

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 ketoacidosis
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		Change to Endpoint		*P-value
			Mean	Std	Mean	Std	
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	0.39	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
	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

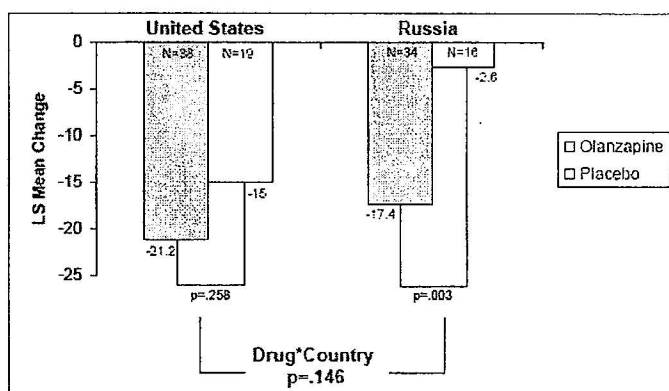
One concern we have for study HGIN is a finding that the positive results for this trial appeared to come predominantly from the Russian sites. For this study, the total sample was roughly split between these 2 regions. Although olanzapine was favored over placebo numerically in both regions, the data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

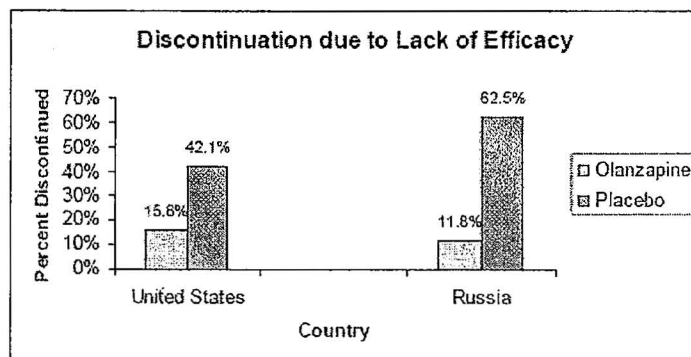
The Sponsor also reiterated in this response that the treatment-by-country interaction was not significant ($p = 0.146$):



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: INACMG1.

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	Baseline			Change to Endpoint		LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy by Country)
			N	Mean	Std	Mean	Std				
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	8.98	-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		Change to Endpoint		LSMean Change	LSMean Diff.	*p-value	**p-value (Therapy by Country)
				Mean	Std	Mean	Std				
BPRS-C Total Score	America	Olanzapine	38	53.18	10.10	-21.31	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	8.98	-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

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

Discrepancies in MMRM analyses depending on model chosen

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).

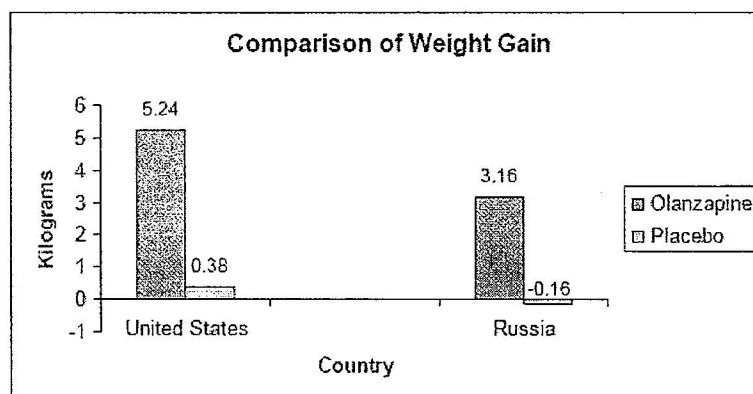
Because of the discrepancy in efficacy findings between the US and Russian sites, the Division requested that The Division of Scientific Investigations (DSI) inspect 2 Russian sites. The Moscow Research Institute of Psychiatry, Moscow, Russia; Valery Kransov, M.D. (principle investigator) was inspected 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 $\geq 1.0\%$ 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
Galactorrhea (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) Difference between LS Means and C.I. P-value	-11.3 (1.33) -16.9 (0.86) -5.6 (-8.7, -2.5) 0.0004		4171.5
Unstructured LS Mean change from baseline (SE) Difference between LS Means and C.I. P-value	-9.4 (1.37) -16.4 (0.92) -6.9 (-10.2, -3.7) <0.0001		3994.6
Compound Symmetry LS Mean change from baseline (SE) Difference between LS Means and C.I. P-value	-10.3 (1.26) -16.8 (0.84) -6.4 (-9.4, -3.5) <0.0001		4038.2
Toeplitz LS Mean change from baseline (SE) Difference between LS Means and C.I. P-value	-9.6 (1.26) -16.4 (0.84) -6.8 (-9.8, -3.8) <0.0001		4005.7
Toeplitz with Two Bands LS Mean change from baseline (SE) Difference between LS Means and C.I. P-value	-9.9 (1.25) -16.6 (0.82) -6.7 (-9.6, -3.7) <0.0001		4043.2
First Order Auto-regression LS Mean change from baseline (SE) Difference between LS Means and C.I. P-value	-9.6 (1.26) -16.4 (0.84) -6.8 (-9.8, -3.9) <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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this page is the manifestation of the electronic signature.**

/s/

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.

