CLINICAL EXECUTIVE SUMMARY

Application Type	NDA 20-592
Submission Number	S-040
Submission Code	SE5
Letter Date	10/30/06
Stamp Date	10/31/06
PDUFA Goal Date	04/30/07
Reviewer Name	Cara Alfaro, Pharm.D.
Established Name	Olanzapine
Trade Name	Zyprexa
Therapeutic Class	Antipsychotic
Applicant	Eli Lilly
Priority Designation	P
Formulation	Oral tablets
Dosing Regimen	2.5 – 5 mg starting, maximum dose 20 mg/day
Indication	Treatment of Bipolar I Disorder
Intended Population	Adolescents (13 – 17 years)

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend that the Division take an approvable action on NDA 20-592 SE5-040 that was filed to support the indication "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents".

A number of additional requests for safety information and analysis regarding this submission are included in the clinical review. If acceptable, these requests could be included in the action letter.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Sponsor included a document discussing risk management in the submission. The actions proposed for risk minimization included product labeling and prescriber education though details for the latter were not included. These actions are the minimum steps that could be taken to manage risk associated with olanzapine therapy in this patient population. Distribution of a medication education guide could reinforce risk information to patients and their families.

1.2.2 Required Phase 4 Commitments

Pivotal trial HGIU (as well as HGIN – schizophrenia; SE5-041) included a flexible-dose paradigm for olanzapine. As such, a dose-response relationship for efficacy and safety cannot be determined since the important parameters of dose and time on drug can only be adequately addressed in a fixed dose trial. To minimize risk, it would be important to use the minimum effective dose to the extent that risk may be dose-related – however, in a flexible-dose design one cannot determine the dose-response for efficacy. I recommend that the Sponsor perform a fixed dose study in adolescent patients with bipolar disorder to better characterize the relationship of dose to efficacy and adverse events so that risk may be reduced.

Since bipolar disorder is a chronic illness, patients will likely require medication for a prolonged period. Some of the adverse events occurring in this adolescent patient population are significant (see Summary of Clinical Findings). It is important not only to identify these risks but to study the effect of interventions on these adverse events. The long-term cardiovascular risk of significant weight gain, hypertriglyceridemia and hypercholesterolemia is significant and efforts to minimize these adverse events is important. I recommend that the Sponsor perform a clinical study to evaluate interventions (e.g. dietary modification, exercise) on these adverse events.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

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 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).

Additional open-label studies were also submitted by the Sponsor primarily in support of safety. The primary supportive studies were LOAY (n = 89 adolescents) and HGMF (n = 107), the latter study was the primary pharmacokinetic study in this population.

1.3.2 Efficacy

The mean modal daily dose of olanzapine was 10.7 mg and the mean daily dose was 8.9 mg. Seventy-nine percent of patients in the olanzapine group and 65% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIU was change from baseline in the Adolescent-Structured YMRS Total Score. The overall study results were statistically significant for olanzapine versus placebo in the primary LOCF analysis as well as the supporting OC and MMRM analyses (see Table). The LOCF analysis for the secondary endpoint CGI-Severity Mania and CGI-Severity Overall were statistically significant favoring olanzapine.

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
LOCF	Olanzapine	105	33.1	6.5	-15.9	10.0	-17.6		
	Placebo	54	32.0	6.2	-7.7	9.4	-10.0	-7.7	< 0.001
OC	Olanzapine	88	33.2	6.5	-17.2	9.7	-19.1		
	Placebo	37	32.4	6.2	-11.1	9.0	-13.4	-5.7	0.001
MMRM	Olanzapine	88	33.2	6.5	-17.2	9.7	-15.8		
	Placebo	37	32.4	6.2	-11.1	9.0	-8.8	-6.9	< 0.001

Subgroup analyses included gender, age (< 15, ≥ 15), Caucasian vs. nonCaucasian, manic vs. mixed, psychotic vs. without psychotic features and rapid vs. nonrapid cycling. Statistically significant differences favoring olanzapine were found for all subgroups except < 15 year olds ($p = 0.094$), patients with psychotic features ($p = 0.111$) and rapid cyclers ($p = 0.271$) – the latter two groups had few patients in those subgroups. A significant treatment-by-age interaction was found (see Table). The Sponsor conducted

three additional posthoc analyses, two of these did not indicate a treatment-by-age interaction.

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
< 15 years	Olanzapine	49	32.8	7.0	-14.6	10.2	-16.6		
	Placebo	20	32.4	5.7	-9.4	11.0	-12.1	-4.5	0.094
≥ 15 years	Olanzapine	56	33.3	6.2	-17.0	9.9	-18.9		
	Placebo	34	31.8	6.6	-6.7	8.4	-9.0	-9.9	< 0.001

Since HGIU was a flexible-dose study, it is not possible to evaluate the dose-response with regard to efficacy. Proposed labeling states the range that was included in the clinical trial, but no data is available to determine whether higher doses confer greater efficacy and it is likely that higher doses confer greater risk from an adverse event perspective.

