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: July 18, 2008

FROM: Ni A. Khin, M.D.
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TO: NDA 20-592/SE5-040 (bipolar I disorder, acute mania)
NDA 20-592/SE5-041 (schizophrenia)
(This overview should be filed with the 02-05-2008 submission in response to the Agency's Approvable Letter dated 04-30-2007)

SUBJECT: Recommendation of an approvable action for use of Zyprexa (olanzapine) in the treatment of 1) Bipolar I disorder, Mania, and 2) schizophrenia in Adolescents.

1. BACKGROUND

Zyprexa (olanzapine) is an atypical antipsychotic agent, approved in the U.S. for treatment of schizophrenia and bipolar disorder, mania or mixed episodes, as monotherapy (both acute and maintenance) or combination therapy in adults. It is available as oral 2.5, 5, 10, 15, or 20 mg strength tablets; 5, 10, 15, or 20 mg oral disintegrating tablets (Zydis). The target dose for adults with schizophrenia is 10 mg/day. Zyprexa intramuscular injection (10 mg) is indicated for agitation associated with schizophrenia and Bipolar I Mania.

Currently, two atypical antipsychotic drugs, Risperdal and Abilify, are approved for treatment of schizophrenia and bipolar disorder in the pediatric population.

In response to the Agency's written request (original 11/30/2001; amended 4/9/02, 7/3/02, 5/7/04, 6/29/05), the sponsor conducted clinical trials for two indications: schizophrenia (F1D-MC-HGIN) and bipolar disorder (F1D-MC-HGIU) in adolescents, and submitted the study results to the above referenced supplemental NDA on 10/30/2006.

The Agency issued an approvable letter (AE letter) on 4/30/07 asking the sponsor to provide additional safety data analysis regarding risks of weight gain, hyperglycemia and hyperlipidemia in patients taking Zyprexa. In the AE letter, we noted our intent to ensure that the Zyprexa label is enhanced with the updated information to characterize these risks. We also requested the sponsor to address the geographic discrepancy in the efficacy results between the US and Russia in adolescent schizophrenia trial, and other information pertaining to high prolactin levels in adolescents. In addition, we asked to provide the MedWatch reports for 4 fatalities.

The sponsor submitted their complete response to the AE letter on 02/05/2008. This submission was reviewed by Cara Alfaro, Pharm.D. Clinical Analyst, DPP (review dated 07/14/2008). Evelyn

Mentari, M.D., Safety Medical Officer (review dated 07/15/2008) reviewed the additional analyses provided by the sponsor regarding the metabolic data. Sally Yasuda, Pharm.D., Safety Team Leader, provided a secondary review of the metabolic data and the sponsor's proposed Risk Minimization Plan (memo dated 07/17/2008).

2.0 CHEMISTRY

No new CMC information required for review in this submission. Dr. Nallaperun Chidambarm, Chemistry Team Leader from the ONDQA, stated that there were no CMC comments regarding the PLR conversion of the Zyprexa labeling included in this submission.

3.0 PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology issues required for review in this submission. Dr. Barry Rosloff, Supervisory Pharmacologist, provided his PLR labeling comments for the pharm/tox sections.

4.0 CLINICAL PHARMACOLOGY

Dr. Andre Jackson has provided labeling comments to reflect the adolescent PK findings (F1D-MC-HGMF) and also, for the clinical pharmacology sections in the PLR labeling.

5.0 CLINICAL DATA

5.1 Efficacy Data

As noted by Dr. Alfaro in her prior review, the sites in Russia appeared to drive the entire efficacy signal for the adolescent schizophrenia clinical trial (HGIN), primarily due to the very low placebo response in the sites in Russia.

The primary endpoint, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia ($p = 0.003$) but not the sites in the United States ($p = 0.258$).

Study HGIN	Placebo	Olanzapine
USA	N=19	N=38
Mean Change From Baseline of BPRS-C Total (SD)	-15.0 (18.3)	-21.2 (16.3)
Russia	N=16	N=34
Mean Change From Baseline of BPRS-C Total (SD)	-2.6 (17.4)	-17.4 (14.5)

In our 04/30/2007 approvable letter, we had asked the sponsor for additional analyses (e.g. baseline illness characteristics) to evaluate potential differences between subjects enrolled in the US and Russian sites. In the sponsor's 02/05/2008 response to the AE letter, the sponsor provided details for further exploratory analyses including:

1. Between-country comparisons, comparison of baseline characteristics, and inclusion of significant baseline characteristics into the ANCOVA model
2. Analyses by country for disposition, effect size, response rate, modal dose, concomitant medication use, and weight gain

3. Visit-wise LOCF and OC mean change for BPRS-C total score by country
4. Analysis of treatment-by-country interaction and within-country effect for secondary efficacy measures
5. Evaluation of data from placebo-treated patients with therapeutic improvements similar to the olanzapine treatment magnitude

As Dr. Alfaro commented in her review dated 07/14/2008, no significant differences that might account for the low placebo response rate at the Russian sites was identified during review of these additional analyses.