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA: 20-592, 21-520
Drug: Olanzapine (ZYPREXA and SYMBYAX (olanzapine/fluoxetine))
Route: Oral
Indication: Schizophrenia, bipolar disorder (ZYPREXA); depressive episodes associated with bipolar disorder, treatment resistant depression (SYMBYAX)
Sponsor: Eli Lilly
Review Date: 7/17/08
Reviewer: Sally Usdin Yasuda, Safety Team Leader
Neurology Drug Products, HFD-120

1. Background

In an approvable letter, received by Lilly on March 28, 2007, for a supplemental New Drug Application (sNDA) for Symbyax® [olanzapine/fluoxetine combination (OFC)] for the treatment of treatment-resistant depression (TRD), FDA requested analyses related to weight gain, hyperlipidemia, and hyperglycemia. FDA included similar requests in the approvable letter for two sNDAs for Zyprexa for the treatment of schizophrenia and bipolar disorder (acute manic or mixed episodes) in adolescent patients, received by Lilly on April 30, 2007. FDA and Lilly established a plan for specific analyses to be submitted; this plan was discussed in a meeting between FDA and Lilly on May 24, 2007. Lilly provided the requested data in a series of 4 rolling submissions, the last of which was received May 12, 2008.

Subject groups evaluated included all adult subjects, pediatric and adolescent subjects, and antipsychotic-naïve subjects. For each group the data were to be from placebo controlled trials, comparator controlled trials, and all data controlled and uncontrolled. The OFC databases were from studies in depression that included an OFC treatment group and at least an olanzapine treatment group or a fluoxetine treatment group. Excluded were studies without a source drug monotherapy arm, studies with duration under 7 days, studies with a relapse-prevention study design in which subjects had source drug exposure prior to randomization, and studies evaluation the source drug using routes of drug delivery other than oral drug delivery.

This memorandum summarizes the safety team review of these submissions. The primary review was conducted by Dr. Evelyn Mentari. In addition to the specific analyses that were agreed upon, the sponsor's proposed labeling includes data on metabolic changes from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies that Dr. Mentari has reviewed. In addition to summarizing the findings from Dr. Mentari's review, I will summarize in more detail the Sponsor's Risk Management Plan.

2. Summary of Findings from the Safety Review

2.1 Weight Gain

In adult placebo controlled trials (3-8 weeks, median exposure approximately 7 weeks) olanzapine-treated patients had a mean weight gain of 2.64 kg compared to a mean weight loss of 0.26 kg in placebo-treated subjects ($P < 0001$). Mean differences in weight change between olanzapine-treated subjects and placebo treated subjects were similar across baseline BMI groups. Mean weight gain in olanzapine-treated subjects increased and mean weight loss in placebo-treated subjects was also successively greater at successive endpoints from 2-48 weeks. In addition, the proportion of olanzapine-treated subjects with clinically significant weight gain generally increased at successive time points from 6 weeks to 36 months. The incidence of treatment-emergent weight gain of at least 7% was 22.2% for olanzapine and 3.0% for placebo (median exposure time of about 8 weeks in both treatment groups).

In comparator-controlled trials, weight gain (mean change in weight, % of patients with potentially clinically significant weight gain, and proportion with upward shift in BMI category) was similar for olanzapine and clozapine-treated patients. Results were also similar for olanzapine compared to quetiapine-treated patients, although Dr. Mentari notes that the majority of patients in that database were overweight or obese at baseline, resulting in limited utility in generalizing beyond that population. Greater weight gain was observed for olanzapine compared to risperidone, olanzapine compared to ziprasidone, and for olanzapine compared to haloperidol.

In the OFC Adult controlled database, mean weight gain in OFC treated subjects was 4.29 kg at 8 weeks compared with a mean weight loss of 0.54 kg in placebo treated subjects ($p < 0.001$). There was no significant difference in weight gain between OFC-treated subjects and olanzapine treated subjects.

Adolescents treated with olanzapine also experienced clinically significant and statistically significant ($p < 0.001$) mean weight gain of 4.6 kg in 3 weeks median exposure time for olanzapine-treated adolescents compared to 0.34 kg in placebo treated patients. As compared to the data above for adults, the rate of increase was greater than that observed in approximately 7 weeks median exposure in adults. In long term studies (at least 24 weeks), the mean weight gain was 11.2 kg. With short-term exposure, 40.6% of adolescents gained (median exposure 3.5 weeks) at least 7% of baseline body weight vs 9.8% of placebo-treated adolescents (median exposure 14 weeks), and with long-term exposure the percentages who gained at least 7%, 15% or 25% of baseline body weight were 89%, 55%, and 29%, respectively. Since OFC has not been systematically studied in adolescents, data from the olanzapine monotherapy studies has been added to the SYMBYAX label to provide information on adolescents.

