

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-173

OTHER ACTION LETTER(s)



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 your new drug application (NDA) dated and received April 30, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa TRADENAME (olanzapine) For Injectable Suspension, 210, 300, and 405 mg/vials.

We acknowledge receipt of your submissions dated –

May 24, 2007	June 8, 2007	June 26, 2007	July 19, 2007
August 13, 2007	August 21, 2007	August 27, 2007	August 28, 2007
September 27, 2007	October 11, 2007	October 18, 2007	October 24, 2007
November 21, 2007	December 20, 2007	January 4, 2008	January 15, 2008
February 8, 2008	February 15, 2008		

This new drug application provides for the use of Zyprexa TRADENAME (olanzapine) For Injectable Suspension for the treatment of schizophrenia.

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Not Approvable Deficiencies

The primary deficiency in this application is the lack of sufficient information on the risk of severe CNS depression that has been observed in approximately 1% of patients who have participated in your development program for OP Depot.

We recognize that, on February 6, 2008, the Psychopharmacologic Drugs Advisory Committee (PDAC) voted 10-0 (with 1 abstention) in favor of OP Depot on questions of whether or not there are circumstances under which OP Depot would be acceptably safe for the treatment of either acutely exacerbated schizophrenia and for the maintenance treatment of schizophrenia. However, these votes occurred at a time when the committee believed that, for all cases of severe CNS depression, onset of the event occurred within a narrow window of up to 3 hours following injection, with most of these

occurring within 1 hour of injection. It is important to note that the committee was not made aware of the details of the most recent case, in particular, the fact that the onset of the CNS depression event in this patient may have been as late as 5 hours after the injection. In fact, in response to a question regarding how confident you were that these CNS depression events would only occur within the narrow window of 3 hours post-injection, you indicated a high degree of confidence, based on a theoretical argument that the diluent would be rapidly reabsorbed from the injection site, certainly within 3 hours, leaving a relatively solid mass of OP Depot that would not be able to easily enter the systemic circulation. We believe this was a determinative factor in the committee's willingness to conclude that OP Depot could be safely used with a relatively brief observation period for this event.

This new case is of critical importance in our thinking about how this drug product could be safely and feasibly used in the community. There is now renewed doubt that the period of risk for onset of these CNS depression events can be reasonably estimated. Simply extending the period of observation to 5 hours does not seem adequate, since this new case now also raises doubts about our understanding of the mechanism underlying such events. Extending the observation period beyond 5 hours raises questions about how such a product could be feasibly used in any outpatient setting.

Thus, it is our view that additional work is needed to better understand the risk and underlying mechanism for this event before this product can be approved. Conducting your planned 5000 patient observational study would help to better characterize the nature of the event and its time course, including both onset and duration. However, we ask that you also consider additional work to try to better understand the mechanism underlying this event. We recognize that these events have not been observed in animal models you have utilized thus far, however, we ask that you consider other animal models that might more closely mimic humans regarding this event. We would be happy to discuss with you your plans for the further development of this product.

Other Deficiencies/Requests

Although not a reason for this not approvable action, you will need to also address the following deficiencies and requests.

Office of Clinical Pharmacology

1. The concentration of 1% sodium lauryl sulfate (SLS) in the pH 6.8 buffer seems to be very high, essentially implying that the entire drug amount is 'solubilized' rapidly. Have you tried experimentation with lower concentrations of SLS? If so, please provide these results.
2. Please explain why you request different release specifications for different doses.

Office of New Drug Quality Assessment

2. The results of all relevant injectability tests to-date were (b) (4) lbf through the product shelf life. This limit will need to be lowered or evidence provided that the product performance of each of the proposed drug product strengths will not be compromised should their administration require an injection force of (b) (4)
3. Include a requirement that the vehicle's physical appearance be "essentially free from visible particles" (USP <1>) in its release and stability specifications. The in-process visual inspection which you previously referred to does not control this parameter through the proposed shelf-life.
4. The comparability protocol supports a CBE-30 filing. It should be noted that some of the batches used to support this protocol do not meet the acceptance criteria for particle size distribution.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 7. Provide English translations of current approved foreign labeling not previously submitted.

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 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you have any questions, contact Keith Kiedrow, PharmD, 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

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Thomas Laughren
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