1.3.3 Safety

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIN is the pivotal trial for schizophrenia) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events (≥ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30% vs. 6%), somnolence (25% vs. 3%), increased appetite (24% vs. 6%), sedation (19% vs. 6%), headache (17% vs. 12%), fatigue (10% vs. 5%), dizziness (7% vs. 2%), dry mouth (6% vs. 0%) and pain in extremity (5% vs. 1%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain

The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with ≥ 7% increase in body weight.

	Olanzapine	Placebo	LS Mean Diff	P-value
HGIN + HGIU Acute Database				
Weight (kg) Mean Change to Endpoint (LOCF)	3.90 (n = 177)	0.24 (n = 88)	3.66	< 0.001
Weight (kg) Mean Change to Endpoint (OC)	3.6 (n = 154)	0.08 (n = 67)	3.57	< 0.001
BMI Mean Change to Endpoint (LOCF)	1.22	0.05	1.17	< 0.001
≥ 7% increase in body weight (%)	43.5%	6.8%	-	< 0.001
Overall Combined Database				
Weight (kg) Mean Change to Endpoint (LOCF)	7.35	-	-	< 0.001 (compared to baseline)
Weight (kg) Mean Change to Endpoint (OC)	10.8	-	-	< 0.001 (compared to baseline)
BMI Mean Change to Endpoint (LOCF)	2.31	-	-	< 0.001 (compared to baseline)
≥ 7% increase in body weight (%)	65%	-	-	-

In the Acute Database, weight gain (mean change from baseline to endpoint) was similar for the groups with baseline BMI < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

Weight changes were evaluated for the subgroups gender and age (< 15, ≥ 15 years). At the time this review was finalized, mean change in weight for the age subgroup analysis was only available for study HGIN (not HGIU or the Acute Database). Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine. A treatment-by-gender interaction was noted in the Acute Database, but was likely due to differences in the placebo groups since mean change in weight was similar in the olanzapine groups for males and females.

Liver Function Abnormalities

Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline $\leq$ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group ($p = 0.009$).

No patients met criteria for Hy's rule (ALT $\geq$ 3x ULN and TBili $\geq$ 1.5 x ULN).

Hyperprolactinemia

The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, $p < 0.001$). The washout period prior to baseline could be as short as 2 days and it was noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to perform further analyses in the subgroup of patients with baseline prolactin within normal limits.

In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU and HGIN.

For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females (15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN + HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$).

Hypertriglyceridemia

The mean change from baseline to endpoint for triglycerides was 29.2 mg/dL for the olanzapine group and -4.4 mg/dL for the placebo group (LS Mean Diff = 33.6, $p < 0.001$). In reviewing the individual lab data, 11 marked outliers were noted for triglycerides at any time (> 250 mg/dL). The most significant was an increase from 103 mg/dL at baseline to 1237 mg/dL. A higher percentage of patients in the olanzapine group had a shift from normal to high triglycerides (12.4%) compared to placebo (1.9%) ($p = 0.039$).

Hypercholesterolemia

The mean change from baseline to endpoint for cholesterol was 13.1 mg/dL for the olanzapine group and -1.2 mg/dL for the placebo group (LS Mean Diff = 14.3, $p < 0.001$). A higher percentage of patients in the olanzapine group had a shift from normal to borderline cholesterol (15.7%) compared to placebo (3.6%) ($p = 0.023$).

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality
Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in patients with bipolar disorder. Suicidal behaviors or ideation are not uncommon in these disorders and, in the absence of a placebo comparator, it is difficult to interpret causality to olanzapine therapy.

Although there are significant risks outlined in this review, there is also significant morbidity and mortality associated with untreated bipolar I disorder.

1.3.4 Dosing Regimen and Administration

Proposed labeling
“Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg. Efficacy in adolescents with

bipolar disorder (manic or mixed episodes) was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 10.7 mg/day (mean dose of 8.9 mg per day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended. The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials."

This dosing regimen is essentially the same as that in the protocol with two differences. In the protocol, the investigator had to increase the dose to 10 mg by the end of week 1 (based on tolerability) and could thereafter increase or decrease dose as necessary. Per protocol, it was suggested that olanzapine should be dosed in the evening due to the adverse event somnolence.

1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies were done as part of this clinical development program and none are needed.

1.3.6 Special Populations

These studies were conducted in accordance with a pediatric Written Request and the Agency has granted the Sponsor's request for pediatric exclusivity.

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

/s/

Ni Aye Khin

4/12/2007 04:48:56 PM

This is the revised version.