Dr. Mentari shows that the mean increases in weight were generally greater for the olanzapine-treated antipsychotic naïve population than for the olanzapine-treated adult

population (naïve and non-naïve) when patients were normal, overweight or obese at baseline.

2.2 Hyperlipidemia

In adult placebo-controlled trials, the Last Observation Carried Forward (LOCF) analyses of mean change from baseline to endpoint showed statistically significantly greater mean increases for olanzapine compared to placebo for fasting and non-fasting total cholesterol, fasting LDL cholesterol and fasting triglycerides (median olanzapine exposure times of 6-8 weeks). Mean increases in fasting lipid measurements were greater in patients without evidence of lipid dysregulation at baseline. Data are also shown to suggest that the mean nonfasting total cholesterol in patients who completed 12 months of therapy did not increase further after approximately 4-6 months. Proportions of patients with clinically significant changes in total cholesterol, LDL cholesterol, or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low were greater in long-term studies compared with short term studies.

The following data were extracted from Dr. Mentari's review.

	Mean Change to Endpoint in Adult Placebo-Controlled (Olanzapine had median exposure times of 6-8 weeks)		Mean Change to Endpoint in Patients with at least 48 weeks of exposure
	OLZ	PLA	OLZ
Fasting total cholesterol (mg/dL)	5.27	-6.07	5.57
Non-Fasting Total cholesterol (mg/dL)	6.75	-4.51	
Fasting LDL (mg/dL)	3.03	-4.26	2.5
Fasting HDL (mg/dL)	-0.4	-0.21	
Fasting Triglycerides (mg/dL)	20.77	-10.74	18.71

Statistically significantly higher proportions of olanzapine-treated patients than placebo-treated patients met criteria for treatment-emergent significant increases for nonfasting total cholesterol, fasting total cholesterol, fasting triglycerides, and fasting LDL cholesterol based on the criteria of the National Cholesterol Education Program (NCEP).

In comparator-controlled trials, patients treated with olanzapine had greater mean increases in total cholesterol than did patients treated with risperidone. Patients treated with clozapine and olanzapine had comparable changes with respect to total cholesterol. In the quetiapine database there were no statistically significant changes in fasting or nonfasting lipid parameters. Dr. Mentari points out that the median exposure time on olanzapine-treated subjects was significantly greater than the median exposure time for quetiapine-treated subjects, and that the study population in one of the studies had overweight or obese as an entry criteria. For the ziprasidone-controlled database, olanzapine-treated patients had significantly different decreased HDL cholesterol, statistically significantly smaller decrease of mean fasting LDL, and a statistically

significant difference in mean fasting triglycerides that increased in olanzapine-treated patients and decreased in ziprasidone-treated patients. Information was also provided from the CATIE study to suggest that patients who received olanzapine had an exposure-adjusted mean increase in total cholesterol and in triglycerides compared to ziprasidone, risperidone, quetiapine, and perphenazine. In that study the mean exposure-adjusted increase in triglycerides was 40.5 mg/dL and in total cholesterol was 9.4 mg/dL in patients who received olanzapine.

In the OFC database, information was available for only total cholesterol and triglycerides. Dr. Mentari reports that OFC-treated subjects had an increase from baseline in mean random total cholesterol of 12.1 mg/dL that was statistically significant compared to an increase of 4.8 mg/dL for olanzapine-treated subjects and a decrease of 5.5 mg/dL for placebo-treated subjects. From controlled clinical studies up of to 12 weeks, there were statistically significantly more patients with increases in nonfasting total cholesterol of ≥ 40 mg/dL in 35% of OFC patients compared to either olanzapine (22.7%) or placebo (9%) and statistically significantly more patients changing from borderline to high or normal to high in OFC vs either olanzapine or placebo. In long-term studies (at least 48 weeks) changes in nonfasting total cholesterol from normal to high occurred at least once in 12% of patients and changes from borderline to high occurred in 56% of patients. Dr. Mentari points out that the incidence of statistically significant changes in lipid parameters in patients treated with OFC and olanzapine in the OFC database was greater than the incidence in patients treated with olanzapine in the olanzapine databases, and hypothesizes that this is due to the different populations in the 2 databases, making them difficult to compare.

