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

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FROM: Thomas P. Laughren, M.D.
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HFD-130

SUBJECT: Recommendation for approvable actions for Zyprexa Pediatric Supplements for bipolar disorder (acute mania) and schizophrenia

TO: File NDA 20-592 (S-040 [bipolar] and S-041 [schizophrenia])
[Note: This overview should be filed with the 10-30-06 original submission of these supplements.]

1.0 BACKGROUND

Zyprexa (olanzapine) is an atypical antipsychotic (5HT2 and D2 receptor antagonist) that is approved for both schizophrenia and bipolar disorder in adults, including maintenance claims for both. We issued a written request (WR) for both indications, and these supplements are a response to that WR. The 10-30-06 response includes the results from acute studies in mania (HGIU) and schizophrenia (HGIN), and also pediatric PK data from study HGMF.

2.0 CHEMISTRY

The only CMC issue requiring review was environmental assessment. The sponsor sought and was granted a categorical exclusion.

3.0 PHARMACOLOGY

There were no pharm/tox issues requiring review for these supplements.

4.0 BIOPHARMACEUTICS

The sponsor utilized pk data from a formal pk study (HGMF) and also from 3 other studies (HGCS, HGCR, and HGGC) to characterize olanzapine pk in adolescents. Based on these data,

they concluded that overall olanzapine pk was similar in adolescents and adults, and that the one observed difference was greater exposure (by 27%) due to lower weights. Dr. Jackson from OCP agreed, except that he felt that the increased exposure by 27% was an underestimate. He estimated that exposure was increased by about 30-63%. This difference has resulted in a slight modification to the labeling regarding exposure.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review focused on 2 short-term, multicenter, double-blind, placebo-controlled, flexible-dose (2.5 to 20 mg/day), randomized, efficacy and safety studies in adolescents (ages 13-17). One of these studies was in patients with acute mania in bipolar I disorder (HGIU) and the other in schizophrenia (HGIN).

5.1.1 Study HGIU (Acute Mania in Bipolar I Disorder)

This was a 3-week study in bipolar I disorder patients with acute manic or mixed episodes. It was mostly conducted in the US (23 sites) but had 2 sites in Puerto Rico as well. N=161 patients were randomized, and the randomization was 2:1 for olanzapine vs placebo. The mean modal olanzapine dose was 10.7 mg, and the mean daily dose was 8.9 mg. The overall dropouts for this trial favored olanzapine (20% for olanzapine vs 35% for placebo). Of these, the dropouts were mostly for lack of efficacy (11% for olanzapine vs 30% for placebo). The primary endpoint was change from baseline to endpoint on an Adolescent Structured YMRS (total score) and the primary analysis was ANCOVA (LOCF). The results on this analysis were highly favorable to olanzapine ($p < 0.0001$), as were the results for the MMRM ($p=0.0004$) and the OC ($p=0.0013$). Drs. Alfaro, Kong, and Khin all considered this a positive study, and I agree.

5.1.2 Study HGIN (Acute Schizophrenia)

This was a 6-week study in adolescent patients with schizophrenia. It was conducted partly in the US (20 sites, comprising 53% of the total sample) and partly in Russia (5 sites, comprising 47% of the total sample). N=107 patients were randomized, and the randomization was 2:1 for olanzapine vs placebo. The mean modal olanzapine dose was 12.5 mg, and the mean daily dose was 11.1 mg. The overall dropouts for this trial again favored olanzapine (32% for olanzapine vs 57% for placebo). Of these, the efficacy dropouts were most striking, with a 51% loss due to lack of efficacy for placebo compared to only 14% for olanzapine. This finding by itself is almost enough, in my view, to convince one of the benefits of olanzapine in this condition. The primary endpoint was change from baseline to endpoint on a children's version of the BPRS (BPRS-C) total score, and the primary analysis was ANCOVA (LOCF). The overall results on this analysis were highly favorable to olanzapine ($p = 0.003$). However, there were 2 aspects to the data that the review team found troubling, resulting in conclusions by Drs. Alfaro, Kong, and Khin that this should be considered a negative study. Their concerns were as follows:

Highly Non-Significant Results on the MMRM and OC Analyses

Dr. Kong conducted an MMRM analysis as a sensitivity analysis, which yielded a p-value of 0.72. An OC analysis was also highly non-significant result (p=0.95).

