapine pamoate) Long Acting Injection
Eli Lilly & Company
Type A meeting; Post NDA action meeting
May 7, 2008

olanzapine long acting injection – discussion of development plans forward following the issued not approvable letter

Participants –

FDA

Robert Temple, MD	Office of Drug Evaluation I Director
Thomas Laughren, MD	Division of Psychiatry Products Director
Jing Zhang, MD	Medical Reviewer
Phillip Kronstein, MD	Medical Reviewer
Barry Rosloff, PhD	Pharmacology/Toxicology Supervisor
Darren Fegley, PhD	Pharmacology/Toxicology Reviewer
Raman Baweja, PhD	Clinical Pharmacology Team Leader
Andre Jackson, PhD	Clinical Pharmacology Reviewer
Peiling Yang, PhD	Statistical Team Leader
George Kordzakhia, PhD	Statistical Reviewer
Keith Kiedrow, PharmD	Regulatory Project Manager

Lilly

Sara Corya, MD	Medical Director, Global Physician Development
Brophy, PhD	Director, US Regulatory Affairs
Matt Kuntz, RPh	Regulatory Scientist, US Regulatory Affairs
Robert Conley, MD	Distinguished Lilly Scholar, US Medical Development
David McDonnell, MD	Medical Advisor, Global Brand Development
Scott Andersen, MS	Sr. Research Scientist, Statistics
Nayan Acharya, MD	Medical Director, Global Patient Safety
Elizabeth Brunner, MD	Medical Advisor, Global Product Safety
Richard Bergstrom, PhD	Research Fellow, Global Pharmacokinetics
Malcolm Mitchell, MD	Director, Biopharmaceutics
Robert Van Lier, PhD	Sr. Research Advisor, Toxicology
Mary Pat Knadler, PhD	Sr. Research Advisor, Drug Disposition
Mike Mason	Team Leader, Zyprexa Global Brand Development
John Kane, MD	Consultant, Chairman, Department of Psychiatry, Zucker Hillside Hospital, Glen Oaks, NY

Background:

On February 25, 2008 the FDA issued Eli Lilly & Company a not approvable letter for NDA 22-173, a long-acting formulation of Zyprexa® (Olanzapine Pamoate [OP] Depot) for the treatment of schizophrenia. The primary deficiency in the Lilly application was the lack of sufficient information on the risk of severe CNS depression events that have been observed in approximately 1% of patients who have participated in the development program for OP Depot. Lilly requested a meeting with FDA to discuss aspects of a proposed amendment to the

application that would address this primary deficiency, including enhanced label language and risk-minimization activities.

Lilly argues that schizophrenia is a serious illness that is associated with increased morbidity and mortality relative to the general population and that OP Depot would provide a critical treatment option. They suggest that there is a population of patients who respond best to olanzapine among the various treatment options but who have difficulty with adherence to oral medications. Lilly feels that the risk of severe CNS depression can be mitigated and managed through labeling and other risk management activities, e.g., extensive education of prescribers.

-Labeling:

- Boxed warning regarding severe CNS depression
- Observation of patients by a health care provider for a minimum of 3 hours post-injection
- Accompaniment of all patients to their destination after leaving the facility
- Vigilance for remainder of day and avoidance of driving and operation of heavy machinery

-Other Risk Minimization Activities:

- Dear HCP letters at time of marketing
- In-person physician and nurse training programs
- Various other ongoing educational programs that emphasize the severe CNS depression event that is of concern

Lilly also argues that the PDAC members were aware of the possibility that severe CNS depression events might occur later than 3 hours at the time they concluded that this product could be approved. [Note: We disagree with this interpretation. It is our view, given Lilly's argument at the time that question was raised, that the committee was persuaded that mechanistically it would be essentially impossible for this to happen given the reabsorption of water from the injection site within 3 hours of an injection.]

Lilly also argues that it should not be necessary to understand the mechanism of this event prior to approval of this product. Alternatively, Lilly feels that several human and animal studies could be conducted in parallel with the approval and marketing of OP Depot.

-Study F1D-MC-B034: a 5000 patient observational cohort study to further characterize the clinical features of this event, risk factors, and the incidence of this event.

-Animal and in vitro studies either ongoing or under consideration:

- Further in vitro solubility studies
- Direct IV injection of OP Depot in animals to better understand the kinetics of direct entry into the vascular system

-Additional clinical pharmacology studies to try to better understand pk variability based on different conditions surrounding injection (resting state, normal activity, excessive exercise, high vs low temperature, etc.)

Question:

Specifically, Lilly would like to discuss the following:

- Modifications to the proposed Risk Management Plan and labeling in relation to the excessive sedation/severe CNS depression
- The feasibility of additional clinical or animal studies to address the mechanism of the event and onset risk interval

In addition, Lilly would like to share additional details and perspectives on excessive sedation case #28 (MedWatch MX200802000384, included in Appendix 4 of the provided briefing document), that was cited specifically in FDA's not approvable action as raising doubts about the mechanism of action and the risk interval.