Placebo-controlled studies in adolescents had a short median duration of exposure at the time of lipid measurement of 2-3 weeks. In the analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescents, olanzapine-treated adolescents had statistically significant increases from baseline in mean fasting total cholesterol, LDL, and triglycerides of 12.9 mg/dL, 6.5 mg/dL, and 28.4 mg/dL, respectively, compared to increases from baseline in 1.3 mg/dL, 1.0 mg/dL for fasting total cholesterol and LDL, respectively and a decrease in triglycerides of 1.1 mg/dL for placebo treated adolescents. In long-term studies (at least 24 weeks), there were increases in mean fasting total cholesterol, LDL, and triglycerides of 5.5 mg/dL, 5.4 mg/dL, and 20.5 mg/dL, respectively and a mean decrease in fasting HDL of 4.5 mg/dL. In a median exposure of 3 weeks, 14.5% of olanzapine-treated adolescents had an increase in fasting total cholesterol of ≥ 40 mg/dL compared to 4.5% of placebo controlled subjects ($p=0.036$); 37% of olanzapine treated subjects had a ≥ 50 mg/dL increase in fasting triglycerides compared with 15.2% of placebo-treated subjects ($p=0.02$). 17.5% of olanzapine subjects had a mean increase in fasting LDL of ≥ 30 mg/dL compared with 11.1% of placebo ($p=0.297$).

Antipsychotic naïve adults treated with olanzapine had mean increases in fasting and nonfasting cholesterol, fasting LDL, and fasting and non-fasting triglycerides all of which were statistically significantly different from decreases observed in placebo-treated antipsychotic naïve adults. There were no statistically significant differences between

olanzapine and placebo on HDL analyses. Changes in non-fasting triglycerides were larger in the antipsychotic naïve subset of patients compared to olanzapine-treated patients overall.

2.3 Hyperglycemia

In olanzapine placebo-controlled monotherapy studies with median duration of up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL vs 0.17 mg/dL). Mean increases in nonfasting glucose and HbA1c were statistically significantly greater for olanzapine-treated subjects than for placebo treated subjects. Differences between olanzapine-treated subjects and placebo-treated subjects in glucose-related laboratory analytes were greater in subjects with baseline potential glucose dysregulation, for example for nonfasting glucose in patients without potential for glucose dysregulation at baseline, the mean change was 11.76 mg/dL for olanzapine vs 4.62 mg/dL for placebo; in patients with potential for dysregulation at baseline, the mean change for olanzapine was 27.03 mg/dL vs. -8.73 mg/dL for placebo. Differences in mean change in fasting or nonfasting glucose occurred in the earliest measurements and Dr. Mentari reports that no clear time-related pattern of mean change in fasting or nonfasting glucose was noted in subsequent measurements in these studies. In an analysis of 8 placebo-controlled studies (median treatment exposure 4-5 weeks), 6.1% of olanzapine-treated subjects (N=855) had treatment-emergent glycosuria compared to 2.8% of placebo-treated subjects (N=599) (P=0.004). Dr. Mentari has summarized data from the CATIE study in which the median time to discontinuation for olanzapine was 9.2 months. In that database, the mean change in blood glucose without adjustment for exposure in olanzapine-treated patients was 15.0 mg/dL. In patients with at least 48 weeks of exposure, the mean change in fasting glucose was 4.2 mg/dL. The sponsor states in the proposed label (b) (4)

. However, Dr. Mentari provides data from the Sponsor's submission that do not strongly support this statement; she has suggested removing this statement from the labeling and I agree.

In comparator-controlled trials, a range of differences was observed between olanzapine and other antipsychotics. In general changes in nonfasting glucose measures were higher for clozapine than for olanzapine. In the quetiapine-controlled database, in which approximately 80% of patients were overweight or obese, there were no statistically significant differences between quetiapine and olanzapine in glucose measures. In the risperidone controlled database, the only statistically significant difference was a higher proportion of olanzapine treated patients going from normal/borderline nonfasting glucose at baseline to high glucose post-baseline. Data in the ziprasidone-controlled database, collected under fasting conditions, suggests that patients treated with olanzapine experience greater adverse changes in glucose-related parameters than patients treated with ziprasidone. Similarly, in the haloperidol-controlled database, collected under nonfasting conditions, patients treated with olanzapine had greater adverse changes in glucose than patients treated with haloperidol. The sponsor states in the proposed labeling (b) (4)

(b) (4)

. This statement is acceptable.

In the OFC database, with treatment duration of up to 12 weeks, OFC was associated with a statistically significantly greater mean change in random glucose compared to placebo (8.65 mg/dL vs -3.86 mg/dL). In an analysis of mean change by baseline values, patients with high fasting glucose at baseline had a mean increase in fasting glucose that was higher than the mean increase in patients with normal glucose at baseline. In an analysis of 6 controlled clinical studies (median exposure 6-8 weeks), 4.4% of SYMBYAX-treated subjects (N=477) had treatment-emergent glycosuria compared to 1.4% of placebo-treated subjects (N=284) (P=0.003).

