# CLINICAL REVIEW

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| Application Type | NDA<br>(Complete Response to Approvable Action) |
| Submission Number | 020592 |
| Submission Code | SE5 040/041 |
| Letter Date | 2/5/2008 |
| Stamp Date | 2/5/2008 |
| PDUFA Goal Date | 8/5/2008 |
| Reviewer Name | Cara Alfaro, Pharm.D. |
| Review Completion Date | 7/14/2008 |
| Established Name | Olanzapine |
| Trade Name | Zyprexa |
| Therapeutic Class | Antipsychotic |
| Applicant | Eli Lilly & Co |
| Priority Designation | S |
| Formulation | Oral tablets |
| Dosing Regimen | 2.5 – 5 mg starting, maximum dose 20 mg/day |
| Indications | Treatment of Bipolar I Disorder (040) and Schizophrenia (041) |
| Intended Population | Adolescents |

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# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

This is a review of the complete response to the approvable action taken on 4/30/07 for NDAs 20-592 SE5-040 "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents" and SE5-041 "treatment of schizophrenia in adolescents". It is recommended that the Division take an approvable action on these supplements and that olanzapine be considered as second line treatment for bipolar disorder and schizophrenia in the adolescent population.

The Sponsor responded to all additional requests for information pertaining to pivotal trials HGIU (bipolar disorder) and HGIN (schizophrenia) outlined in the 4/30/2007 approvable letter (other requests for additional safety data in adults and adolescents were also submitted and reviewed by another clinical reviewer). A review of these data did not reveal new safety risks or significant changes to already known safety risks that warranted significant changes to proposed product labeling beyond the changes suggested in the approvable letter. However, it is recommended that gynecomastia and galactorrhea be included as adverse events in product labeling as they appear to occur more frequently in the adolescent population compared to adults. The Sponsor also adequately addressed the disparity in the efficacy signal primarily driven by the differential placebo response between the United States and Russian sites in study HGIN (schizophrenia).

The recommendation for an approvable action (rather than an approval action) is based on the need for the development of a medication guide discussing significant adverse events in adolescents (b) (4) . Though these adverse events are well known for olanzapine, they occur much more frequently in the adolescent population. Weight gain, hyperglycemia, and hyperlipidemia are significant risk factors for cardiovascular morbidity, especially in disease states such as schizophrenia or bipolar disorder in which it is likely that patients will be taking these medications chronically.

Given these safety concerns, it is recommended that olanzapine be considered as second line therapy for the treatment of bipolar disorder and schizophrenia in the adolescent population. Recently two other antipsychotics, risperidone and aripiprazole, received approval for treatment of bipolar disorder and schizophrenia in adolescents. In comparison to olanzapine, these antipsychotics are not associated with the same magnitude of risk with regard to weight gain, hyperglycemia and hyperlipidemia.

## 1.2 Recommendation on Postmarketing Actions

### 1.2.1 Risk Management Activity

The Sponsor submitted a "risk management plan" document, however, it was not a typical risk management plan. The Sponsor has proposed education, labeling changes and some further clinical trials to address the safety risks of olanzapine in both adults and adolescents.

### 1.2.2 Required Phase 4 Commitments

The Sponsor is planning to conduct a 52-week open-label safety study (Study F1D-MC-HGMX) in adolescent subjects with bipolar disorder or schizophrenia (see Section 7 of review - Studies to be Conducted In Adolescents ). This study is being considered as a Phase 4 commitment. As of this time, the protocol for this study has not been submitted.
No additional Phase 4 commitments are recommended.

# 2 INTRODUCTION AND BACKGROUND

On 10/30/06, Eli Lilly and Company submitted NDA 20-592 SE5-040 and SE5-041 to support the indications "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents" and "treatment of schizophrenia in adolescents" respectively. An approvable action was taken 4/30/2007 and the Sponsor was asked to submit additional safety analyses as well as further exploration of the disparity in efficacy results between the US and Russian sites (largely driven by a very low placebo response in the Russian sites) in the pivotal adolescent schizophrenia trial (HGIN). The Sponsor was also asked to submit updated information on risks of weight gain, hyperglycemia and hyperlipidemia that would be reflected not only in Zyprexa labeling, but also in Symbyax labeling.

The Sponsor submitted a response on 8/30/2007, this response was considered incomplete (letter date 9/13/2007) since the submission did not include all requested data regarding the risks of weight gain, hyperglycemia and hyperlipidemia. The Sponsor submitted a response on 2/5/2008 and it was considered a complete response. For the purposes of this review, this reviewer is addressing the portions of the complete response pertaining to SE5-040 and SE5-041, specifically the questions posed to the Sponsor for issues relating to the pivotal trials for the bipolar and schizophrenia adolescent trials. Another clinical reviewer (Evelyn Mentari, M.D.) will be reviewing the requested safety information relating to risks of weight gain, hyperglycemia and hyperlipidemia for both adult and adolescent populations.

## 2.1 Brief Overview of Pivotal Trials HGIU and HGIN

Study HGIU was the pivotal trial for establishing efficacy and safety for the indication "treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with bipolar I disorder. The study consisted of a 3-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 107), or placebo (n = 54).

Study HGIN was the pivotal trial for establishing efficacy and safety for the indication "treatment of schizophrenia in adolescent patients". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with schizophrenia. The study consisted of a 6-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 72), or placebo (n = 35).

## 2.2 Summary Table of Clinical Trials in Original Submission

This summary table is included in this review as some of the Sponsor's responses included additional data from some of the supportive trials.

| Study | Description | Length | Age Range (years) | Number of Patients |
|---|---|---|---|---|
| HGIN | MC, DB, PC study in adolescent patients with schizophrenia.<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S. and Russia sites | 6 weeks DB<br>26 weeks OL extension | 13 to 17 | 107<br>(n = 72 olanzapine, n = 35 placebo) |
| HGIU | MC, DB, PC study in adolescent patients with mixed/manic episode of bipolar I disorder.<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S., Puerto Rico | 3 weeks DB<br>26 weeks OL extension | 13 – 17 | 161<br>(n = 107 olanzapine, n = 54 placebo) |
| LOAY | OL study in patients with schizophrenia, schizoaffective, and schizophreniform disorders<br>Flexible dose olanzapine (5 – 20 mg)<br>German sites | 24 weeks | 12 – 21 | 96<br>(n = 89, 13-17 years) |
| HGMF | OL study in adolescent patients with schizophrenia or bipolar I disorder<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S., Puerto Rico, Russia | 4.5 weeks | 13 – 17 | 107<br>(n = 37 schizophrenia, n = 70 bipolar) |
| HGCS | OL study in adolescent patients with schizophrenia<br>Dosing: 2.5 to 20 mg/day<br>Single site | 8 weeks | 10 – 18 | 8 |
| HGCR | DB study in adolescent patients with schizophrenia, haloperidol as active comparator<br>Dosing: 2.5 qod – 20 mg/day<br>Single site | 8 weeks | 12 – 16 | 2 |
| HGGC | OL study in children and adolescents with bipolar disorder<br>Dosing: 2.5 to 20 mg/day<br>Single site (U.S.) | 8 weeks | 5 – 14 | 23 |

# 3. REQUESTS FOR INFORMATION

This section includes the requests for information that were outlined in the 4/30/2007 approvable letter, the Sponsor's response and reviewer's comments.

Table 3.1, below, is from the original NDA submission and defines the different databases used to address various safety signals. Some of the requests for information asked for reanalysis in the Overall Olanzapine Exposure Database.

Table 3.1. Sponsor's Table – Databases for Summary of Clinical Safety

**Table 2.7.4.1. Databases for Summary of Clinical Safety**

| Database | Indication | Studies Used | Number of Patients |
|---|---|---|---|
| Acute Placebo-Controlled Databases | Schizophrenia | HGIN | N=107 (Olz=72, Pla=35) |
| | Bipolar | HGIU | N=161 (Olz=107, Pla=54) |
| | Combined | HGIN, HGIU | N=268 (Olz=179, Pla=89) |
| Overall Olanzapine Exposure Databases | Schizophrenia | HGIN, LOAY, HGMF[a] | N=227 |
| | Bipolar | HGIU, HGMF[a] | N=227 |
| | Combined | HGIN, HGIU, LOAY, HGMF | N=454 |

a Because Study HGMF enrolled patients with schizophrenia or bipolar disorder, some patients from Study HGMF were included in the Overall Olanzapine Exposure Bipolar Database and some patients from Study HGMF were included in the Overall Olanzapine Exposure Schizophrenia Database.

## 3.1 Prolactin

*Division Request #1*

For the acute phases of HGIU and HGIN, many patients have 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.

*Data Submitted in the Original Submission*

Prolactin reference ranges for adolescents (13 – 17 years) in study HGIN and HGIU[1]: males = 2.8 – 11 ng/ml; females = 3.2 – 20 ng/ml

In the original analysis of the HGIN + HGIU acute studies, the following change from baseline to endpoint in prolactin concentrations were provided (Table 3.1.1). However, this analysis included subjects with abnormal (usually elevated due to prior therapies) prolactin concentrations making a change from baseline difficult to interpret.