Lilly proposes the following question for discussion at the meeting:

- 1) Given the additional proposed labeling concepts and risk minimization activities outlined in this document, does FDA agree that a path toward approval for OP Depot can be identified?

Preliminary Comments: *We are willing to discuss with you approaches to the approval and marketing of OP Depot in a manner that would minimize the risk of the adverse event of most concern for this product, i.e., severe CNS depression. If, as you suggest, it is unlikely to be possible to understand the mechanism of this event prior to approval, we would like you to consider, as an alternative to study B034, the initial marketing of this product under a strict registry. The registry could include all the features of study B034, but would then apply to all patients exposed to this product. Such a registry would make it possible to ensure that we could discover as efficiently as possible the true incidence of this event and the true distribution of time to onset of this event under conditions of more typical use in the community. Given the limited number of prescribers who would likely use this product and the limited number of patients who would likely be candidates for treatment, according to your projections, this would not seem to be a burden.*

Discussion at Meeting: *Lilly has considered our suggestion of a strict registry as an option for the initial marketing of OP Depot and is agreeable to this approach. Such a registry would have similar features to study B034 and would provide an opportunity to relatively quickly develop a database to better estimate the true incidence of this event and the true distribution of time to onset of this event under conditions of more typical use in the community. Participating physicians would need to agree to collect and report certain data about patients participating in this program and would need to agree to the conditions of a risk management plan that would include careful monitoring and observation of patients post injection. Their proposed labeling would include many of the features noted above and patients would need to sign consent forms to participate. We indicated our agreement with this approach as a path forward with this application. There was agreement that further studies to try to understand the mechanism of this event represented a considerable challenge, and will not be a precondition for resubmitting the application. We also agreed that a registry should be considered a temporary requirement until sufficient data could be accumulated to provide reassurance that this product could be safely used in the community. Finally, we agreed to consider alternative names to better characterize the adverse event of concern.*

Conclusions:

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Eli Lilly & Company is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

Keith Kiedrow, Pharm.D.
Regulatory Project Manager

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/s/

Thomas Laughren
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FDA Preliminary Responses

NDA 22-173; Zyprexa (olanzapine pamoate) Long Acting Injection
Eli Lilly & Company
Type A meeting; Post NDA action meeting
May 7, 2008

olanzapine long acting injection – discussion of development plans forward following the issued not approvable letter

Participants –

FDA

Thomas Laughren, MD	Division of Psychiatry Products Director
Mitchell Mathis, MD	Deputy Director
Jing Zhang, MD	Medical Reviewer
Phillip Kronstein, MD	Medical Reviewer
Barry Rosloff, PhD	Pharmacology/Toxicology Supervisor
Shiny Mathew, PhD	Pharmacology/Toxicology Reviewer
Darren Fegley, PhD	Pharmacology/Toxicology Reviewer
Raman Baweja, PhD	Clinical Pharmacology Team Leader
Andre Jackson, PhD	Clinical Pharmacology Reviewer
Peiling Yang, PhD	Statistical Team Leader
George Kordzakhia, PhD	Statistical Reviewer
Keith Kiedrow, PharmD	Regulatory Project Manager

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- Other Risk Minimization Activities:
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Question:

Specifically, Lilly would like to discuss the following:

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Discussion at Meeting:

General Comments:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion during the face to face meeting scheduled for May 7, 2008 between Eli Lilly & Company and the Division of Psychiatry Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to [your development plan/the purpose of the meeting/to the questions] (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

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Keith Kiedrow
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Keith Kiedrow

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IND 60,701

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for olanzapine long-acting injection.

We also refer to your submission dated September 25, 2007, containing the request to evaluate the proposed tradename Relprev.

With the aid of the Division of Medication Errors and Technical Support of the Office of Surveillance and Epidemiology we have completed the review of your submission and have the following comments.

Proprietary Name

DMETS does not recommend the use of the proprietary name, Zyprexa Relprev, because the modifier/suffix Relprev is an ambiguous term that does not have a recognized meaning among healthcare professionals, it does not convey the extended-release properties of this product, and it contains the U.S. Adopted Name (USAN) stem “-rev”.

We recommend that the applicant submit alternate proprietary names for consideration by DMETS.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

Labels and Labeling

We recommend that a failure mode and effects analysis (FMEA) be conducted on this product and its associated labels, labeling, and packaging. This analysis will identify the failure modes most likely to occur in real use settings that have not already been identified. Once the failure modes are identified, the product and its associated labels, labeling, and packaging can be redesigned to minimize the failures. Once redesigned, the testing should be repeated in a real use environment to determine if the redesign is successful. This process should be repeated until most failures have been adequately addressed.