In adolescent subjects in placebo controlled trials (trial duration 3-6 weeks), the mean change in fasting glucose was statistically significantly different for olanzapine (increase of 2.68 mg/dL) and placebo (decrease of 2.59 mg/dL). In patients with at least 24 weeks exposure, mean change in fasting glucose was 3.13 mg/dL. In patients taking olanzapine for up to 12 weeks or for at least 24 weeks, the percentage of patients shifting from borderline to high fasting glucose while taking olanzapine was generally greater than the percentage switching from normal glucose at baseline to high glucose, although the numbers of adolescent patients in these groups were very small, particularly those with baseline borderline glucose (n<15).

Olanzapine-treated antipsychotic naïve adults had mean increases in both fasting and nonfasting glucose, which were greater than increases observed in placebo-treated antipsychotic-naïve adults, but not statistically significant. In the placebo controlled databases, compared to olanzapine-treated adults as a whole, mean changes in fasting and nonfasting glucose were greater for olanzapine-treated antipsychotic-naïve adults, but proportions with categorical changes were generally lower.

2.4 Labeling

Dr. Mentari has suggested changes to the Sponsor's proposed labeling for the weight gain and hyperglycemia sections of WARNINGS and PRECAUTIONS based on her review of the Sponsor's submitted data. She does not recommend changes to the hyperlipidemia section. She has also recommended additions to the Highlights section of the prescribing information and to the laboratory tests section. I agree with Dr. Mentari's recommendations. Please refer to her review for her recommendations.

In addition to the changes proposed by Dr. Mentari for the WARNINGS and PRECAUTIONS section, the Sponsor has included a listing of several metabolic changes in Section 6.1 under (b) (4)

According to the definition in the label, infrequent adverse events are those occurring in 1/100 to 1/1000 patients and frequent events are those occurring in at least 1/100 patients. In this case, hyperglycemia would be considered frequent. However, I do not believe that

inclusion of these events in section 6.1 contributes substantially to the information that is in the WARNINGS and PRECAUTIONS section regarding hyperglycemia.

2.5 Postmarketing Risk Management Plan

The Sponsor has submitted a Risk Management Plan that I will discuss only with respect to the metabolic changes that are the subject of Dr. Mentari's review.

- The Sponsor describes in the Risk Management Plan a retrospective cohort study to characterize the risks of diabetes and dyslipidemia among adolescents with schizophrenia or bipolar disorder and in the adolescent general population. This was a retrospective claims database analysis using eligibility and medical claims from a U.S health insurance plan. Outcomes were defined by 1) the presence of specific ICD-9 diagnosis codes in at least 2 physician visits or 2) at least one dispensing of specific medications. The Study has been completed and was submitted with the 2/5/08 submission. The Sponsor concludes that adolescents with bipolar disorder or schizophrenia had an increased risk of developing diabetes and dyslipidemia compared to adolescents without these disorders in the general population and that patients treated with antipsychotics were at higher risk of developing diabetes and dyslipidemia than those not treated with antipsychotics. The study investigated antipsychotics as a class rather than individual drugs. This study report has not been reviewed by the safety team.
- The sponsor states in the Action Plan (Section 2.4.2) that a long-term (52-week) open label safety study of oral olanzapine in the treatment of adolescents with bipolar disorder or schizophrenia will be conducted with measurements to include assessment of body weight, fasting glucose, and fasting lipids. Only a protocol outline for study F1D-MC-HGMX has been provided. The Sponsor should submit a full protocol for review.
- The sponsor states that the risk minimization plan (Section 4 of the Risk Management Plan 1.1) includes labeling and the product website that is accessible to the general public and provides advice on weight management and nutrition.
- The Risk Minimization Plan in NDA 20-592 refers to the Lilly Wellness Program that has been in place for 5 years that the Sponsor states is a successful program of healthcare professional and patient education. (b) (4)

Outcomes of this program in terms of random blood glucose or dyslipidemia are not provided.

- I believe that the Sponsor's currently proposed approach to risk mitigation is not adequate. Dr. Mentari recommends that olanzapine and OFC will require Medication Guides regarding the metabolic issues. I agree. The Sponsor should be requested to develop Medication Guides and to outline in more detail appropriate educational plans for healthcare professionals that would highlight to a larger extent these risks to healthcare professionals.

3. Conclusions

Dr. Mentari's review supports labeling that she has proposed for weight gain, hyperlipidemia, and hyperglycemia. In addition to the labeling changes, we recommend

Safety Team Leader Memo
NDA 20-592, 21-520

that a proposal for risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide, be requested from the Sponsor. Future studies that include evaluation of metabolic changes might benefit from dose-response consideration.