[1] Covance did not have pediatric reference ranges for prolactin. The Sponsor obtained these reference ranges from the Tietz Textbook of Clinical Chemistry (Burtis CA and Ashwood ER 1999).

Table 3.1.1. Prolactin: Change from Baseline To Endpoint, All Subjects (HGIN + HGIU)

| | | | Baseline | | **Change to Endpoint** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | **Mean** | Std | LS Mean Change | LS Mean Difference | P-value |
| Prolactin (mcg/L) | Olanzapine<br>Placebo | 163<br>80 | 14.06<br>14.95 | 9.92<br>11.86 | **11.44**<br>**-0.16** | 14.52<br>10.69 | 10.51<br>-1.15 | 11.66 | < 0.001 |

The Sponsor also included a prolactin analysis by gender since it is well established that females have a more pronounced elevation in prolactin concentration with antipsychotic therapy.

Table 3.1.2. Prolactin Analysis by Gender

| Laboratory Evaluations | Gender | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value | **P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PROLACTIN | Female | Olz | 63 | 15.87 | 10.06 | 15.63 | 16.86 | 14.26 | 14.25 | <.001 | .236 |
| | | Placebo | 37 | 15.25 | 7.59 | 1.35 | 9.20 | 0.00 | | | |
| | Male | Olz | 100 | 12.92 | 9.71 | 8.80 | 12.20 | 8.70 | 10.12 | <.001 | |
| | | Placebo | 43 | 14.70 | 14.67 | -1.46 | 11.78 | -1.42 | | | |

In the original analysis, the Sponsor did not provide a prolactin analysis by age.

*Sponsor's Response*
Seventy percent of olanzapine-treated subjects (114/163) and 71% of placebo-treated subjects (57/80) had normal baseline prolactin concentrations. Table 3.1.3 provides the reanalysis by the Sponsor including only those subjects with normal baseline prolactin levels.

Table 3.1.3. Prolactin: Change from Baseline To Endpoint, Subjects with Normal Baseline Prolactin (HGIN + HGIU)

| | | | Baseline | | **Change to Endpoint** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | **Mean** | Std | LS Mean Change | LS Mean Difference | P-value |
| Prolactin (mcg/L) | Olanzapine<br>Placebo | 114<br>57 | 11.72<br>12.07 | 6.63<br>6.34 | **12.98**<br>**2.32** | 11.93<br>7.30 | 12.24<br>1.48 | 10.76 | < 0.001 |

From Sponsor table APP.1.1 in Regulatory Response document

Table 3.1.4. Prolactin Analysis by Gender and Age, Subjects with Normal Baseline Prolactin (HGIN + HGIU)

| Laboratory Evaluations | Subgroup | Group | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value | **P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PROLACTIN | Gender | Female | Olz | 47 | 14.65 | 8.68 | 15.14 | 15.25 | 12.66 | 11.96 | <.001 | .574 |
| | | | Placebo | 29 | 15.14 | 7.21 | 3.19 | 8.98 | 0.70 | | | |
| | | Male | Olz | 67 | 9.67 | 3.53 | 11.47 | 8.72 | 11.57 | 10.01 | <.001 | |
| | | | Placebo | 28 | 8.90 | 2.99 | 1.41 | 5.01 | 1.56 | | | |
| | Age | <15 | Olz | 46 | 12.02 | 6.37 | 14.70 | 13.60 | 11.15 | 14.86 | <.001 | .080 |
| | | | Placebo | 18 | 10.97 | 2.98 | -0.22 | 3.72 | -3.71 | | | |
| | | >=15 | Olz | 68 | 11.52 | 6.84 | 11.82 | 10.61 | 11.76 | 8.53 | <.001 | |
| | | | Placebo | 39 | 12.58 | 7.38 | 3.49 | 8.24 | 3.23 | | | |

*Reviewer Comments*
In the reanalysis including only those subjects with normal baseline prolactin (Table 3.1.3), the change from baseline to endpoint in olanzapine-treated subjects is slightly greater (12.98 mcg/L) compared to the original analysis (11.44 mcg/L). However, change from baseline to endpoint in placebo-treated subjects was also greater (2.32 mcg/L) compared to the original analysis (-0.16 mcg/L) such that the LS mean difference is lower in this analysis (10.76) compared to the original analysis (11.66). Both analyses found these differences between treatment groups to be statistically significant ($p < 0.001$).

For the gender analysis, the results from this reanalysis including only those subjects with normal baseline prolactin concentrations was similar to the original analysis; however, the change from baseline to endpoint in olanzapine-treated males was higher in this analysis (11.47 mcg/L) compared to the original analysis (8.80 mcg/L). The LS mean differences in this analysis were less than the original analysis primarily due to an increase in change from baseline to endpoint in placebo-treated subjects. The overall results are essentially the same – no differential gender effects were noted; olanzapine increases prolactin concentrations to the same degree in both male and female adolescents.

The Sponsor had not provided an age subgroup analysis in the original submission. This analysis (including only those subjects with normal baseline prolactin concentrations) found a statistically significant ($p = 0.08$) increase in prolactin concentrations in olanzapine-treated subjects < 15 years old compared to subjects $\geq$ 15 years old. Mean change from baseline to endpoint for olanzapine-treated subjects < 15 years old was 14.7 mcg/L compared to 11.82 mcg/L in subjects $\geq$ 15 years old. It does appear, however, that the statistical differences may have been driven by differences in the placebo-treated subjects: change in prolactin for subjects < 15 years old was -0.22 mcg/L compared to 3.49 mcg/L for subjects $\geq$ 15 years old.

*Division Request #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.

*Data Submitted in the Original Submission*
In the original submission, the Sponsor had included prolactin concentrations for all subjects in the Overall Olanzapine Exposure Combined Database (see Table 3.1.5). However, it was difficult to evaluate patterns over time in subjects completing the trials since these data also included subjects who dropped out over the course of these trials. Therefore, the Sponsor was asked to provide these data only for subjects completing these trials in order to evaluate a potential pattern in prolactin concentration for subjects with exposures up to 6 -8 months.

Table 3.1.5 Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints: Overall Olanzapine Exposure Combined Database

**Table APP.2.7.4.7.4.24. Mean Prolactin Values at Various Time Points Overall Olanzapine Exposure Combined Database**

| | | Summary | | | | |
|---|---|---|---|---|---|---|
| Database | Olz Exposure | N | Mean | Std | Median | Max |
| Bipolar | Baseline | 217 | 15.35 | 12.58 | 11.28 | 110.30 |
| | 1-6 weeks | 174 | 26.60 | 16.18 | 23.10 | 129.66 |
| | 7-18 weeks | 122 | 19.24 | 11.89 | 16.71 | 59.49 |
| | 19-32 weeks | 83 | 18.03 | 10.42 | 14.36 | 49.53 |
| Schizophrenia | Baseline | 214 | 18.84 | 19.97 | 11.87 | 131.57 |
| | 1-6 weeks | 190 | 31.82 | 20.75 | 26.48 | 110.84 |
| | 7-18 weeks | 88 | 22.75 | 16.24 | 18.62 | 112.00 |
| | 19-32 weeks | 93 | 19.01 | 15.60 | 14.81 | 109.97 |
| Overall | Baseline | 431 | 17.08 | 16.74 | 11.60 | 131.57 |
| | 1-6 weeks | 364 | 29.33 | 18.86 | 25.00 | 129.66 |
| | 7-18 weeks | 210 | 20.71 | 13.95 | 17.13 | 112.00 |
| | 19-32 weeks | 176 | 18.55 | 13.38 | 14.70 | 109.97 |

*Sponsor's Response*

Table 3.1.6. Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints: Overall Combined Database for Subjects Completing 19-32 weeks of Olanzapine Exposure

| | | Summary | | | | |
|---|---|---|---|---|---|---|
| Database | Olz Exposure | N | Mean | Std | Median | Max |
| Bipolar | Baseline | 83 | 12.91 | 8.04 | 10.36 | 37.41 |
| | 1-6 weeks | 49 | 27.21 | 11.65 | 25.86 | 60.72 |
| | 7-18 weeks | 83 | 18.88 | 10.78 | 17.11 | 59.49 |
| | 19-32 weeks | 83 | 18.03 | 10.42 | 14.36 | 49.53 |
| Schizophrenia | Baseline | 93 | 18.03 | 17.37 | 11.98 | 100.00 |
| | 1-6 weeks | 74 | 31.22 | 21.54 | 24.34 | 104.00 |
| | 7-18 weeks | 55 | 20.03 | 11.60 | 16.83 | 54.11 |
| | 19-32 weeks | 93 | 19.01 | 15.60 | 14.81 | 109.97 |
| Overall | Baseline | 176 | 15.62 | 13.98 | 11.17 | 100.00 |
| | 1-6 weeks | 123 | 29.62 | 18.30 | 24.68 | 104.00 |
| | 7-18 weeks | 138 | 19.34 | 11.09 | 16.87 | 59.49 |
| | 19-32 weeks | 176 | 18.55 | 13.38 | 14.70 | 109.97 |

*Reviewer Comments*
For this reanalysis (as in the original analysis), sample sizes vary by timepoint likely due to differences in the various protocols. Similar to the original analysis, the increase in mean prolactin values appears to occur early (1-6 weeks) and decreases at subsequent timepoints; though still elevated compared to baseline concentrations. This analysis was requested so that data could be evaluated over time in the same group of subjects – however, obviously, if subjects dropped out of the study due to prolactin elevations (or other reasons but also had elevated prolactin concentrations), this analysis would not include those subjects and may underestimate the effect. However, the prior analysis did include all subjects and results between the analyses were very similar.