General Comments

1. For consistency and to minimize confusion, revise so that the correct term, either solution or suspension, is consistently used throughout the labels and labeling to describe the product after reconstitution.
2. The applicant must address how the color of the reconstituted solution impacts the safe administration of this product.
3. The applicant must provide strategies for minimizing the risk associated with having reconstitution volumes and injection volumes which differ.
4. DMETS recommends that the applicant implement an educational campaign that informs practitioners of the introduction of this new dosage form and educates them on the differences between Zyprexa (b) (4) and the currently marketed Zyprexa product intramuscular administration. Education of practitioners will also allow them to make appropriate entries into their computer databases to differentiate the listings of Zyprexa products in their product menus to minimize computer selection errors. This educational campaign should begin before introducing this product into the marketplace and should continue for at least one year following marketing.
5. To help inform practitioners of this new dosage form, DMETS recommends that the applicant include a “New Dosage Form” banner on the primary display panel of all Olanzapine container labels and convenience kit labeling. However, we remind you that such banners are only permitted for a period of time not to exceed six months.
6. We recommend that the use of codes such as (b) (4) be deleted from all labels and labeling.
7. All references to (b) (4) with regards to the product used for reconstitution of Zyprexa Relprev should be revised to read “diluent” throughout the labels and labeling.
8. Delete the statement (b) (4)

Container Labels

A. Olanzapine Powder

1. Revise the presentation of the proprietary name so that the entire name appears in a print font of the same size, color, and style. Additionally, assure that the font color utilized for the proprietary name contrasts with the background color and is not the same as any color used for product strength differentiation.

2. Increase the prominence and specificity of the route of administration statement to read “For Deep Intramuscular Gluteal Injection Only.” Increased prominence may be achieved by increasing the font size and bolding.
3. Revise so that the statement “Upon reconstitution with x.x mL of diluent, x.x mL will deliver xxx mg of Olanzapine (each mL will contain 150 mg of Olanzapine).” appears on each label.
4. Ensure the established name is at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2).
5. Delete the statement (b) (4).
6. Decrease the prominence of the applicant’s name.
7. Relocate the route of administration statement so that there is no intervening information between the established name and product strength.

B. Solution for Zyprexa Relprev (the diluent)

1. Revise the presentation of the proprietary name so that the entire name appears in a print font of the same size, color, and style. Additionally, assure that the font color utilized for the proprietary name contrasts with the background color and is not the same as any color used for product strength differentiation.
2. The applicant should supply a volume of diluent in the kit that corresponds to the amount of diluent required for reconstitution of that particular product strength. However, if the Division chooses to approve this application as proposed (i.e., with the same volume of diluent in each kit), revise the label so that the statement “IMPORTANT: This vial contains more diluent than is needed for reconstitution.” appears prominently on the principal display panel.
3. Revise “Solution for Zyprexa Relprev” to read “Diluent for Zyprexa Relprev” and reduce the prominence of the proprietary name “Zyprexa Relprev”. For example, “Diluent for Zyprexa Relprev”. Additionally, ensure the established name is at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2).
4. Delete the statement (b) (4).
5. List the diluent ingredients horizontally on the primary display panel below the statement “Diluent for Zyprexa Relprev”.
6. Decrease the prominence of the applicant’s name.
7. Revise to include a statement warning that the diluent for Zyprexa Adhera should not be used to reconstitute any other product.

Convenience Kit Labeling

1. Revise the presentation of the proprietary name so that the entire name appears in a print font of the same size, color, and style. Additionally, assure that the font color utilized for the proprietary name contrasts with the background color and is not the same as any color used for product strength differentiation.
2. Increase the prominence and specificity of the route of administration statement to read “For Deep Intramuscular Gluteal Injection Only.” Increased prominence may be achieved by increasing the font size and bolding.
3. Relocate the statement “Upon reconstitution with....” from the back panel to the primary display panel.

4. Revise so that that the dosing frequency appears prominently on the principal display panel (e.g., ONCE EVERY TWO OR FOUR WEEKS).
5. Relocate the product strength so that it appears immediately following the established name without any intervening manner. Additionally, revise the font color of the product strengths statements which are presented in white to match the color used for product strength differentiation (e.g., blue for the 405 mg/vial strength).
6. Ensure the established name is at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2).

Package Insert Labeling

1. Increase the prominence and specificity of the route of administration statement to read “For Deep Intramuscular Gluteal Injection Only.”
2. Revise the statement in Section 3 (Dosage Forms and Strengths) that describes the color of the reconstituted solution to more accurately reflect the true color.

Instructions to Reconstitute and Administer Zyprexa Adhera

Revise so that the font colors utilized for the text have greater contrast with the background colors.

If you have any questions, call Keith Kiedrow, Pharm.D., Regulatory Project Manager, at 301-796-1924.