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/s/

Sally Yasuda
7/17/2008 03:19:57 PM
BIOPHARMACEUTICS

Review and Evaluation of Clinical Data - Addendum

Application Type: NDA 20-592
Submission Number: S-041 SE5
Established Name: Olanzapine (Zyprexa)
Therapeutic Class: Antipsychotic
Indication: Treatment of schizophrenia in adolescent patients
Letter Date: 10/30/06
Stamp Date: 10/31/06
Priority Designation: P
PDUFA Goal Date: 4/30/07
Reviewer: Cara Alfaro, Pharm.D.
Date: 5/19/07

Background

This is an addendum to the Clinical Review of NDA 20-592 S-041 SE5 that was completed (signed off) on 4/18/07. Prior to the action date of this NDA, a conference call was held to discuss issues related to this NDA. During this discussion, it was mentioned that the MMRM analysis conducted by the statistical reviewer was not statistically significant ($p = 0.72$) while the MMRM analysis conducted by the Sponsor was statistically significant ($p = 0.015$). The statistical reviewer was not able to explain the discrepancy and was going to recheck his analysis.

This addendum describes the results of the statistician's reanalysis as well as an additional analysis requested by this reviewer. It is noteworthy that this new information did not alter the final recommendation of this reviewer for a not approvable action (though the Division did take a different action).

MMRM Analysis

The primary analysis for this submission was the LOCF analysis for the BPRS-C total score mean change from baseline at endpoint. The Sponsor included OC and MMRM as secondary analyses for this primary endpoint.

The results from the Sponsor's analyses are in the table below:

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
LOCF	Olanzapine	72	50.3	10.0	-19.4	15.5	-19.3		
	Placebo	35	50.1	8.6	-9.3	18.7	-9.1	-10.1	0.003
OC	Olanzapine	50	50.6	10.6	-24.5	13.5	-24.4		
	Placebo	15	49.0	8.5	-23.7	14.6	-24.1	-0.26	0.947
MMRM	Olanzapine	50	50.6	10.6	-24.5	13.5	-21.3		
	Placebo	15	49.0	8.5	-23.7	14.6	-12.4	-8.90	0.015

The results from the MMRM analysis conducted by the statistician (Fanhui Kong) are as follows*:

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
MMRM	Olanzapine	50	50.6	10.6	-24.5	13.5	-24.7		
	Placebo	15	49.0	8.5	-23.7	14.6	-23.5	-1.25	0.72

*In the addendum to Dr. Kong's review, a recalculation of this MMRM analysis provided a p-value of 0.90

In the addendum to Dr. Kong's review, he stated that the reason for the discrepancy between MMRM analyses was due to the different models/assumptions used for these calculations. In his investigation of the different models, Dr. Kong did indicate that the best fit for the data was the unstructured variance-covariance model which the Sponsor used and that yielded significant results. However, it is also noteworthy that the results of the various MMRM analyses are quite variable and not consistent yielding p-values from 0.015 to 0.90 and LS mean differences ranging from -0.43 to -8.9 (table from Dr. Kong's addendum):

Table 2.1 MMRM Analysis Results Using Different Variance-Covariance Structure in Study HGIN

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.

One of the reasons that this reviewer recommended a not approvable action was the disparity between results from the U.S. and Russia sites. The Sponsor included the LOCF analysis for evaluation of the primary endpoint between the two geographic regions, but did not include companion OC or MMRM analyses. This reviewer asked Dr. Kong to perform an MMRM analysis between the U.S. and Russia sites (table from Dr. Kong's addendum):

Table 2.2 Treatment Effect by Country by MMRM Analysis

Country	Placebo	Olanzapine
Russia		
N (Number of patients)	16	34
LS Mean change from baseline (SE)	-5.3 (4.46)	-19.0 (2.73)
Difference between LS Means and C.I.	-13.7 (-23.9, 3.3)	
P-value	0.012	
US		
N (Number of patients)	19	35
LS Mean change from baseline (SE)	-18.7 (4.13)	-23.5 (2.89)
Difference between LS Means and C.I.	-4.8 (-14.7, -5.1)	
P-value	0.35	

While exploratory in nature, this analysis is consistent with the LOCF analysis – robust findings in the Russia sites and not the U.S. sites.

Due to the inconsistent findings in the various MMRM analyses performed by Dr. Kong for study HGIN, this reviewer asked him to perform similar MMRM analyses for the HGIU study (SE5-040, bipolar disorder in adolescent patients) since the LOCF, OC and MMRM analyses performed by the Sponsor were consistent and statistically significant. Dr. Kong provided the summary table below (this table is not included in Dr. Kong's addendum). It is noteworthy that the different MMRM analyses for HGIU were consistent and robustly positive – in contrast to the inconsistent findings for these same analyses for study HGIN.