*Proposed Language in Product Labeling re: Prolactin*
The Sponsor was asked to include the frequency of hyperprolactinemia in adolescents in this section and also included this data for the adult populations.

Section 5 – WARNINGS AND PRECAUTIONS; 5.16 Hyperprolactinemia
"In clinical studies, plasma prolactin concentrations were elevated in 34% of adults treated with olanzapine. These elevations were mild and transient (end-point mean not above upper limits of normal and not statistically significantly different from placebo). Associated clinical manifestations (e.g. gynecomastia, galactorrhea, and breast enlargement) were rare. In most patients, levels returned to normal ranges without cessation of treatment.
In placebo-controlled olanzapine monotherapy studies in adolescent patients with schizophrenia or bipolar disorder (manic or mixed episodes), elevated prolactin concentrations occurred in 47.4% of olanzapine-treated patients compared to 6.8% of patients in the placebo group."

This frequency data is also reflected in Section 6 ADVERSE REACTIONS, 6.2 Vital Signs and Laboratory Studies.
The frequency data do not indicate the magnitude of the elevations in prolactin, the adult data included in currently approved labeling also do not indicate the magnitude of prolactin elevation (only the frequency of occurrence). Unlike adverse events of weight gain or ALT increases, there is not a well recognized potentially clinically significant change in which to further categorize these increases. Therefore, it is reasonable to include only the frequencies of prolactin increases and then to note elsewhere in labeling adverse events that may be related to hyperprolactinemia.

Since the Sponsor has now included data about the frequency of potentially prolactin-related adverse events for adults, this data should also be included for adolescents – however, these effects are not rare in the latter population (refer to Sections 3.2 [Additional Narrative Summaries] and 4 [Safety Update] of review).
I would propose to add the following data which is from the original submission (Table 2.7.4.31 in summary-clin-safety document):
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).

These adverse events (gynecomastia and galactorrhea) should also be noted in the section of labeling: 6 ADVERSE REACTIONS, 6.1 Clinical Trials Experience, Other Adverse Events Observed During the Clinical Trial Evaluation of Oral Olanzapine. These events would be considered frequent (based on the 1/100 definition).

**3.2 Additional Narrative Summaries**
*Division Request #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.

The Sponsor supplied the requested narratives. This reviewer compiled a table (Table 3.2.1) summarizing some of the relevant information for the cases of gynecomastia (7 cases, one subject experienced the adverse event twice).

Prolactin reference ranges for adolescents (13 – 17 years) in study HGIN and HGIU: males = 2.8 – 11 ng/ml; females = 3.2 – 20 ng/ml

Prolactin reference ranges for adolescents in study LOAY:
Males $\geq$ 12 but $\leq$ 13 years = 2.8 – 24 ng/ml; $\geq$ 14 but $\leq$ 16 years = 2.8 – 16.1 ng/ml; > 16 but $\leq$ 19 years = 2.1 – 17.7 ng/ml
Females $\geq$ 12 but $\leq$ 13 years = 2.5 – 16.9 ng/ml; $\geq$ 14 but $\leq$ 16 years = 4.2 – 29 ng/ml; > 16 but $\leq$ 19 years = 2.8 – 29.2 ng/ml

Table 3.2.1. Summary Table for Gynecomastia Cases

| Patient ID | Demographics | Baseline Prolactin (mcg/L) | Prolactin During Study (mcg/L) *indicates prolactin at time of AE report | Clinical Description | Resolved? |
|---|---|---|---|---|---|
| HGIN-910-9103* | 15 YOM | 6.12 | 21.3 (~5 weeks)*<br>19.1 (3 months)<br>12.2 (7 months) | Left side gynecomastia (mild) | Ongoing at study completion |
| LOAY-400-4008 | 17 YOM | 10.50 | 23.0 (~2 weeks)*<br>16.8 (1 month)<br>16.8 (2 months)<br>7.4 (6 months) | Gynecomastia (mild) | Ongoing at study completion |
| LOAY-400-4009 | 14 YOM | 3.90 | 30 (2 weeks)<br>28 (3 weeks)<br>32 (5 weeks)<br>NA*<br>41 (2 months) | Gynecomastia (moderate) | Noted at baseline visit. Severity changed to severe at 2 months. Ongoing at time of discontinuation. |
| LOAY-406-4063 | 17 YOM | 5.50 | 25 (2 weeks)<br>36 (1 month)<br>34 (5 weeks)<br>30 (6 weeks)* | Gynecomastia (mild) | NA |
| LOAY-407-4074 | 17 YOM | 9.50 | 23 (2 weeks)<br>24 (1 month)<br>20 (5 weeks)<br>12.80 (6 months)* | Gynecomastia (mild) | AE noted at last study visit |
| LOAY-407-4077 | 16 YOM | 17.7 | 31 (2 weeks)<br>37 (1 month)<br>37 (6 weeks)<br>14.7 (7 months)* | Gynecomastia (mild) | AE noted at last study visit |
| LOAY-407-4201 | 16 YOM | 17.3 | 27 (2 weeks)<br>24 (1 month)*<br>20 (6 weeks)*<br>28 (2 months) | Gynecomastia (mild) | Ongoing at study discontinuation. |

* Sponsor indicates that 2 cases of gynecomastia occurred in this patient – the narrative indicates that the subject had these symptoms "periodically" since ~2 years prior to study participation. It is noteworthy that this subject had a prolactin concentration of 95.35 mcg/ml at Visit 1 (presumably screening visit).

*Reviewer Comments*

Seven subjects participating in the clinical trials for bipolar disorder and schizophrenia had an adverse event "gynecomastia". Interestingly, six of these subjects participated in the 24-week open label LOAY study conducted exclusively in Germany (these cases occurred at 3 different sites and 3 different investigators). These cases were associated with some elevations in prolactin concentration and most were considered by the investigators to be of mild severity. Though the narratives did not include vital sign data, this reviewer wanted to evaluate the weight gain in these subjects since fat deposition in the breast area, "pseudogynecomastia", might be mistaken as gynecomastia. Not surprisingly, these subjects gained a significant amount of weight over the course of these studies – from 9.1 to 24.6 kg over ~24 weeks (Table 3.2.2).

Table 3.2.2. Weight Changes in Subjects with the Adverse Event Gynecomastia

| | Baseline | | End of Study | | Change from Baseline to Endpoint | |
|---|---|---|---|---|---|---|
| | Weight | BMI | Weight | BMI | Weight | BMI |
| HGIN-910-9103 | 58 kg | 20.1 | 82 kg | 28.4 | 24 kg | 8.3 |
| LOAY-400-4008 | 83.5 kg | 24.7 | 108.1 kg | 31.9 | 24.6 kg | 7.2 |
| LOAY-400-4009 | 66.6 kg | 23.6 | 78.8 kg | 27.9 | 12.2 kg | 4.3 |
| LOAY-406-4063 | 62.7 kg | 20 | 71.8 kg | 22.9 | 9.1 kg | 2.9 |
| LOAY-407-4074 | 65.9 kg | 20.3 | 82.6 kg | 25.5 | 16.7 kg | 5.2 |
| LOAY-407-4077 | 63.3 kg | 19.8 | 82 kg | 25.6 | 18.7 kg | 5.8 |
| LOAY-407-4201 | 65.5 kg | 22.7 | 81.7 kg | 28.3 | 16.2 kg | 5.6 |

According to Harrison's medical textbook, gynecomastia is not uncommon in teenage boys with 65% of 14 year-old boys having gynecomastia that usually goes away on its own in 2 or 3 years (hormonally-related). However, the temporal association with olanzapine therapy may implicate the antipsychotic in this adverse event. These cases are not, however, associated with remarkably elevated prolactin concentrations (upper range of normal in males in this age range = 16 to 18 ng/ml for reference ranged used in LOAY) such that it is not clear that these were in fact cases of gynecomastia and may be cases of pseudogynecomastia secondary to significant weight gain. However, since the investigators used the term "gynecomastia" as an adverse event term for these cases, this reviewer will assume this to be correct (since it does not appear to have been queried by the Sponsor) and will recommend some labeling changes to reflect this information (see Section 3.1 [Prolactin] of review). It is not clear to this reviewer why the majority of these cases were from one clinical trial (LOAY).

Elevated Prolactin Cases

HGIN-005-0503 14 YOF. Baseline prolactin 17.2 mcg/L, increased to 90.68 mcg/L at ~6 weeks (no other labs available between these two values). Subsequent prolactin concentrations were 40.2 mcg/L at ~4.5 months and 45.5 mcg/L at ~7.5 months. The subject was receiving olanzapine 20 mg/day when the 90.68 and 45.5 mcg/L concentrations were obtained. No adverse events reported that were associated with elevated prolactin.

