CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020592Orig1s040s041

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592 / S-040
NDA 20-592 / S-041

Eli Lilly & Company
Attention: Catherine A. Melfi, Ph.D.
Scientific Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Melfi:

Please refer to your supplemental new drug applications dated October 30, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg tablets.

We acknowledge receipt of your submissions dated November 15, 2006, December 11, 2006, January 10, 2007, January 11, 2007, January 24, 2007, February 6, 2007, February 27, 2007, March 27, 2007, and April 12, 2007.

Please note that your submission dated March 27, 2007 was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

These supplemental new drug applications provide for the use of Zyprexa (olanzapine) tablets in the treatment of bipolar disorder (manic or mixed episodes) in adolescent patients (supplement 040) and the treatment of schizophrenia in adolescent patients (supplement 041).

We have completed our review of these applications, and they are approvable. Before the applications may be approved, however, you must address the following deficiencies:

Updated Information on Risks of Weight Gain, Hyperglycemia, and Hyperlipidemia
A primary concern with these applications is that we lack important safety information needed to adequately update the labeling with all relevant risk information. You must fully address these concerns before we will be able to take a final action on these applications.

Please refer to our January 12, 2007 letter regarding recent New York Times coverage of issues related to weight gain, hyperglycemia, and hyperlipidemia in patients taking olanzapine. Please also refer to our March 28, 2007 letter regarding your supplemental new drug application for Symbyax capsules [NDA 21-520, S-012].

Our overall goal is to improve labeling with regard to these findings, in both the adolescent and adult populations, so that clinicians will be better informed on what the risks are for their patients. They cannot make reasonable treatment decisions until they have such information. We do not feel that

current labeling for Zyprexa provides sufficient information on these risks, and we fully intend to insure that this label is enhanced with the best available information to characterize these risks.

Additional Clinical Questions

Please note that some of these questions address information in the overall combined database, and therefore may require information from both the bipolar disorder trial submitted in supplement S-040, and the schizophrenia trial submitted in supplement S-041 to this NDA.

1. For the acute phases of HGIU and HGIN, many patients had elevated prolactin at baseline, therefore the change from baseline to endpoint analyses can be difficult to interpret. Please provide additional analyses for the change from baseline to endpoint on the subset of patients with baseline prolactin within the normal range. Please also provide a separate analysis for gender and age.

2. Table APP.2.7.4.24 in summary-clin-safe-app provides prolactin data over time for the overall combined database. Please provide a similar table for only those patients who completed 19-32 weeks in the study (n = 83 bipolar, n = 93 schizophrenia) - e.g. provide baseline, 1-6 week, 7-18 week and 19-32 week data for only those patients completing 19-32 weeks.

3. Please provide narrative summaries for the following: 8 cases of gynecomastia, 2 cases with high prolactin concentrations (HGIN 005-503, HGIN 900-9009) and the case with a CPK of 7289 U/L .

4. The summary-clin-safe-app document includes comparisons of adult and adolescent data for metabolic parameters and prolactin but not for hepatic laboratory analytes. Please provide these comparisons for hepatic laboratory analytes. Although it was stated in the submission that the hepatic laboratory analyte comparisons were not provided due to differences in reference ranges for adults and adolescents, these comparisons were provided for the prolactin data despite differences in reference ranges for these populations.

5. Please review the MedWatch reports for fatalities and submit updates where possible for incomplete data. It was noted that these MedWatch reports had “DRAFT” at the top of the page and the date of the report was 7/27/06. Have all of these reports been previously filed with the Agency?

6. For MedWatch fatality case US_010158510, the narrative states “This is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in (b) (6). The reporter stated he has also notified the FDA...". The only MedWatch report included in this submission is for US_010158510. Please provide the MedWatch reports for the additional 4 deaths indicated in this narrative.

7. Please provide an analysis of AIMs individual items and total score (change from baseline to endpoint) for the completers in the overall combined database.

8. One concern we have for study HGIN is a finding that the positive results for this trial appeared to come predominantly from the Russian sites. For this study, the total sample was roughly split between these 2 regions. Although olanzapine was favored over placebo numerically in both regions, the data from the Russian sites appeared to be driving the overall result. For the US patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -21 and -15, respectively (p=0.258). For the Russian patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -17 and -3, respectively (p=0.003). So the treatment effect in olanzapine patients was roughly the same in both regions, however, the placebo response was much larger in the US sites compared to the Russian sites. Please address this geographic discrepancy in the efficacy results.

Pediatric Research and Equity Act (PREA)
All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that, with regard to both bipolar disorder and schizophrenia, you have fulfilled the requirements for adolescents aged 13-17 years, but have not studied the drug for either safety or efficacy in children aged 10 - 13 years. We are waiving the requirement for assessment of the safety and effectiveness of the product in pediatric patients aged 10-13 years with regard to both indications; your current studies have met the terms of the initial Pediatric Written Request.

Post Marketing Commitments
Both bipolar disorder and schizophrenia are chronic illnesses, and patients will likely require medication for a prolonged period. The long-term cardiovascular risk of significant weight gain, hypertriglyceridemia and hypercholesterolemia is significant, and efforts to minimize these adverse events are important.

We note that you are planning to conduct a long-term safety study in adolescents with schizophrenia or bipolar disorder, to estimate the incidence and prevalence of identified and potential risks of olanzapine treatment in this population. We recommend that you consider examining the effect of interventions on weight gain in adolescents treated with Zyprexa as part of this study.

Please provide updated information on your planned study in your Complete Response to this letter. Since this will be considered a required Phase 4 commitment, please propose dates for submitting your protocol, and your final study report, to the Agency. Please note that this commitment applies to both indications and the same commitment will be applied to both supplements; your Complete Response should address this commitment in terms of both supplement S-040 and S-041.

Labeling
For both S-040 and S-041, you must submit draft/final printed labeling revised as indicated in the attached marked-up labeling. The marked-up version is based on your submitted proposed labeling; we have used track changes to indicate our additions and deletions, and have added bracketed comments to explain our actions or requests where needed. You may submit identical consolidated labeling in your Complete Response to both supplemental applications. We are willing to meet with you to discuss the proposed changes in the context of the additional safety information requested above and elsewhere in this letter.

In addition, all previous revisions, as reflected in the most recently approved package insert, must be included in the labeling proposed with your complete response to this letter. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes you have proposed.

If additional information relating to the safety or effectiveness of this/these drug(s) becomes available, revision of the labeling may be required.

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

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Prior to an approval action, we require an updated report on the world's archival literature pertaining to the safety of Zyprexa. Please provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. This report should include only literature not covered in your previous submissions. We will need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of 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.

7. 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. Provide English translations of current approved foreign labeling not previously submitted.

Promotional Materials

In addition, submit three copies of the introductory promotional materials that you propose to use for this product in both of the proposed indications. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend the applications, notify us of your intent to file an amendment to each, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with either or both of these changes before approval of the relevant supplemental application.

If you have any questions, call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 796-2260, or contact her via secure email at doris.bates@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas P. Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: FDA revised labeling (package insert)

26 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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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