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

Conclusions

This reviewer continues to be troubled by the disparity in the results of the statistical analyses between the U.S. and Russia sites. While the overall LOCF and MMRM were positive, these results are largely driven by the Russia sites. It is noteworthy that of the various MMRM analyses that were performed by the statistician, results range from a p-value of 0.015 to 0.90 and LS mean differences ranging from -0.43 to -8.9. However, when the statistician performed this same set of MMRM analyses on the data from HGIU (a study in which the LOCF, OC and MMRM analyses were significant), the results were consistent and robust.

It is unclear why there is such a disparity in the efficacy results between the U.S. and Russia sites. While the Sponsor did include the LOCF analysis evaluating the efficacy endpoint between the U.S. and Russia sites, there is no further discussion on the disparate findings. The Sponsor has been asked to address this issue in the action letter.

Cara Alfaro, Pharm.D.
Clinical Reviewer
May 19, 2007

Cc: Khin/Bates/Laughren/Alfaro

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this page is the manifestation of the electronic signature.**

/s/

Cara Alfaro
5/19/2007 04:02:20 PM
PHARMACIST

Ni Aye Khin
5/21/2007 07:37:22 PM
MEDICAL OFFICER

CLINICAL EXECUTIVE SUMMARY

Application Type NDA 20-592
Submission Number S-041
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 Schizophrenia
Intended Population Adolescents (13 – 17 years)

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend that the Division take a not approvable action on NDA 20-592 SE5-041 that was filed to support the indication “treatment of schizophrenia in adolescents”.

Fifty-three percent of randomized patients in pivotal trial HGIN were from sites in the United States and 47% of randomized patients were from 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 ($p = 0.258$). The sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia.

Though the LOCF analysis was the primary analysis, it is also concerning that the OC and MMRM analyses (the latter by recalculation by the reviewing statistician in the Division) are substantially different from the LOCF analysis and not statistically significant.

I recommend that the Sponsor conduct another clinical trial in this population if they wish to pursue this indication. The majority of patients in this clinical trial should be from sites in the United States and efficacy will need to be established in these patients. It is also strongly recommended that this clinical trial be a fixed dose design since dose-response data for efficacy or safety cannot be evaluated in a flexible dose design.

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

Since a not approvable action is recommended, there are no recommendations for postmarketing actions.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

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 ($n = 35$).

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 12.5 mg and the mean daily dose was 11.1 mg. Seventy-five percent of patients in the olanzapine group and 56% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIN was change from baseline in the BPRS-C Total Score. The overall study results were statistically significant for olanzapine versus placebo in the primary LOCF analysis but not the supporting OC and MMRM (recalculated by statistician reviewer) analyses (see Table).

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
LOCF	Olanzapine	72	50.3	10.0	-19.4	15.5	-19.3		
	Placebo	35	50.1	8.6	-9.3	18.7	-9.1	-10.1	0.003
OC	Olanzapine	50	50.6	10.6	-24.5	13.5	-24.4		
	Placebo	15	49.0	8.5	-23.7	14.6	-24.1	-0.26	0.947
MMRM	Olanzapine	50	50.6	10.6	-24.5	13.5	-24.7		
	Placebo	15	49.0	8.5	-23.7	14.6	-23.5	-1.25	0.72

When evaluating the efficacy signal for the sites in the United States and the sites in Russia, only the latter were statistically significant in favor of olanzapine. The low placebo response in the sites in Russia appears to be driving these results.

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
U.S.	Olanzapine	38	53.2	10.1	-21.1	16.3	-20.9		
	Placebo	19	51.4	8.6	-15.0	18.3	-15.6	-5.3	0.258
Russia	Olanzapine	34	47.0	8.9	-17.4	14.5	-17.4		
	Placebo	16	48.5	8.5	-2.6	17.4	-2.5	-14.9	0.003

Since efficacy could not be demonstrated in patients in sites from the United States, this reviewer recommended a not approvable action.

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 (HGIU is the pivotal trial for bipolar disorder) 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 ($\geq 5\%$, 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 $\geq 7\%$ increase in body weight.

	Olanzapine	Placebo	LS Mean Diff	P-value
<i>HGIN + HGIU Acute Database</i>				
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
$\geq 7\%$ increase in body weight (%)	43.5%	6.8%	-	< 0.001
<i>Overall Combined Database</i>				
Weight (kg) Mean Change to Endpoint (LOCF)	7.35	-	-	< 0.001 (compared to baseline)
Weight (kg) Mean Change to Endpoint	10.8	-	-	< 0.001 (compared to baseline)

(OC)				
BMI	2.31	-	-	< 0.001 (compared to baseline)
Mean Change to Endpoint (LOCF)				
≥ 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 ≤ 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 ≥ 3x ULN and TBili ≥ 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 (n = 1) and HGIN (n = 1).

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 also 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 is not uncommon in these disorders and, in the absence of a placebo comparator, it is difficult to interpret causality to olanzapine therapy.