HGIN-900-9009 17 YOF. Baseline prolactin 17.5, elevation to 109.97 mcg/L noted at study completion (~8 months); prolactin concentration prior to this was 17.0 mcg/L at ~4 months. Subject was receiving olanzapine 10 mg/day when elevated concentration obtained. No adverse events associated with elevated prolactin were noted.

CPK Elevation Case

HGIN-004-0401 14 YOM. No baseline CPK available. Elevated CPK of 7289 U/L (reference range = 0 – 363 U/L noted one week after randomization – this was the highest CPK value obtained. CPKs were monitored weekly/monthly thereafter and ranged from 445 – 1766 U/L with no clear trend; last CPK noted as 781 U/L at ~8 months. CK-MB concentrations were obtained at some timepoints and most were elevated (5.2 – 10 ng/ml; reference range 0 – 4.9 ng/ml). Urine myoglobin obtained once (at ~2 months when CPK = 531 U/L) and was < 0.006.

Of note, the subject was receiving haloperidol decanoate prior to the study and, if narrative is correct, received his last dose approximately 9 days prior to randomization. No comments regarding extent of exercise or other potential contributing causes.

*Reviewer Comments*
This reviewer has recommended some labeling language to reflect the gynecomastia cases (see section 3.1 [Prolactin] of review).
The elevated prolactin cases appear to be related to olanzapine therapy and both occurred in female subjects who tend to have a more robust prolactin response to antipsychotics. These were the most significant elevations noted during the original review and appear to represent outliers. Per the Sponsor, there were no adverse events associated with the elevated prolactin, though it is not clear how this was determined (spontaneous reports vs. specific queries for prolactin-related adverse events).
The elevated CPK case was impressive and the highest value (7289 U/L0 was noted one week after randomization – it is possible that this could have been secondary to a haloperidol decanoate injection which appears to have been received 9 days prior to randomization (protocol violation). The CPK was consistently elevated over the course of the 8 month trial, though concentrations were quite variable.
No further labeling changes based on these additional cases (elevated prolactin and CPK) is recommended.

**3.3 Hepatic Analytes**
*Division Request #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 is 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.

*Sponsor's Response*
The Sponsor provided the following data for mean change from baseline to endpoint in hepatic analytes using normalized units for comparing the adolescent and adult populations. Statistically significant, though small, changes were noted for alkaline phosphatase (adolescents > adults) and total bilirubin (decreases noted in both populations).

Table 3.3.1. Sponsor's Table. Mean Change from Baseline to Endpoint in Hepatic Analytes (Normalized Units). Comparison of Adult Versus Adolescent Patients (Overall Exposure Database)

| Laboratory Evaluations | Unit | Population | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| AST/SGOT | %URL | Adolescent | 446 | 59.35 | 51.72 | 9.00 | 54.59 | 7.29 | -0.81 | .767 |
| | | Adult | 7074 | 63.19 | 36.97 | 7.99 | 59.21 | 8.10 | | |
| ALT/SGPT | %URL | Adolescent | 446 | 57.30 | 74.23 | 21.39 | 82.65 | 18.09 | 3.49 | .520 |
| | | Adult | 7084 | 66.00 | 57.78 | 14.39 | 115.43 | 14.60 | | |
| ALKALINE PHOSPHATASE | %URL | Adolescent | 446 | 65.27 | 30.13 | 4.38 | 18.19 | 4.33 | 1.96 | .019 |
| | | Adult | 7132 | 65.59 | 20.42 | 2.37 | 17.36 | 2.37 | | |
| GGT (GGPT/SGGT/YGGT) | %URL | Adolescent | 446 | 43.60 | 31.34 | 8.19 | 32.44 | 5.88 | 1.33 | .582 |
| | | Adult | 7051 | 54.40 | 52.99 | 4.40 | 51.93 | 4.54 | | |
| BILIRUBIN, TOTAL | umol/L | Adolescent | 446 | 8.56 | 5.96 | -1.12 | 4.60 | -1.19 | -0.94 | <.001 |
| | | Adult | 7182 | 8.71 | 5.22 | -0.26 | 6.05 | -0.25 | | |

The Sponsor also provided an analysis for treatment-emergent abnormally high hepatic analyte values (> 1X ULN) at anytime for adolescent and adult populations – the Sponsor did not include these data for ALT $\geq$ 3x ULN. In general, a greater percentage of adolescent subjects had increases in AST, ALT and alkaline phosphatase compared to adult subjects.

Table 3.3.2. Sponsor's Table. Treatment-Emergent Abnormally High Hepatic Analyte Values (> 1X ULN) at Anytime, Adult versus Adolescents (Overall Exposure Database)

| Laboratory Analyte | Direction | Population | N | n | (%) | *P-Value |
|---|---|---|---|---|---|---|
| AST/SGOT | High | Adolescent | 418 | 127 | 30.4% | <.001 |
| | | Adult | 6338 | 1459 | 23.0% | |
| ALT/SGPT | High | Adolescent | 396 | 169 | 42.7% | <.001 |
| | | Adult | 5891 | 1791 | 30.4% | |
| ALKALINE PHOSPHATASE | High | Adolescent | 387 | 52 | 13.4% | <.001 |
| | | Adult | 6655 | 469 | 7.0% | |
| GGT (GGPT/SGGT/YGGT) | High | Adolescent | 432 | 34 | 7.9% | .136 |
| | | Adult | 6292 | 642 | 10.2% | |
| BILIRUBIN, TOTAL | High | Adolescent | 423 | 9 | 2.1% | .054 |
| | | Adult | 7080 | 75 | 1.1% | |

*Reviewer Comments*
The mean change from baseline to endpoint in hepatic analytes for adult versus adolescents (including the open-label trials) did not indicate significant differences between these populations. In contrast, the percentage of subjects experiencing an abnormally high hepatic analyte concentration was generally higher for adolescents compared to adults; especially for AST, ALT and alkaline phosphatase.

*Proposed Language in Product Labeling re: Hepatic Analytes*

The proposed labeling includes data from the placebo-controlled trials and indicates the increased incidence of elevations in ALT (≥ 3x ULN) in adolescents compared to adults. This reviewer has no additional recommendations for further labeling based on these additional analyses.

In Section 5 Warnings and Precautions (5.12 Transaminase Elevations)
"In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from < 3 times the upper limit of normal at baseline to > 3 times the upper limit of the normal range) were observed in 12% (21/174) of patients exposed to olanzapine compared to 2% (2/87) of the placebo-treated patients. Discontinuation due to transaminase increases occurred in 3.4% (6/179) of patients exposed to olanzapine".

In Section 6.2 Vital Signs and Laboratory Studies
"In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT (> 3x ULN in patients with ALT at baseline < 3 X ULN) (12.1% vs. 2.3%); elevated AST (27.6% vs 3.8%); low total bilirubin (22.1% vs 6.7%); elevated GGT (10.1% vs 1.2%)…"

**3.4 Fatalities**

*Division Request #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?

*Sponsor's Response*
The Sponsor indicated that because these MedWatch forms were generated for the purposes of a submission dossier, they all showed the date that they were generated (7/27/06) and were marked "draft". The Sponsor also stated that all of the MedWatch forms for fatalities had been previously filed to NDA 20-592 (submission dates 12/16/97 to 5/19/06).

*Reviewer Comments*
No further information is requested.

*Division Request #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 Roane County, Tennessee. The reported 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.

*Sponsor's Response*
The Sponsor stated that all these cases had been previously filed to NDA 20-592. The Sponsor included brief narrative summaries for these cases. This reviewer compiled a table summarizing data from these cases (Table 3.4.1). As with most MedWatch cases, these patients were taking numerous concomitant medications.

Table 3.4.1. Summary of Additional Requested Fatality Narratives

| | Demographics | Olanzapine dose/duration | Diagnosis | Date of Death | Cause of Death |
|---|---|---|---|---|---|
| US_010158520 | 52 YOWF | 20 mg ~1 year | MDD with psychotic features | (b) (6) | Unknown, found dead in home. No autopsy |
| US_010158524 | 29 YOWF | 30 mg ~9 months | MDD with psychotic features | (b) (6) | Diabetic ketoacisosis |
| US_010158498 | 19 YOWM | 5 mg ~7 weeks | Intermittent explosive disorder, antisocial PD | (b) (6) | Unknown |
| US_010158510 | 17 YOWM | 2.5 mg not provided | Dysthymic disorder, schizophreniform disorder | (b) (6) | Accidental overdose vs. suicide |
| US_010158537 | 34 YOWF | 30 mg ~9 months | Psychotic disorder | (b) (6) | Unknown, found dead in home. No autopsy. Coroner comments indicate possible narcotic overdose. |

*Reviewer Comments*
It is difficult to interpret the relatedness of these fatalities to olanzapine therapy especially in light of the usual confounds inherent in MedWatch spontaneous reports. It is of interest that these cases were clustered in one geographic area with the majority occurring in 2000, but this could reflect reporting bias to some extent. It is troubling that there is very little data available for 3 of these cases – the narratives indicate that the Sponsor did attempt to obtain further information but was unable to do so.