> Comment: In my tertiary evaluation, I found this discrepancy between LOCF and MMRM quite unusual, in my experience, and asked for further exploration. As it turned out, Dr. Kong's MMRM analysis was quite discrepant with the sponsor's MMRM analysis (p=0.015). Upon further evaluation, Dr. Kong discovered that the program he had used to conduct the analysis included, as a default, a variance-covariance structure that required independence between the repeated observations for any subject. This is an unusual requirement, and not the variance-covariance structure that we generally recommend. In fact, we almost always recommend an unstructured variance-covariance structure, i.e., the same one used by the sponsor, and a goodness-of-fit exploration for different variance-covariance structures revealed the best fit for this structure. Thus the biometrics group has now recommended that we accept the sponsor's highly significant MMRM result (see addendum to original biometrics review).
>
> Regarding the OC analysis, this remains a discrepancy with the LOCF and the revised MMRM analyses. However, I am not as troubled by this outcome on the OC analysis. As noted, the dropouts on placebo were very substantial, and I'm inclined to view the patients completing a study such as this to 6 weeks on placebo as quite different than the remaining patients. I think the diagnosis of schizophrenia in this younger population is challenging, and likely results in the inclusion of some patients who improve spontaneously, and thus, are doing as well as drug-treated patients at 6 weeks simply because they represent a very different group of patients. This, I think the OC results for this trial can be largely discounted.

Treatment by Geographic Region Interaction

A second problem for the review team was a finding that the positive results were coming 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.

Comment: In addition to the difference in outcome by region, Dr. Alfaro expressed concern that the Russian sites were far more successful in recruiting patients than the US sites. Implicit in such a concern is a suggestion of a problem in study conduct. It is important to note that we did have DSI inspect the Russian sites, and they found no evidence for fraud. It is also important to point out that there are alternative explanations for more successful recruitment at the Russian sites and also a more successful outcome. The sites may have been drawing patients from larger catchment areas than US sites, many of which were single investigators. There also may have been less competition for patients than is the case in the US. There are numerous studies ongoing in the US, and routine treatment is likely also more readily available in the US than in Russia. These same factors may also explain the different results. If difficulty in recruitment in the US sites led to enrollment of a more heterogeneous group of subjects, this could have led to a higher placebo response rate. It is possible that the Russian patients were the more representative schizophrenic patients who typically have very little response to placebo. There is also the expressed concern about relying primarily on non-US data for an approval action. Although I agree this is generally a concern, I think it is more a concern for an initial claim than it is in this case, where we already have a very strong prior belief that olanzapine is an effective treatment for schizophrenia, based on an abundance of positive data in adults. In summary, while I agree this geographic discrepancy is a concern, I do not think it is, by itself, a sufficient justification for a nonapproval action, when the trial is positive overall on the primary analysis and on the MMRM. Nevertheless, we will ask the sponsor to further address our concern about this discrepancy.

5.1.3 Summary of Efficacy

There is unanimous agreement within the review team on the positive outcome for study HGIU. For study HGIN, I disagree with the review team on the recommendation for a nonapproval action. One of the concerns, namely Dr. Kong's original finding on the MMRM, has now been addressed, and we are in agreement that an appropriate MMRM analysis yields a highly significant outcome. On the issue of geographic differences in outcome, I disagree that this is of sufficient concern to justify a nonapproval action. Nevertheless, we will ask the sponsor to further address this concern.