In the 02/05/2008 response, the sponsor reiterated that discontinuation due to lack of efficacy was significantly greater among placebo-treated patients compared with olanzapine-treated patients in both the US (15.8% in olazapine; 42.1% in placebo; $p = 0.049$) and Russia (11.8% in olazapine; 62.5% in placebo; $p < 0.001$). The effect sizes were 0.63 for all patients, 0.32 for the US and 0.96 for the Russian patients. The mean modal doses were 13.2 mg for the U.S. and 11.8 mg for Russia. The sponsor also reiterated that the treatment-by-country interaction was not significant ($p = 0.146$).

Dr. Alfaro mentioned in her review that she also looked at the data from two recently approved drugs in adolescent population in the treatment of schizophrenia [i.e., for the aripiprazole (NDA 21-436/SE5-017) and risperidone (NDA 20-272/SE5-046) adolescent schizophrenia programs]. By comparing Russian data from these programs, Dr. Alfaro's concerns are seemed satisfactorily addressed.

5.2 Safety Data

Metabolic Effects

As stated in Dr. Mentari's safety review, the sponsor's additional analysis results and their labeling proposals for the Weight Gain, Hyperglycemia and Hyperlipidemia sections seemed adequately addressed our concerns on the issue.

There was statistically significant treatment emergent increase in lipid profile, glucose and weight in both olanzapine treated adults and adolescents as compared to placebo. It should be noted that the magnitude of mean changes from baseline was greater in adolescents treated with olanzapine than changes for the adults in total cholesterol, LDL and triglycerides. In addition, adolescents were likely to gain more weight and have greater increases in prolactin and hepatic transaminase levels.

Dr. Mentari recommended some further modification in the labeling for weight gain (adding description of data on treatment emergent glycosuria) and hyperglycemia sections to more clearly communicate the information in both adult and adolescent subsections. She also recommended fasting blood glucose testing and lipid profile at the beginning of and periodically during olanzapine treatment be added as part of the laboratory tests.

Additionally, Dr. Mentari noted that a proposal for a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide to be requested from the sponsor. The same was reflected by Dr. Yasuda in her secondary safety review memo. I agree with their recommendations, and we should ask the sponsor to do so.

Response to Other Additional Data: Hyperprolactinemia, Hepatic Analytes, AIMS analysis and Case Narratives

In Dr. Alfaro's review dated 07/14/08, she provided her item-by-item evaluation of the sponsor's response to the clinical safety questions imposed in the 04/30/2007 approvable letter. She reviewed results from additional requested analysis on prolactin, hepatic analytes and AIMS scores.

The sponsor provided additional analyses on the subset of patients with baseline prolactin within the normal range and also, a subgroup analysis for gender and age. The sponsor was asked to include the frequency of hyperprolactinemia in adolescents in the hyperprolactinemia section and the information was now included in the proposed labeling. In clinical trials of olanzapine in adolescents, gynecomastia occurred in 2.4% of males (7/286) and galactorrhea occurred in 1.8% of females (3/168). Dr. Alfaro recommends that these adverse events (gynecomastia and galactorrhea) should also be noted in the Adverse Events section of labeling. I have no objection to add these events. A greater percentage of adolescent subjects had treatment emergent increases in AST, ALT and alkaline phosphatase compared to adult subjects. The hepatic results are reflected in the sponsor's proposed labeling. Dr. Alfaro recommends no further labeling changes based on results of AIMS analysis provided in this submission.

She also reviewed case narratives of 8 cases of gynecomastia, 2 cases with elevated prolactin, and one CPK elevation case. Most of these cases were from the open-label studies. Based on the limited information provided, Dr. Alfaro's review of the 4 additional requested fatalities narratives from the MedWatch reports revealed that these subjects were on multiple concomitant medications. Based on her review of these requested case narratives, no further labeling changes was recommended.