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

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Thomas Laughren
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CMC BRANCH CHIEF MEMORANDUM

To: NDA 22-173
From: Ramesh Sood, Branch Chief, ONDQA
Date: 15-Feb-2008
Drug name: Zyprexa Tradename (olanzapine) for injectable suspension
Subject: “**Approvable**” recommendation for NDA 22-173

Introduction: Zyprexa[®] Tradename is a sustained release, long-acting, intramuscular injection (depot) for the chronic or maintenance treatment of psychotic disorders. The active ingredient in the drug product is olanzapine pamoate monohydrate. Olanzapine is the active ingredient in the approved marketed product, Zyprexa[®]. The pamoate salt of the olanzapine molecule provides the drug product with its extended release characteristics. It is supplied as a kit of three strengths (210 mg, 300 mg and 405 mg). Each kit contains a vial of olanzapine pamoate, a vial of vehicle, a 3 ml syringe and three 19-gauge needles. The powder requires reconstitution with the vehicle provided in the kit prior to use. The volume of vehicle added to each strength differs so that they share a common concentration of 150 mg/ml. Care must be taken to administer the suspension “immediately” after withdrawing it into the syringe. This avoids the settling of the solid in the suspension which may result in blockages of the syringe and injection failures.

(b) (4)

Drug Product: Olanzapine pamoate drug product is a solid, yellow powder in a vial supplied as dosages of 210 mg, 300 mg and 405 mg of olanzapine base (present as the salt, olanzapine pamoate monohydrate 483 mg, 690 mg and 931 mg, respectively). In addition each vial contains an (b) (4) of olanzapine pamoate monohydrate (equivalent to (b) (4) olanzapine base and (b) (4) of final suspension after suspension). The product is suspended in the provided vehicle at a concentration of 150 mg/ml (based on the olanzapine base) immediately prior to the injection. The length of drug release (and its bioavailability and the drug product performance) is

dependant on the volume introduced and the solid-state properties of the drug substance (each strength has the same concentration). The release is mass (dose) limited and therefore volume administered decides the length of action.

(b) (4)

Pending CMC issues: There are some pending CMC issues related to the specification of the vehicle used for suspending drug product prior to injection. The sponsor is asking for a much wider viscosity range than the range observed for clinical trial batches and commercial batches manufactured to date. The higher viscosity of the vehicle can have a potential negative effect on injectability, suspension preparation and entrapment of air bubbles resulting in accurate dose determination problems, and filtration problems during manufacturing. The company is also being asked to justify the proposed range for the force needed to inject the product.

The OCP reviewer has not finalized the adequacy of dissolution method and the acceptance limits at this time. Therefore, a tentative expiration period of 36-month and 24-month are being assigned to the olanzapine pamoate powder drug product and the vehicle, respectively, based on the dissolution method and the acceptance limits proposed by the applicant in the submission.

All manufacturing sites have been found acceptable by the Office of Compliance.

Recommended action: The application is recommended as “**Approvable**” from CMC perspective. The outstanding CMC issues have been discussed above. Additionally, the clin/pharm reviewer has not yet accepted the applicant’s proposed dissolution method and the dissolution acceptance limits. Any changes to the dissolution method or acceptance limits as proposed by the applicant will necessitate a re-evaluation of the provided stability data and expiration date.

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Ramesh Sood
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**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: January 7, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: February 6, 2008 Meeting of the Psychopharmacologic Drugs Advisory
Committee (PDAC)

TO: Members, PDAC

This one-day PDAC meeting will focus on NDA 22-173 for a Zyprexa Olanzapine Long Acting Injection, a depot formulation of olanzapine intended for administration every 2-4 weeks. This is a pamoate formulation of olanzapine and has been referred to as OP Depot by the sponsor.

The efficacy of OP Depot has been established in studies HGJZ and HGKA.

-Study HGJZ was an 8-week study involving acutely ill patients with schizophrenia. This was a double-blind trial in which patients were randomized in a 1:1:1:1 ratio to 3 fixed doses of OP Depot (300 mg q 2 weeks; 405 mg q 4 weeks; 210 mg q 2 weeks) or placebo. No oral antipsychotic supplementation was permitted. The primary endpoint was change from baseline to endpoint in PANSS total score, and all 3 active drug groups were statistically significantly superior to placebo.

-Study HGKA was a 24-week maintenance study in stable schizophrenic patients who were initially switched from whatever antipsychotic drug they were stable on to oral olanzapine monotherapy. After a minimum of 4 weeks of continued stability on oral olanzapine, patients were randomized in a 2:1:1:1:2 ratio to OP Depot (405 mg q 4 weeks; 300 mg q 2 weeks; 150 mg q 2 weeks; 45 mg q 4 weeks) or oral olanzapine (10, 15, or 20 mg/day). One objective was to show noninferiority of OP Depot to oral olanzapine monotherapy and a second was to show superiority of the 3 higher dose OP Depot arms to the 45 mg q 2-week arm on time to worsening of positive symptoms. FDA has focused on the superiority hypothesis. All 3 of the higher dose OP Depot arms were statistically significantly superior to the 45 mg q 2-week arm.