**3.5 AIMS Analysis**
*Division Request #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.

This item was requested to evaluate potential emergent tardive dyskinesia for subjects who completed the long-term extension phases of the acute studies – since duration of antipsychotic use is a risk factor for development of this adverse event.

*Sponsor's Response*

Table 3.5.1. Sponsor's Table. Mean Change from Baseline to Endpoint in AIMS Scores. All Patients who Completed the Study – Overall Exposure Database.

| EPS Variables | Database | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | *P-value |
|---|---|---|---|---|---|---|---|
| AIMS Non-Global Total(1-7) | Bipolar | 129 | 0.06 | 0.35 | -0.04 | 0.29 | .132 |
| | Schizophrenia | 85 | 0.29 | 0.88 | -0.22 | 0.88 | .021 |
| | Overall | 214 | 0.15 | 0.63 | -0.11 | 0.60 | .007 |
| AIMS Total(1-10) | Bipolar | 129 | 0.10 | 0.50 | -0.05 | 0.54 | .332 |
| | Schizophrenia | 85 | 0.59 | 1.77 | -0.51 | 1.76 | .010 |
| | Overall | 214 | 0.29 | 1.20 | -0.23 | 1.21 | .006 |
| AIMS Item 1 - Muscles of Facial Expression | Bipolar | 129 | 0.00 | 0.00 | 0.01 | 0.09 | .319 |
| | Schizophrenia | 85 | 0.11 | 0.44 | -0.07 | 0.51 | .203 |
| | Overall | 214 | 0.04 | 0.28 | -0.02 | 0.33 | .298 |
| AIMS Item 2 - Lips and Perioral Area | Bipolar | 129 | 0.00 | 0.00 | 0.00 | 0.00 | |
| | Schizophrenia | 85 | 0.04 | 0.19 | -0.04 | 0.19 | .083 |
| | Overall | 214 | 0.01 | 0.12 | -0.01 | 0.12 | .083 |
| AIMS Item 3 - Jaw | Bipolar | 129 | 0.01 | 0.09 | -0.01 | 0.09 | .319 |
| | Schizophrenia | 85 | 0.00 | 0.00 | 0.00 | 0.00 | |
| | Overall | 214 | 0.00 | 0.07 | -0.00 | 0.07 | .318 |
| AIMS Item 4 - Tongue | Bipolar | 129 | 0.02 | 0.12 | -0.02 | 0.12 | .158 |
| | Schizophrenia | 85 | 0.04 | 0.33 | -0.04 | 0.33 | .320 |
| | Overall | 214 | 0.02 | 0.23 | -0.02 | 0.23 | .132 |
| AIMS Item 5 - Upper Extremity | Bipolar | 129 | 0.01 | 0.09 | 0.00 | 0.12 | 1.00 |
| AIMS Item 5 - Upper Extremity | Schizophrenia | 85 | 0.06 | 0.28 | -0.05 | 0.30 | .159 |
| | Overall | 214 | 0.03 | 0.19 | -0.02 | 0.22 | .207 |
| AIMS Item 6 - Lower Extremity | Bipolar | 129 | 0.02 | 0.12 | -0.01 | 0.09 | .319 |
| | Schizophrenia | 85 | 0.05 | 0.34 | -0.04 | 0.36 | .369 |
| | Overall | 214 | 0.03 | 0.24 | -0.02 | 0.24 | .249 |
| AIMS Item 7 - Neck, Shoulders, Hips | Bipolar | 129 | 0.02 | 0.12 | -0.02 | 0.12 | .158 |
| | Schizophrenia | 85 | 0.01 | 0.11 | 0.00 | 0.15 | 1.00 |
| | Overall | 214 | 0.01 | 0.12 | -0.01 | 0.14 | .318 |
| AIMS Item 8 - Global Severity | Bipolar | 129 | 0.00 | 0.00 | 0.01 | 0.09 | .319 |
| | Schizophrenia | 85 | 0.13 | 0.48 | -0.12 | 0.47 | .024 |
| | Overall | 214 | 0.05 | 0.31 | -0.04 | 0.31 | .049 |
| AIMS Item 9 - Global Incapacitation | Bipolar | 129 | 0.00 | 0.00 | 0.00 | 0.00 | |
| | Schizophrenia | 85 | 0.05 | 0.21 | -0.05 | 0.21 | .045 |
| | Overall | 214 | 0.02 | 0.14 | -0.02 | 0.14 | .045 |
| AIMS Item 10 - Patient's Awareness | Bipolar | 129 | 0.04 | 0.19 | -0.02 | 0.28 | .529 |
| | Schizophrenia | 85 | 0.12 | 0.45 | -0.12 | 0.45 | .018 |
| | Overall | 214 | 0.07 | 0.32 | -0.06 | 0.36 | .023 |

*Reviewer Comments*

For the AIMS non-global (items 1-7), AIMS total (items 1-10) and most individual AIMS items, there was a decrease in score rating at endpoint compared to baseline for the bipolar, schizophrenia and overall (bipolar + schizophrenia) treatment groups. Based on this mean change analysis, there is no signal for increased risk of tardive dyskinesia in this dataset.

### 3.6 Disparity in Efficacy Results US vs. Russian Sites in HGIN

*Division Request #8*

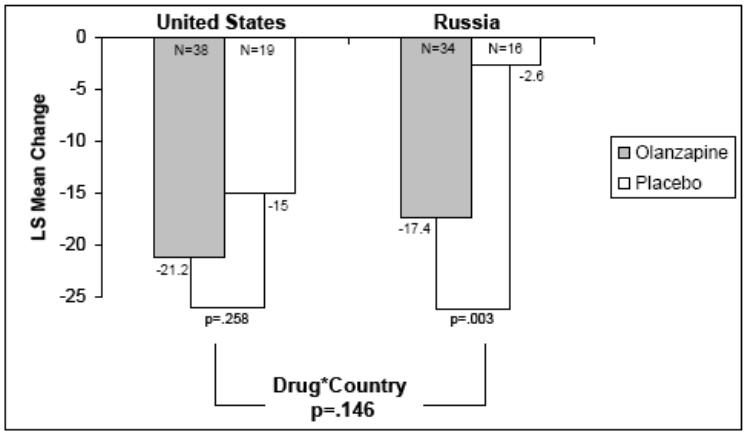
One concern we have for study HGIN is a finding that the positive results for this trial appeared to come predominantly from the Russian sites. For this study, the total sample was roughly split between these 2 regions. Although olanzapine was favored over placebo numerically in both regions, the data 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.

*Sponsor's Response*

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 observed case (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

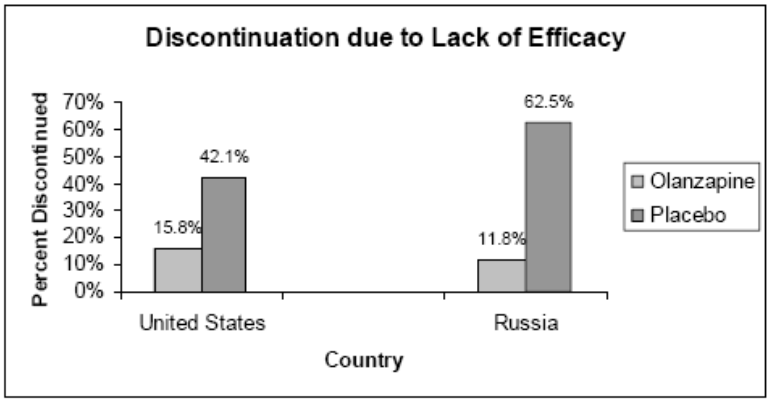
The Sponsor also reiterated in this response that the treatment-by-country interaction was not significant (p = 0.146):




Abbreviation: LS = least-squares.
Source: CLOBPRA1, CLOBPRA4.

**Figure APP.4.1. Brief Psychiatric Rating Scale for Children Total score mean change by country.**

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 ($p = 0.049$) and Russia ($p < 0.001$). "This result is supportive of the efficacy demonstrated with olanzapine treatment compared with placebo treatment in both countries."




Source: INACMGA1.

**Figure APP.4.2. Percentage of patients discontinuing due to lack of efficacy in the United States and Russia.**

- The effect sizes were .63 for all patients, .32 for the US patients, and .96 for Russian patients.
- Protocol-defined response rate was not statistically different between the two treatment groups in either the United States (39.5% for olanzapine; 31.6% for placebo; p=.772) or in Russia (35.3% for olanzapine; 18.8% for placebo; p=.328).
- Use of concomitant benzodiazepine medication was not statistically significantly different in the United States (26.3% for olanzapine; 42.1% for placebo; p=.244) or in Russia (32.4% for olanzapine; 62.5 % for placebo; p=.066).
- The mean modal doses were calculated for patients in both countries. The mean modal doses were 13.2 mg for the United States and 11.8 for Russia.