5.2 Safety Data

Safety data for these supplements were derived from the 2 pivotal controlled trials (HGIU and HGIN), and also from studies LOAY and HGMF. The combined total for these studies was n=454 patients, and this included 89 placebo patients from the 2 controlled trials. Thus, there were 365 olanzapine-exposed patients in this safety database. This included 136 patients who were treated with olanzapine for at least 23 weeks.

There were no deaths among the olanzapine-exposed patients. There were 44 serious adverse events, the majority of which represented a worsening of psychiatric symptoms. Overall, the profile of common and drug-related adverse events included events already well-recognized for olanzapine, i.e, increased appetite and weight gain, somnolence, sedation, fatigue, dizziness, and dry mouth. Other findings included the following:

-Weight Gain: For the 2 short-term trials (HGIU and HGIN), olanzapine patients gained almost 4 kg more than placebo patients ($p<0.001$). Almost 44% of olanzapine patients gained > 7% of their body weight compared to only 7% of placebo patients ($p<0.001$).

-Transaminase Increases: For the 2 short-term trials (HGIU and HGIN), 12% of olanzapine patients compared to only 2% of placebo patients had ALT increases to > 3xULN ($p=0.009$). None of these patients had bilirubin abnormalities, and transaminase elevation is a well-known finding for olanzapine.

-Hyperprolactinemia: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in prolactin of 11.44 mcg/L compared to a decrease of -0.16 mcg/L for placebo ($p<0.001$).

-Hyperlipidemia: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in triglycerides of 29.2 mg/dL compared to a decrease of -4.4 mg/dL for placebo ($p<0.001$). For total cholesterol, olanzapine patients had a mean increase from baseline of 13.1 mg/dL compared to a decrease of -1.2 mg/dL for placebo ($p<0.001$).

-Hyperglycemia: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in fasting glucose of 2.7 mg/dL compared to a decrease of -2.9 mg/dL for placebo ($p<0.001$).

-Heart Rate Increase: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in heart rate of 6.3 bpm compared to a decrease of 5.1 bpm for placebo. These changes were thought to be related to orthostatic changes seen with olanzapine, especially early in treatment.

Summary of Safety Experience with Olanzapine in Adolescents: Overall, the adverse event profile and other safety parameters for olanzapine in the adolescent population is similar to that seen in adult patients treated with this drug, however, with some differences in magnitude. These differences will need to be reflected in labeling. In addition, we have recently asked the sponsor to provide more complete information generally with regard to effects on weight, glucose regulation, and lipid levels so that labeling for olanzapine can be enhanced with regard to these risks.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have asked the sponsor to make a number of changes, and in some cases, provide new information.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they reviewed the literature and found no relevant papers that would add important new information to the existing database regarding the safety of olanzapine in the treatment of schizophrenia or bipolar disorder in adolescents.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, olanzapine is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in adolescents.

8.0 DSI INSPECTIONS

Inspections were conducted at 2 US sites and at 2 Russian sites, and data from these sites were deemed to be acceptable.

9.0 LABELING AND APPROVABLE LETTER

10.1 Labeling

We have included an extensively modified version of labeling with the approvable letter.

10.2 Foreign Labeling

Olanzapine is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in adolescents.

10.3 Approvable Letter

The approvable letter includes our proposed labeling and requests for additional data.

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has submitted sufficient data to support the conclusion that olanzapine is effective and acceptably safe in the treatment of adolescents with schizophrenia and acute mania/mixed episodes in bipolar disorder. However, before we can take an approval action, the sponsor needs to respond to various requests we have made and we need to reach agreement on labeling. Thus, we will issue the attached approvable letter along with our proposal for labeling.

cc:
Orig NDA 20-592/S-040 and 041
HFD-130/TLaughren/MMathis/NKhin/CAlfaro/KKiedrow/DBates/SHardeman

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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/

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4/29/2007 10:55:29 AM
MEDICAL OFFICER