FDA agrees that the sponsor has shown that OP Depot is effective in both the acute and maintenance treatment of schizophrenia. We also agree that the usual profile of adverse events with OP Depot is comparable to that seen with oral olanzapine. Our concern about this product has focused on an adverse event that appears to be unique for this formulation of olanzapine, i.e., what the sponsor has referred to as “inadvertent intravascular (IAIV) injection events.” These are instances of sometimes profound sedation occurring shortly after an injection (generally 1 to 3 hours). These are believed to have resulted from rapid release of olanzapine into the systemic circulation, and this view is supported by the limited pk data available suggesting that patients

having these events had unusually high plasma concentrations of olanzapine. These events have occurred in 24 out of 1915 patients exposed to OP Depot (i.e., roughly 1.2% of patients).

The Division's presentation for this meeting will be by the clinical reviewer for this NDA, Jing Zhang, M.D., PhD. Her focus will be on the safety findings for this program, primarily on these instances of profound sedation. The Division's background package includes Dr. Zhang's review of the sponsor's NDA and also a statistical review of the efficacy data by George Kordzakhia, PhD.

The Division of Psychiatry Products has not yet reached a conclusion on this matter, and seeks the advice of the PDAC before reaching a conclusion.

After you have heard all the findings and arguments, we will ask you, first of all, to discuss and comment on several questions pertinent to the safety of OP Depot. Then we will ask you to vote on two questions.

The questions for discussion and comment are as follows:

1. What are the public health consequences of a depot antipsychotic that leads unpredictably to profound sedation in 1% or more of patients exposed to this product?
2. If OP Depot were to be approved and marketed, what risk management procedures would be necessary, including labeling advice, to ensure the safe use of this product? For example, would the labeling changes include a second line status and a black box warning?

The questions for a vote by the committee are as follows:

1. Has OP Depot been shown to be effective for the treatment of schizophrenia?
3. Has OP Depot been shown to be acceptably safe for the treatment of schizophrenia?

cc:

HFD-130/TLaughren/MMathis/GZornberg/JZhang/KKiedrow

DOC: PDAC Feb2008 Memo 01.doc

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/s/

Thomas Laughren
1/8/2008 08:38:32 AM
MEDICAL OFFICER



INFORMATION REQUEST LETTER

NDA 22-173

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D., Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa® Adhera™ (olanzapine) Injection, 210 mg, 300 mg, and 405 mg.

We also refer to your submission dated September 27, 2007.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide justification (e.g. literature reference) for the toxicology limits of the potential leachables listed in Table 3.2.P.2-18. Provide analytical data (not just 'pass') for each of the entries shown in Table 3.2.P.2-18 (if available).
2. The label requires that once the suspension is removed from the vial that it be injected 'immediately'. In your developmental studies how long does the suspension need to remain in the syringe before you begin to detect injection failures? Has the effect on drug substance particle size on these failures been investigated?
3. A relatively high rejection rate was reported for the 405 mg dose (13% rejected). Has the source of this error been determined? What steps are taken to reduce this rate in future lots?
4. For the drug product you propose that a "significant change" in appearance is reported as "pass" and that only a "major change" in appearance will be reported as a "failure". Provide data that demonstrate that drug product which has undergone a "significant change" in appearance can still be of acceptable quality through the proposed expiry period. Further, your defined observations (no change, slight change, significant change, and major change) as defined in Table 4: Evaluation of Observations for a Stability

Sample after Storage (3.2.P.5.2.4) are vague in nature. Provide more specific criteria in the determination of failed samples by physical appearance.

5. Provide updated drug product stability data on both the powder and the vehicle.
6. An expiry period of (b) (4) months for both the vehicle and drug product is proposed. How is the expiry period of the kit assigned if the vehicle and powder parts of the kit were manufactured at different times?
7. Describe how the vehicle batches were chosen for the drug product stability studies. Was older powder investigated with both newer and older vehicle batches?

(b) (4)

9. Has a limit been set as to by how much the NCCW feedback control mechanism can correct the fill-weight from the initial nominal setting? For example, if the feedback control resulted in (b) (4) more solid being added to the vials than the initial nominal setting, would this result in the discontinuing of the filling operation to investigate the cause? One would expect that such large corrections might result from outlying results (from spillages, contamination) or from measurement errors in the NCCW system.
10. Provide a summary of the results from the study in which you demonstrated particle-size distribution homogeneity in the manufacture of drug product for the clinical studies using (b) (4)
11. Provide available stability data which support the comparability protocol.
12. Provide data that demonstrate that drug product suspended with vehicle manufactured from components at the extremes of the proposed weight range (“reasonable variations” Table 3.2.P.1-1) will meet all drug product acceptance criteria through the proposed (b) (4) month expiry period.
13. Recommend that the acceptance criteria for the vehicle’s physical appearance test include a requirement that it be "essentially free from visible particles” (USP <1> for injection).

If you have questions, call Scott Goldie, Ph.D., Regulatory Project Manager, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Blair Fraser, Ph.D.