Overall conclusion by Sponsor:

Despite numerous statistical and clinical evaluations, an explanation for the difference in placebo response between the United States and Russia remains unclear. It is possible that factors such as population heterogeneity or cultural availability of adjunct therapy may have influenced the placebo response, but this cannot be proven with the available data. Lilly believes that the lack of a clear explanation for the difference in placebo response in the two countries should be considered in light of the fact that a similar magnitude of efficacy response was observed for the olanzapine treatment group in both countries, and that the treatment-by-country interaction was not significant. Furthermore, the overall results of the trial are positive, and are consistent with the abundance of positive efficacy data for the use of olanzapine for the treatment of schizophrenia in adults.

*Reviewer Comments*
During the review of the original submission, this reviewer 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. No significant differences that might account for the low placebo response rate at the Russian sites was identified during review of these additional analyses.

Discontinuations Due to Lack of Efficacy
The Sponsor commented that the discontinuations due to lack of efficacy were significantly greater among placebo-treated patients compared with olanzapine-treated patients in both the US ($p = 0.049$) and Russia ($p < 0.001$) and that this result is supportive of the efficacy demonstrated with olanzapine treatment compared with placebo treatment in both countries. While this statement is true, the p-value for the US sites is marginally significant and could change depending on how you might categorize "lost to follow up" (1.4% in olanzapine group vs. 0% in placebo) and "patient decision" (5.6% in olanzapine group vs. 2.9% in placebo group). It bears mentioning that lack of efficacy, though different between the olanzapine and placebo groups, is the main reason for study discontinuation in both groups.

This reviewer also referred to the recent NDA submissions for the aripiprazole (NDA 21436 SE5-021) and risperidone (NDA 20272 SE5-046) adolescent schizophrenia programs (both recently granted approval actions). Though there are obvious limitations in comparing study HGIN to the pivotal trials for these other antipsychotics, there are certainly noteworthy differences with respect to several issues including discontinuations due to lack of efficacy:

Table 3.6.1. Subject Disposition: Adolescent Schizophrenia Pivotal Trials for Olanzapine, Aripiprazole, and Risperidone

| | Sample Size | Discontinuation Rates | DC due to Lack of Efficacy | DC due to AE | Withdrew Consent/Patient Decision | Lost to Follow-up |
|---|---|---|---|---|---|---|
| Olanzapine | 72 | 32% | 13.9% | 6.9% | 5.6% | 1.4% |
| Placebo | 35 | 57% | 51.4% | 0 | 2.9% | 0 |
| Aripiprazole 10 mg | 99 | 16% | 5% | 7% | 4% | 0 |
| Aripiprazole 30 mg | 97 | 18% | 1% | 3.9% | 11.8% | 0 |
| Placebo | 98 | 10% | 1% | 2% | 5% | 1% |
| Risperidone 1-3 mg | 54 | 18% | 5% | 5% | 5% | NA |
| Risperidone 4-6 mg | 50 | 14% | 2% | 8% | 2% | NA |
| Placebo | 54 | 33% | 24% | 4% | 4% | NA |

Comparing across these trials, the overall discontinuation rates for the olanzapine study (HGIN) are much higher compared to the aripiprazole and risperidone pivotal trials. This disparity is also reflected in the discontinuations due to lack of efficacy across these trials including what appear to be significant differences between the olanzapine-treated subjects compared to aripiprazole or risperidone-treated subjects. However, the discontinuations due to lack of efficacy in the aripiprazole 30 mg group may be more similar to the olanzapine group depending on the definition of "withdrew consent".

Evaluating the Low Placebo Response in Russian Sites Compared to US Sites.

Table HGIN.14.21. BPRS-C Total Score
Mean Change from Baseline to Endpoint (LOCF) by Country
Double-Blind Period

| Efficacy Variable | Country | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Diff. | *P-value | **P-value (Therapy by Country ) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BPRS-C Total Score | America | Olanzapine | 38 | 53.18 | 10.10 | -21.21 | 16.30 | -20.89 | -5.26 | .258 | .146 |
| | | Placebo | 19 | 51.42 | 8.64 | -15.00 | 18.28 | -15.64 | | | |
| | Russia | Olanzapine | 34 | 47.00 | 8.88 | -17.41 | 14.55 | -17.44 | -14.95 | .003 | |
| | | Placebo | 16 | 48.50 | 8.52 | -2.56 | 17.38 | -2.49 | | | |

Source: Original NDA submission

This reviewer again referred to the recent NDA submissions for the aripiprazole and risperidone adolescent schizophrenia programs to compare placebo response between the Russian sites in HGIN compared to the aripiprazole and risperidone pivotal schizophrenia trials. For these latter pivotal trials, the primary efficacy variable was the PANSS total score.

Approximately 32 % (93/294) of subjects in the aripiprazole pivotal trial were from US sites and 22% (64/294) from Russian sites (the remaining from Argentina, Bulgaria, Croatia, India, Jamaica, Mexico, Romania, Serbia, South Africa, south Korea and Ukraine). In the statistical analysis for this NDA, a separate subgroup analysis for the Russian sites was not performed by

the statistician. However, upon request from this reviewer, the statistician (Yeh Fong, Ph.D.) did provide an analysis of change from baseline for the Russian sites (Table 3.6.2). Contrary to the olanzapine pivotal trial (HGIN), the placebo response in the Russian sites was similar to the US sites (-17.8 vs. -23.7).

Table 3.6.2. Region Subgroup Analysis: Adolescent Schizophrenia Pivotal Trials for **Aripiprazole**

Table 7 Sponsor's Region Subgroup Analysis Results for Change from Baseline to End Visit of PANSS Total Score (by LOCF Data) for Study 31-03-239

| Treatment | Visit | Mean (SD) | Change from Baseline to Last Visit Mean (SD) |
|---|---|---|---|
| US | | | |
| Arip-10 mg (N=31) | Baseline | 97.2 (16.5) | -31.4 (22.5) |
| | Last Visit (Week 6) | 65.8 (21.8) | |
| Arip-30 mg (N=31) | Baseline | 101.3 (15.1) | -30.7 (21.4) |
| | Last Visit (Week 6) | 70.5 (24.1) | |
| Placebo (N=31) | Baseline | 98.6 (17.0) | -23.7 (20.9) |
| | Last Visit (Week 6) | 74.9 (26.8) | |

| Treatment | Visit | Mean (SD) | Change from Baseline to Last Visit Mean (SD) |
|---|---|---|---|
| **Russia** | | | |
| Arip-10 mg (N=21) | Baseline | 91.14 (15.56) | -19.57 (21.70) |
| | Last Visit (Week 6) | 71.57 (21.43) | |
| Arip-30 mg (N=25) | Baseline | 88.28 (12.31) | -19.76 (16.77) |
| | Last Visit (Week 6) | 68.52 (17.59) | |
| Placebo (N = 18) | Baseline | 95.72 (13.46) | -17.83 (14.33) |
| | Last Visit (Week 6) | 77.89 (11.67) | |

Approximately 21 % (33/160) of subjects in the risperidone pivotal trial were from US sites and 23% (37/160) from Russian sites (the remaining from India and Ukraine). In the risperidone pivotal trial, the placebo response in the Russian sites is consistent with the olanzapine HGIN pivotal trial (Table 3.6.3). Interestingly, the risperidone change from baseline is also much lower in the Russian sites compared to the US sites.

Table 3.6.3. Region Subgroup Analysis: Adolescent Schizophrenia Pivotal Trials for **Risperidone**

| Treatment | Change from Baseline to Endpoint LS Mean Change | P-value |
|---|---|---|
| **Russia** | | |
| Risperidone 1-3 mg (N=12) | -9.29 | 0.23 |
| Risperidone 4-6 mg (N=13) | -11.6 | 0.09 |
| Placebo (N = 12) | -0.44 | |

| Treatment | Change from Baseline to Endpoint LS Mean Change | P-value |
|---|---|---|
| **United States** | | |
| Risperidone 1-3 mg (N= 12) | -29.2 | 0.030 |
| Risperidone 4-6 mg (N= 11) | -27.7 | 0.046 |
| Placebo (N = 10) | -11.1 | |

Overall, though the placebo response is quite low in the Russian sites in the olanzapine pivotal trial HGIN, a similarly low placebo response in Russian sites has been noted in similar studies in similar populations (risperidone) though not all (aripiprazole). This reviewer did not look at individual investigators or individual sites within Russia for any further comparisons.

Evaluating the Change from Baseline to Endpoint in Olanzapine Groups (US vs. Russia)
The Sponsor states that although the olanzapine vs. placebo comparisons were statistically significant for the Russian sites and not the US sites (primarily due to the low placebo response rate in the Russian sites), the change from baseline to endpoint in the olanzapine groups are similar between the these geographic sites. This reviewer agrees that the overall decrease from baseline to endpoint between the olanzapine groups in the US and Russian sites is similar. Again the overall statistically significant finding is largely driven by the low placebo response in the Russian sites and not due to disparities between the olanzapine groups. It is also entirely likely that, when the US sites are evaluated separately, there is insufficient power to detect a statistical difference. In efforts to further evaluate efficacy signals, this reviewer also looked at the adolescent schizophrenia pivotal trials for aripiprazole and risperidone. It should be noted that the primary efficacy variable in the pivotal trials for aripiprazole and risperidone was the PANSS total score. MMRM analyses were not available for the aripiprazole and risperidone pivotal trials.