Safety Update

In this submission, the sponsor provided an analysis of their database (Lilly Safety System) for spontaneously reported adverse events occurring from the time of product launch to May 31, 2007. Based on Dr. Alfaro's review this safety update, no new safety signals emerged that would require additional changes to product labeling.

Risk Minimization Plan (RMP)

The sponsor's proposed RMP includes routine pharmacovigilance of spontaneous case reports with target AEs, a long term open-label safety study (study F1D-MC-HCMX) and a pharmacoepidemiology study with retrospective cohort analysis of a large US health claims database to estimate the incidence and prevalence of diabetes mellitus and dyslipidemia among adolescent patients with schizophrenia or bipoloar disorder compared with the general adolescent population. The sponsor also states that the RMP would include the labeling and the product website which would provide advice on weight management and nutrition, and the Lilly Wellness Program which is a program of heath care professionals and patients education. The sponsor has not submitted the full protocol for study HCMX yet. Dr. Yasuda noted in her safety memo that we should ask the sponsor to submit a full protocol for review. The outcome of the Lilly Wellness Program in terms of random blood glucose or dyslipidemia has not been provided.

Given the metabolic safety profile observed with olanzapine, Drs. Alfaro, Mentari and Yasuda unanimously recommended the need to highlight to a larger extent of these metabolic risks in development of a Medication Guide for this product, and should ask the sponsor to do so. I am agreeing with them.

The OSE was consulted on this proposed risk management plan. The OSE would provide their input on the appropriateness of the RMP after the sponsor submits a complete response to the action letter.

5.3 Conclusion Regarding Overall Efficacy and Safety Data

I concur with Dr. Alfaro that the sponsor has adequately responded to our concern regarding the discrepancy in the efficacy data primarily driven by the differential placebo response between the United States and Russian sites in the schizophrenia study HGIN.

As mentioned before, significant safety signals that emerged in these adolescent clinical trial databases were a greater magnitude of weight gain, hypertriglyceridemia, hypercholesterolemia, hyperprolactinemia and transaminase elevations. These findings should be adequately described in the labeling. We will be asking the sponsor to develop a Medication Guide as well.

The greater metabolic risks observed in the adolescent population should be considered in our overall risk benefit evaluation. I concur with Dr. Alfaro's recommendation of olanzapine as a second-line treatment in adolescent schizophrenia and bipolar disorder given the greater metabolic risks and the morbidity associated with potential chronic use of this product in the patient population once approved.

As a second-line treatment of olanzapine for the acute treatment in adolescent schizophrenia and bipolar disorder, I have no further objection to giving as a similar statement as in recently approved other atypical psychotics that maintenance treatment effect may be extrapolated from adult data in the clinical studies section of the labeling.

6.0 WORLD LITERATURE

The sponsor provided a comprehensive literature review pertaining to the safety of olanzapine for the time period August 25, 2006 through May 31, 2007. The sponsor reported that adverse events and changes in laboratory parameters described in the citations are consistent with the types of adverse events reported for adult patients receiving olanzapine.

7.0 FOREIGN REGULATORY ACTION

According to the information provided by the sponsor in this submission, as of August 21, 2007, olanzapine has not been approved for pediatric use in any country.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take these supplemental NDA to the PDAC.

9.0 DSI INSPECTIONS

No additional DSI inspection requested. Refer to the DSI Clinical Inspection Summary from the first review cycle.

10.0 LABELING AND ACTION LETTER

Although there are some improvements in the labeling language by the sponsor, we have made further modifications so that all pertinent safety findings are clearly reflected in the labeling. Our modified version of draft labeling in the PLR format should be attached in our action letter.

11.0 CONCLUSION AND RECOMMENDATION

In my opinion, the sponsor has adequately addressed the issues noted in our 04/30/2007 approvable letter. I have no doubt about effectiveness of olanzapine in the treatment of schizophrenia and bipolar disorder in both adults and adolescents. However, a greater safety risk observed in adolescents treated with olanzapine in terms of significant weight gain and metabolic effects should be accounted in our risk-benefit determination. I concur with Dr. Alfaro that we should make olanzapine as a second-line treatment in the adolescent population. I also concur with Drs. Alfaro, Mentari and Yasuda that we should ask the sponsor to provide a proposal for a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide. Therefore, I recommend the Division issue a second approvable letter for this set of NDA supplements.

Cc: HFD-130/Laughren/Mathis/Alfaro/Grewal
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/s/

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MEDICAL OFFICER