Director
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Blair Fraser

1/4/2008 11:50:30 AM

Updegraff, Kimberly

From: Updegraff, Kimberly
Sent: Wednesday, December 26, 2007 3:27 PM
To: Matt Kuntz
Cc: Kiedrow, Keith; Updegraff, Kimberly
Subject: Accumulative Risk Analysis on IAIV: NDA 22173 Zyprexa

Importance: High

Attachments: BetaBinomial1.pdf

Dear Matt,

Hello. I am a project manager working with Keith Kiedrow in the Division of Psychiatry Products and I have the following request from the review team concerning NDA 22-173.

Please provide a data set that contains a list of patients with the following variables: patient ID, study ID, treatment group, the number of injections received by each patient, time intervals between injections (for example 2 weeks, 4 weeks, etc.) , the number of IAIV injection events experienced by each patient, and the number of injections received before each IAIV event occurred.

Considering that the set up and the model you employed are as described in the attached file (BetaBinomial1), please provide the following:

How are the parameters of beta binomial model estimated? If this is done by maximizing likelihood, what is the maximization method?

(If the set up and methods are different, please state your model.)

In addition, you mentioned that your program uses data from the 120-day safety update (all injections through January 31, 2007). However, five (out of 25) injection events occurred between January 31, 2007 and September 30, 2007. Were those events included in your analysis data set?

(b) (4)



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/s/

Kimberly Updegraff
6/3/2008 03:46:11 PM
CSO



NDA 22-173

INFORMATION REQUEST LETTER

Eli Lilly and Company
Attention: Robin Wojcieszek, R.Ph.
Associate Director
U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Wojcieszek:

Please refer to your April 27, 2007 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for olanzapine long acting injection 210 mg, 300 mg, 405 mg vials.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA:

1) **S.2.3 Control of Materials – Starting Material** (b) (4)
(b) (4) **Specification:**

Cross-reference the CMC information for the manufacture of olanzapine in NDA 20-592 to support its use in this NDA (22-173) as per the agreement reached at the 22-Jul-2003 sponsor-FDA meeting (ref. Lilly question 4.A – Drug Substance Starting and Raw Materials). Provide commitment that any CMC changes to the manufacture of olanzapine will be appropriately communicated to the Agency.

2) **S.2.4 Control of Critical Steps and Intermediates:**

Any expansion of PAR will have to be communicated to FDA. This comment is related to your statement in this section that a deviation from PAR of a critical process parameter will trigger an investigation that may or may not result in material being forward processed/released in compliance with GMPs and SOPs.

3) **S.2.6 Manufacturing Process Development:**

a. DOE Derived Final Process Parameters: Provide a summary of the statistical analysis [i.e. mathematical model, values of correlation and regression coefficients, and standard error] employed in the DOE.

- b. Provide a summary of the statistical analysis [mathematical model, values of correlation and regression coefficients, and standard error] employed in the initial multivariate model.
- c. Partial Least Squares Calibration Model: Provide a summary of the statistical analysis [i.e. mathematical model, values of correlation and regression coefficients, and root mean square error of prediction-RMSEP_{cv}] employed in the PLS prediction model.
- d. Determination of Critical Process Parameters:
 - a. Has the effect of any interaction between the critical CPPs, or any other process parameters, been considered and if so, provide information on this effect, if any?
 - b. Describe the basis for selection of target and PAR numerical values for the two critical process variables. (b) (4)
(b) (4) in your 'Critical Process Parameter Determination'.
- e. Provide analytical data of lots manufactured at the extremes of PAR of these two critical process parameters. Provide numerical values of these two critical process parameters for lots used in pivotal clinical and registration stability studies.

4) S.4.1 Drug Substance Specification:

- a) Tighten the acceptance criteria for particle size based on the physical characteristics of the (b) (4) DS generated by the (b) (4) (b) (4) manufactured at different sites and at different lot sizes, presented in Table 3.2.S.2-12 (Final (b) (4) OPM Characteristics Prior to Filling), the batch analysis data for the lots made at the commercial site (Section S.4.4), and data presented in Table LOBS.5.2 and Figure LOBS.5.3 (ref. F1D-EW-LOBS Main Report).
- b) Incorporate a test and an acceptance criterion for the pamoate counter-ion.
- c) Incorporate a test and an acceptance criterion for the (b) (4) (b) (4) to confirm that the (b) (4) (b) (4) (described in S.4.3 for the X-ray powder diffraction method) is (b) (4)

5) S.7.2 Postapproval Stability Protocol and Stability Commitment:

Confirm that stability at 40°C/75% RH at the 3 and 6 months time point will be performed on these batches.