In general, when comparing the change from baseline to endpoint in the olanzapine group in the US sites (-21.2), it is of a similar magnitude to changes from baseline in other antipsychotic clinical trials in similar populations (most of these clinical trials enrolled ~20% of subjects from

US sites). Since study HGIN used the BPRS as the primary endpoint whereas the aripiprazole and risperidone pivotal trials used the PANSS, a decrease of this magnitude in HGIN (-21.2) may be more significant given the higher baseline scores in the latter trials due to the differences in the BPRS and PANSS instruments.

It is noteworthy that, largely due to differences in subject discontinuation rates (see Table 3.6.1), the OC analyses for the aripiprazole and risperidone pivotal trials were statistically significant whereas the OC analysis for the olanzapine HGIN trial was not (Table 3.6.4). Due to the 2:1 randomization scheme in HGIN, only 35 subjects received placebo and 57% of subjects in the placebo group discontinued the study leaving 15 subjects for the OC analysis.

Table HGIN.14.21. BPRS-C Total Score
Mean Change from Baseline to Endpoint (LOCF) by Country
Double-Blind Period

| Efficacy Variable | Country | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Diff. | *P-value | **P-value (Therapy by Country ) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BPRS-C Total Score | America | Olanzapine | 38 | 53.18 | 10.10 | -21.21 | 16.30 | -20.89 | -5.26 | .258 | .146 |
| | | Placebo | 19 | 51.42 | 8.64 | -15.00 | 18.28 | -15.64 | | | |
| | Russia | Olanzapine | 34 | 47.00 | 8.88 | -17.41 | 14.55 | -17.44 | -14.95 | .003 | |
| | | Placebo | 16 | 48.50 | 8.52 | -2.56 | 17.38 | -2.49 | | | |

Table 3.6.4. LOCF and OC Analyses: Adolescent Schizophrenia Pivotal Trials for Olanzapine (US + Russian sites), Aripiprazole, and Risperidone

| | | | Change from Baseline to Endpoint or LS Mean Change | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Primary Endpoint | Baseline | LOCF analysis | | | OC analysis | | |
| | | | Change | P-value | Sample Size | Change | P-value | Sample Size |
| Olanzapine<br>Placebo | BPRS | 50.3<br>50.1 | -19.3<br>-9.1 | p = 0.003 | 72<br>35 | -24.5<br>-23.7 | p = 0.947 | 50<br>15 |
| Aripiprazole 10 mg<br>Aripiprazole 30 mg<br>Placebo | PANSS | 93.7<br>94.9<br>95.0 | -26.7<br>-28.6<br>-21.2 | p = 0.04<br>p = 0.006 | 99<br>97<br>98 | -30.6<br>-31.9<br>-22.3 | p = 0.001<br>p = 0.0002 | 84<br>84<br>90 |
| Risperidone 1-3 mg<br>Risperidone 4-6 mg<br>Placebo | PANSS | 95.4<br>93<br>93.2 | -21.3<br>-21.2<br>-8.9 | p < 0.001<br>p < 0.001 | 54<br>50<br>54 | -24.6<br>-24.5<br>-13.6 | p < 0.001<br>p < 0.001 | 44<br>43<br>35 |

<u>Discrepancies in MMRM analyses depending on model chosen</u>
The primary efficacy endpoint for study HGIN was change from baseline in the BPRS-C total score by LOCF analysis with OC and MMRM as supportive analyses. The LOCF analysis was statistically significant favoring olanzapine (LS mean difference = -10.12; p = 0.003) as was the MMRM analysis (LS mean difference = -8.90; p = 0.015). The OC analysis was not statistically significant (LS mean difference = -0.26; p = 0.947).

In his original review, the statistician had indicated that the MMRM analysis was not statistically significant based on his analysis (not the Sponsor's). In an addendum to his review, he indicated that he had used a different model for the MMRM analysis (default variance-covariance structure model) than the Sponsor had used (unstructured model); however, he indicated that the unstructured model was the most appropriate to use based on the fit of the data.
However, it should be noted that, based on the MMRM model, the p-values are very different:

| Variance-covariance Structure | Placebo | Olanzapine | AIC |
|---|---|---|---|
| **Variance Components** | | | |
| LS Mean change from baseline (SE) | -24.1 (3.13) | -24.5 (1.73) | |
| Difference between LS Means and C.I. | -0.43 (-6.6,7.5) | | |
| P-value | 0.90 | | 4691 |
| **Unstructured** | | | |
| LS Mean change from baseline (SE) | -12.6 (2.99) | -21.5 (1.97) | |
| Difference between LS Means and C.I. | -8.9 (-16.0, -1.9) | | |
| P-value | 0.015 | | 4055.2 |
| **Compound Symmetry** | | | |
| LS Mean change from baseline (SE) | -17.8 (2.61) | -22.9 (1.60) | |
| Difference between LS Means and C.I. | -5.1 (-11.1, 0.9) | | |
| P-value | 0.10 | | 4353.0 |
| **Toeplitz** | | | |
| LS Mean change from baseline (SE) | -14.3 (2.68) | -21.9 (1.65) | |
| Difference between LS Means and C.I. | -7.67 (-13.8, -1.5) | | |
| P-value | 0.015 | | 4129.0 |
| **Toeplitz with Two Bands** | | | |
| LS Mean change from baseline (SE) | -21.7 (2.70) | -24.4 (1.53) | |
| Difference between LS Means and C.I. | -2.68 (-8.8, 3.4) | | |
| P-value | 0.39 | | 4356.0 |
| **First Order Auto-regression** | | | |
| LS Mean change from baseline (SE) | -15.4 (2.71) | -22.3 (1.64) | |
| Difference between LS Means and C.I. | -7.0 (-13.8, -0.8) | | |
| P-value | 0.029 | | 4129.0 |

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

Source: Statistician's review – addendum to review

Evaluating the different MMRM models for the data for study HGIU (bipolar study) yields very consistent results with p-values ranging from < 0.0001 to 0.0004 (see Appendix). It appears that the MMRM analyses are very unstable for the schizophrenia data (HGIN) and are quite dependent on the specific MMRM model used in contrast to the very stable results for the bipolar data (HGIU). It should also be noted that the drop-out rates in the two studies were different with more subjects remaining in study HGIU – how this impacts the various MMRM models is beyond the expertise of this clinical reviewer. The OC analysis for study HGIU was statistically significant.

Since the Sponsor prespecified the LOCF as the primary analysis and the statistician agrees that the unstructured MMRM model is the most appropriate, it would appear that the Sponsor's data support efficacy of olanzapine versus placebo in study HGIN.

DSI inspections for Russian sites

Fifty subjects were enrolled in Russian sites – 10 subjects in each of 5 sites in Moscow. Upon query, the Sponsor indicated that the maximum number of subjects any one site could enroll was 10. 20 US sites enrolled 57 subjects (only one US site enrolled 10 subjects).

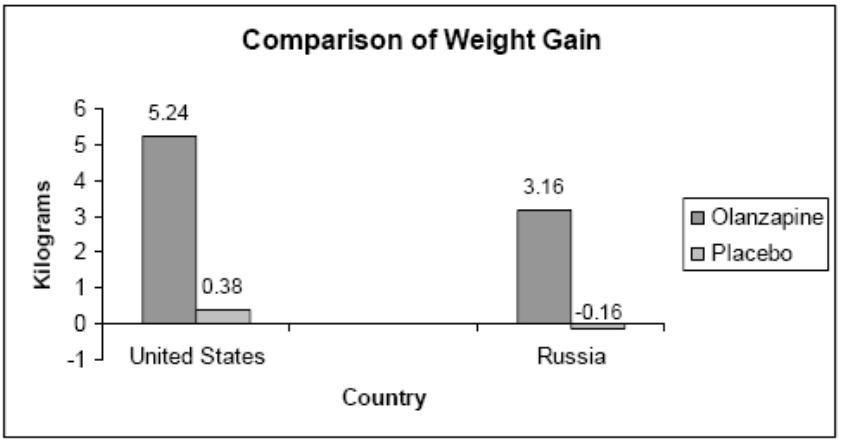
Because of the discrepancy in efficacy findings between the US and Russian sites, the Division requested that The Division of Scientific Investigations (DSI) inspect 2 Russian sites. The Moscow Research Institute of Psychiatry, Moscow, Russia; Valery Kransov, M.D. (principle investigator) was inspected between February 26 – March 2, 2007. The Moscow Medical University, Moscow, Russia; Leonid Bardenstein, M.D. (principle investigator) was inspected between February 19 – 22, 2007.

An audit of all subjects' records at these two sites was conducted and revealed few protocol violations. The overall conclusions of the DSI medical officer was that the study appeared to have been conducted adequately and the data generated by these sites may be used.

**3.7 Other Issues**

In this complete response document, the Sponsor included data comparing weight gain between the US and Russian sites:

- Comparison of weight gain in the 2 countries is illustrated in Figure APP.4.3. The significant differences between countries in weight do not explain the placebo effect difference seen within countries, but do suggest potential cultural differences in the two countries that may impact weight gain.




Source: INACMGA6.