6) S.7.3 Stability Data:

The provided 18-month long-term stability data can support a maximum of 30-month reevaluation date for the drug substance as per ICH Q1E. Therefore, include a 30-month test time point in your current stability protocol.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
11/21/2007 11:09:29 AM

Executive CAC

Date of Meeting: November 13, 2007

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Chuck Resnick, Ph.D., DCRP, Alternate Member
Todd Bourcier, Ph.D., DMEP, Alternate Member
Barry Rosloff, Team Leader
Sonia Tabacova, Presenting Reviewer

Author of Draft: Sonia Tabacova

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 22-173

Drug Name: Zyprexa Adhera (Olanzapine Pamoate Monohydrate, i.m. depot formulation)

Sponsor: Eli Lilly and Company

Rat Carcinogenicity Study

Study title: An Oncogenicity Study in Fischer 344 Rats Given Intramuscular Injections of Olanzapine Pamoate Monohydrate Once Monthly for 2 Years

Background:

Olanzapine is approved for use in the United States. The rapid acting intramuscular injection formulation of olanzapine (a solution of the free base, which is intended for immediate absorption upon injection) was approved in 2004 for the indication of agitation associated with schizophrenia and bipolar mania (Zyprexa IntraMuscular; NDA 21-253). The pamoate monohydrate salt of olanzapine (OPM) was developed as a sustained-release formulation because of its low solubility and its potential to meet the needs for a depot i.m. administration.

The positive result of pamoic acid testing in the in vitro chromosome aberration assay in CHO cells prompted some concern that pamoic acid might be carcinogenic, although all other genetic toxicology studies were negative. Therefore, a 2-year IM study in rats was conducted using once/4 weeks injections of OPM; pamoic acid alone was also evaluated in this study. The carcinogenicity protocol of OPM i.m. depot formulation was reviewed under IND 60701 (N 038 and 041) by Dr. Lois Freed (3/26/2003). In consultation with the Division, it was agreed that in view of the limitations of repeated i.m. injections to rodents by the volume that can be injected into the relatively small muscle mass available and the attainable concentration of drug substance in the formulation, a once/4 weeks dosing was acceptable for use in the OPM rodent carcinogenicity study even though the clinical development program was intended to support labeling for IM administration in humans using either once/4 weeks or once/2 weeks injections.

The protocol of the 2-year carcinogenicity study of OPM in the rat was approved by the Executive CAC and the doses were selected in accordance with the Executive CAC recommendations (IND 60701, Executive CAC Meeting Minutes of 3/11/2003). As the active substance of OPM is olanzapine that had been previously tested for carcinogenicity in two species (mice and rats), it was agreed that a carcinogenicity study in one species would be sufficient for the assessment of the olanzapine pamoate depot formulation.

Key study findings: In the 2-year study to evaluate the carcinogenic potential of a sustained-release formulation of olanzapine administered by once per 4 weeks intramuscular injections of olanzapine pamoate monohydrate (OPM) to Fischer 344 rats (60/sex/dose) at doses of 0 (vehicle), 0 (pamoic acid), 5, 10, and 20 mg /kg for males and 0, 0, 10, 25, and 50 mg /kg for females (dose range equivalent to 0.1-1.2x the MRHD of 405 mg/ 4 weeks on a mg/m² basis), there was no carcinogenic effect attributable to OPM or pamoic acid since there was no dose-related effect on incidence and distribution of neoplastic lesions and they were similar among groups. Survival at the end of 2 years (45%, 48%, 48%, 45%, or 35% for males and 65%, 55%, 72%, 70%, or 72% for females in vehicle control, pamoic acid alone, LD, MD, or HD groups, respectively) showed that enough animals of both sexes were exposed for sufficient amount of time. In the high dose group, the mortality rate was 12% higher than the vehicle control in the males, and 6% lower than control in the females (statistically non-significant). There were no drug-related clinical signs. There were small but significant decreases in body weight gain of both genders in OPM dosed groups relative to control throughout treatment (by about 2% and 4% in HD males and females, respectively), while food consumption was slightly increased (by about 6%) in both genders. Pamoic acid alone did not affect body weight or food consumption. The only non-neoplastic pathologic finding attributable to OPM was the presence of residual test article formulation in injection sites and an associated chronic inflammatory response and muscle degeneration. The incidence and severity of residual test article accumulation and associated changes in the injection sites was clearly dose-proportional (out of 60 rats/sex/group, the incidence of this finding was 0, 1, 14, 34 and 52 for males and 0, 0, 22, 48 and 50 for females in vehicle control, pamoic acid alone, LD, MD, and HD groups, respectively).

Plasma concentrations of olanzapine and pamoic acid determined over 14 days (336 h) following 3, 12 and 18 months of dosing showed a dose-dependent increase in olanzapine exposure; the AUC_{0-336h} values achieved at HD were lower or equal to those in humans at MRHD. Exposures to pamoic acid (AUC_{0-336h}) achieved at HD were equal to or higher than those in humans at MRHD. Dose-limiting factors were the amount of test article feasible to be injected i.m. in the rat and the local injection site reaction. In animals receiving pamoic acid alone, C_{max} values of pamoic acid were higher compared to the high-dose OPM groups.

Adequacy of the carcinogenicity study and appropriateness of the test model:

The study was conducted according to standard procedures to assess the carcinogenic potential of the test article.

The Fischer 344 rat was selected because this species and strain is commonly used as the test system for pharmaceuticals and because this was the same species and strain used in the existing oral carcinogenicity studies with olanzapine.

The intramuscular route was selected because it is the intended route of exposure in humans with this formulation. The justification of injection volume of 0.1 ml/100 g of body weight with a total volume not to exceed 0.2 ml was based on “the maximum that should be injected intramuscularly in rats as accepted by most Institutional Animal Care and Use Committees, supported by US and European humane societies” and on “practical limitations of injectability through a 21 or 23 gauge needle”.

Pamoic acid was also evaluated in this study since it “represents that part of the molecule that would be released upon ionization and since no published carcinogenicity data could be cited supporting its long term safety by this or any other route of administration”.

The selection of doses for the 2-year study was based on the 3-month study in the same species and strain at doses of 0, 20, 50, and 100 mg/kg of OPM administered i.m. once a month for 3 months, that resulted in 26% to 39% reduction in body weight gains in HDM, HDF and MDM and in absolute body weight reductions of < 10%, as compared with the controls. The MD and HD in the 3-month study induced significant, dose-limiting, chronic inflammatory reactions in the injection site characterized by atrophy, degeneration, or necrosis of myocytes, fibroplasias, and increased collagen deposition observable for at least 2 months after injection. Injection-site reactions induced by administration of pamoic acid alone were infrequent and less severe than those for the OPM-treated rats.

The doses for the 2-year carcinogenicity study (0, 5, 10, 20 mg/kg of OPM for males and 0, 10, 25, 50 mg/kg of OPM for females, i.m.) were selected in accordance with the Executive CAC recommendations (IND 60701, Executive CAC Meeting Minutes of 3/11/2003). The employed dose range was equivalent to 0.1-1.2 times the MRHD of intramuscular OPM in humans (405 mg/4 weeks) on mg/m² basis. Effect of pamoic acid alone at i.m. doses similar to those administered in the high-dose OPM group (37 mg/kg in males and 92.5 mg/kg in females) was assessed in parallel in additional groups of rats. A MTD was achieved in this study based on dose-related injection site adverse effects in both genders (chronic inflammatory reactions and residual test substance accumulation in the injection site affecting nearly all animals of both genders at HD); additionally, a non-significant (12%) increase in mortality occurred in HD males by the end of the study, and a small decrease in body weight gain in females (4% lower than the control by the end of the study), as determined by the statistical reviewer, Dr. Rahman. Plasma exposures to olanzapine and pamoic acid increased with the increase in OPM dose. Olanzapine AUC_{0-336h} values achieved at HD were lower or equal than those in humans at MRHD (300 mg every 2 weeks or 405 mg every 4 weeks). Exposures to pamoic acid (AUC_{0-336h}) achieved at HD were equal to or higher than those in humans at MRHD. Dose-limiting factors were the amount of test article feasible to be injected i.m. in the rat and local injection site reaction.

It is concluded that this is a valid carcinogenicity study.

Evaluation of tumor findings:

Sponsor's analysis: The sponsor's analyses did not show statistically significant dose-response relationship among vehicle control, LD, MD, and HD groups or between vehicle control and pamoic acid alone in any of the tested tumor types.

Statistical reviewer analysis: Statistical review and evaluation of the results of this study was independently conducted by the statistical reviewer Dr. Mohammad Atiar Rahman. Adjustment for the multiple dose-response relationship testing was done using the results of Lin and Rahman (1998). Adjustment for multiple pairwise comparisons was done using the results of Haseman (1983).

According to Dr. Rahman's review, "tests did not show statistically significant dose-response relationship or pairwise difference in tumor incidence between the untreated (i.e., vehicle) control and any of the treated groups in any observed tumor types."

This reviewer agrees with Dr Rahman's conclusion. The adequacy of the doses used is mainly supported by the amount of test article feasible to be injected i.m. in the rat and the local injection site reaction (presence of residual test article formulation in injection sites and an associated chronic inflammatory response and muscle degeneration). The incidence and severity of residual test article accumulation and associated chronic inflammatory changes in the injection sites was clearly dose-proportional and affected the majority of the treated animals at MD and HD.

In conclusion, based on the lack of a dose-response relationship or difference in tumor incidence between control and any of the treated groups in any of the observed tumor types in a valid carcinogenicity study, there was no carcinogenic effect attributable to the test article (OPM) or pamoic acid alone.

Executive CAC Recommendations and Conclusions:

- * The Committee agreed that the study was adequate, noting prior Exec CAC concurrence with the doses
- * The Committee determined that the study was negative for statistically significant drug related tumors.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DPP
Barry Rosloff /Team leader, DPP
Sonia Tabacova /Reviewer, DPP
Keith Kiedrow/Kimberly Updegraff /CSO/PM, DPP
/ASeifried, OND IO

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David Jacobson-Kram
12/13/2007 07:47:25 AM