**Figure APP.4.3. Comparison of weight gain in the United States and Russia.**

For the HGIN study (US + Russian sites), the increase in weight was 4.26 kg in the olanzapine group and 0.13 kg in the placebo group. The Sponsor did not include additional weight analyses between these geographic sites such as % of subjects having $\geq$ 7% weight gain. However, these

data do indicate a difference in the magnitude of weight gain in the US and Russian populations. The currently proposed labeling with regard to weight gain does not differentiate between these populations and the Sponsor was not asked to perform separate analyses for differences in geographic sites for the adult data either. However, the important issue of weight gain is being evaluated by another clinical reviewer and significant changes to proposed labeling are being made to further highlight this issue for both the adult and adolescent populations - though these data may underestimate the weight gain in the US population.

# 4. SAFETY UPDATE

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. The purpose of the review was to identify differences in the safety information between adolescent and adult patients treated with olanzapine.

As in the original submission, a proportional reporting ratio (PRR) and Chi-square value were calculated to compare the frequency of adverse event reports between the adolescent and adult populations. The Sponsor indicated the following general guidelines that may indicate an adverse event signal: at least 3 reports, a PRR > 2 and a Chi-square > 4.

The following table includes adverse events that indicate an increased frequency in the adolescent compared to the adult populations, again, based on spontaneous reports. It is noteworthy that galactorrhea occurs more frequently in the adolescent population and is further evidence that this adverse event should be included in product labeling (as recommended in section 3.1 of review).
The Sponsor commented that when evaluated the cases of aggression, some reported a history of the event, some reported use of concomitant medications, some of the events were considered to be disease-related, and some cases lacked sufficient information for an evaluation.

**Table 6. Adverse Events Reported with a PRR ≥2 in Olanzapine-Treated Patients Aged 13-17 Years Compared with Events Reported in Patients Aged 18-64 Years, with a Proportion of the Event of Interest ≥1.0% of All Events Reported in Patients Aged 13-17 Years, and with a Chi-Square Value ≥4**

| MedDRA Preferred Term (# of events in patients 13-17 years) | Proportion of Event in Patients 13-17 years (%) (N=3,754 events) | Proportion of Event in Patients 18-64 years (%) (N=85,420 events) | PRR[a] | Chi-Square Value |
|---|---|---|---|---|
| Somnolence (118) | 3.14 | 1.40 | 2.24 | 73.69 |
| Aggression (47) | 1.25 | 0.29 | 4.38 | 102.90 |
| Galactorrhoea (43) | 1.15 | 0.31 | 3.72 | 73.51 |
| Sedation (40) | 1. 07 | 0.41 | 2.62 | 35.80 |

[a] Ratio of event proportion in patients aged 13-17 years to event proportion in patients aged 18-64 years.

Based on this safety update, no new safety signals emerged that would require additional changes to product labeling.

# 5. LITERATURE UPDATE

A worldwide literature search was conducted for the time period August 25, 2006 through May 31, 2007 using Ovid Embase and Ovid Medline. Per the Sponsor, all resulting articles were reviewed by a Lilly clinical research physician. The Sponsor indicated that the 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.

# 6. FOREIGN REGULATORY UPDATE

As of August 21, 2007, olanzapine has not been approved for pediatric use in any country.

# 7. STUDIES TO BE CONDUCTED IN ADOLESCENTS

In the Risk Management Plan document, the Sponsor indicated that they would be conducting a 52-week open-label safety study (Study F1D-MC-HGMX) in adolescent subjects.

The Sponsor provided a very brief synopsis of this safety study. The primary objective of this study is to evaluate the long-term safety of oral olanzapine in these adolescent populations. The study will enroll (b) (4) patients recruited at sites in the US and possibly other countries. Measurements to be included in the protocol are assessment of body weight, reported adverse events, vital signs, ECG parameters, and clinical laboratory tests including hepatic enzymes, insulin, fasting glucose, fasting lipids (total cholesterol, LDL and HDL cholesterol, triglycerides), and prolactin. The secondary objectives are to evaluate efficacy of olanzapine in these adolescent populations as well as the effect of an intervention program on weight gain.

The protocol for this study has not yet been submitted to the Division for review.

# 8. OVERALL ASSESSMENT

## 8.1 Recommendation on Regulatory Action

This is a review of the complete response to the approvable action taken on 4/30/07 for NDAs 20-592 SE5-040 “treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents” and SE5-041 “treatment of schizophrenia in adolescents”. It is recommended that the Division take an approvable action on these supplements and that olanzapine be considered as second line treatment for bipolar disorder and schizophrenia in the adolescent population.

The Sponsor responded to all additional requests for information pertaining to pivotal trials HGIU (bipolar disorder) and HGIN (schizophrenia) outlined in the 4/30/2007 approvable letter (other requests for additional safety data in adults and adolescents were also submitted and

reviewed by another clinical reviewer). A review of these data did not reveal new safety risks or significant changes to already known safety risks that warranted significant changes to proposed product labeling beyond the changes suggested in the approvable letter. However, it is recommended that gynecomastia and galactorrhea be included as adverse events in product labeling as they appear to occur more frequently in the adolescent population compared to adults. The Sponsor also adequately addressed the disparity in the efficacy signal primarily driven by the differential placebo response between the United States and Russian sites in study HGIN (schizophrenia).

The recommendation for an approvable action (rather than an approval action) is based on the need for the development of a medication guide discussing significant adverse events in adolescents (b) (4) . Though these adverse events are well known for olanzapine, they occur much more frequently in the adolescent population. Weight gain, hyperglycemia, and hyperlipidemia are significant risk factors for cardiovascular morbidity, especially in disease states such as schizophrenia or bipolar disorder in which it is likely that patients will be taking these medications chronically.

Given these safety concerns, it is recommended that olanzapine be considered as second line therapy for the treatment of bipolar disorder and schizophrenia in the adolescent population. Recently two other antipsychotics, risperidone and aripiprazole, received approval for treatment of bipolar disorder and schizophrenia in adolescents. In comparison to olanzapine, these antipsychotics are not associated with the same magnitude of risk with regard to weight gain, hyperglycemia and hyperlipidemia.

## 8.2 Recommendation on Postmarketing Actions

### 8.2.1 Risk Management Activity

The Sponsor submitted a “risk management plan” document, however, it was not a typical risk management plan. The Sponsor has proposed education, labeling changes and some further clinical trials to address the safety risks of olanzapine in both adults and adolescents.

### 8.2.2 Required Phase 4 Commitments

The Sponsor is planning to conduct a 52-week open-label safety study (Study F1D-MC-HGMX) in adolescent subjects with bipolar disorder or schizophrenia (see Section 7 of review - Studies to be Conducted In Adolescents ). This study is being considered as a Phase 4 commitment. As of this time, the protocols for this study has not been submitted.
No additional Phase 4 commitments are recommended.

# 9 APPENDICES

## 9.1 MMRM Analyses for HGIU (Bipolar Study)

**Table 1 MMRM Analysis Results Using Different Variance-Covariance Structure in Study HGIU (Without Country in Model)**

| Variance-covariance Structure | Placebo | Olanzapine | AIC |
|---|---|---|---|
| **Sample Size** | 54 | 105 | |
| **Variance Components (Default)** | | | |
| LS Mean change from baseline (SE) | -11.3 (1.33) | -16.9 (0.86) | |
| Difference between LS Means and C.I. | -5.6 (-8.7,-2.5) | | |
| P-value | 0.0004 | | 4171.5 |
| **Unstructured** | | | |
| LS Mean change from baseline (SE) | -9.4 (1.37) | -16.4 (0.92) | |
| Difference between LS Means and C.I. | -6.9 (-10.2, -3.7) | | |
| P-value | <0.0001 | | 3994.6 |
| **Compound Symmetry** | | | |
| LS Mean change from baseline (SE) | -10.3 (1.26) | -16.8 (0.84) | |
| Difference between LS Means and C.I. | -6.4 (-9.4, -3.5) | | |
| P-value | <0.0001 | | 4038.2 |
| **Toeplitz** | | | |
| LS Mean change from baseline (SE) | -9.6 (1.26) | -16.4 (0.84) | |
| Difference between LS Means and C.I. | -6.8 (-9.8, -3.8) | | |
| P-value | <0.0001 | | 4005.7 |
| **Toeplitz with Two Bands** | | | |
| LS Mean change from baseline (SE) | -9.9 (1.25) | -16.6 (0.82) | |
| Difference between LS Means and C.I. | -6.7 (-9.6, -3.7) | | |
| P-value | <0.0001 | | 4043.2 |
| **First Order Auto-regression** | | | |
| LS Mean change from baseline (SE) | -9.6 (1.26) | -16.4 (0.84) | |
| Difference between LS Means and C.I. | -6.8 (-9.8, -3.9) | | |
| P-value | <0.0001 | | 4003.4 |

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

Source: Statistician, upon request

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/s/
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Cara Alfaro
7/14/2008 12:33:38 PM
PHARMACIST

Ni Aye Khin
7/18/2008 09:57:26 AM
MEDICAL OFFICER
I concur with Dr. Alfaro's recommendations; see memo to file for additional comments.