1.3.4 Dosing Regimen and Administration

This section not completed since a not approvable action was recommended.

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.

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/s/

Ni Aye Khin
4/12/2007 12:52:53 PM

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 schizophrenia. 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 HGMP. 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 ($\geq 5\%$, 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 $\geq 7\%$ increase in body weight.

	Olanzapine	Placebo	LS Mean Diff	P-value
<i>HGIN + HGIU Acute Database</i>				
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
$\geq 7\%$ increase in body weight (%)	43.5%	6.8%	-	< 0.001
<i>Overall Combined Database</i>				
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)
$\geq 7\%$ 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 $\leq 3 \times$ ULN who had ALT $> 3 \times$ 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 $\geq 3 \times$ ULN and TBili $\geq 1.5 \times$ 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

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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.

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this page is the manifestation of the electronic signature.**

/s/

Ni Aye Khin
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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 ($\geq 5\%$, 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 $\geq 7\%$ increase in body weight.

	Olanzapine	Placebo	LS Mean Diff	P-value
<i>HGIN + HGIU Acute Database</i>				
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
$\geq 7\%$ increase in body weight (%)	43.5%	6.8%	-	< 0.001
<i>Overall Combined Database</i>				
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)
$\geq 7\%$ 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 $\leq 3 \times$ ULN who had ALT $> 3 \times$ 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 $\geq 3 \times$ ULN and TBili $\geq 1.5 \times$ 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 ($p < 0.001$).

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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%) ($p = 0.039$).

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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

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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.

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this page is the manifestation of the electronic signature.**

/s/

Ni Aye Khin
4/12/2007 04:48:56 PM
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CLINICAL REVIEW

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.
Review Completion Date 04/06/07

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

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1 EXECUTIVE SUMMARY

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 at the end of this review. If acceptable, these requests could be included in the action letter.

Recommendation on Postmarketing Actions

1.1.1 Risk Management Activity

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1.1.2 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.

Summary of Clinical Findings

1.1.3 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 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).

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1.1.4 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 (LOCF analysis). The overall study results were statistically significant for olanzapine versus placebo (LS Mean Diff = -7.66, p < 0.001).

Efficacy Variable	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value
			Mean	Std	Mean	Std			
YMRS _{TOT} , Total (1-11)	Olanzapine	105	33.08	6.55	-15.90	10.03	-17.65	-7.66	<.001
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The supportive OC analysis was similar to the LOCF analysis (LS Mean Diff = -5.74, p = 0.001). The supportive MMRM analysis was similar to the LOCF analysis (LS Mean Diff = -6.95, p < 0.001). The LOCF analysis for the secondary endpoint CGI-Severity Mania and CGI-Severity Overall were statistically significant favoring olanzapine.

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.

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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 ($\geq 5\%$, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). 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 $\geq 7\%$ increase in body weight.

	Olanzapine	Placebo	LS Mean Diff	P-value
<i>HGIN + HGIU Acute Database</i>				
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	1.22	0.05	1.17	< 0.001

Mean Change to Endpoint (LOCF)				
≥ 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 ≤ 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 ≥ 3x ULN and TBili ≥ 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 (n = 1) and HGIN (n = 1).

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 is 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.

1.1.6 Dosing Regimen and Administration

Proposed labeling

(b) (4)

This dosing regimen is

(b) (4)

2 INTRODUCTION AND BACKGROUND

Product Information

Olanzapine (Zyprexa) is an atypical antipsychotic. Olanzapine oral tablets were approved on 9/30/1996 for the treatment of schizophrenia in adults. Olanzapine is also available as Zyprexa Zydis, orally disintegrating tablets and Zyprexa IntraMuscular for injection.

Olanzapine oral tablets are currently approved for the following indications: treatment of schizophrenia, treatment of acute mixed or manic episodes associated with bipolar I disorder, maintenance monotherapy for bipolar I disorder, and combination therapy (with lithium or valproate) for the short-term treatment of acute mixed or manic episodes associated with bipolar I disorder.

Olanzapine is not currently indicated for use in child/adolescent populations.

Currently Available Treatment for Indications

Other currently available atypical antipsychotics include clozapine (Clozaril), risperidone (Risperdal), aripiprazole (Abilify), quetiapine (Seroquel), ziprasidone (Geodon). Many of these atypical antipsychotics are approved for the indication treatment of acute mixed or manic episodes associated with bipolar I disorder, but none are approved for use in children/adolescents.

Risperidone (Risperdal) was recently approved for the indication "treatment of irritability associated with autistic disorder in children and adolescents" (5 to 16 years of age).

Lithium (various salts) and divalproex sodium are indicated in the treatment of manic episodes of bipolar I disorder in adults.

Important Issues With Pharmacologically Related Products

Although the atypical antipsychotics have less extrapyramidal side effects compared to typical antipsychotics, the adverse event profile is notable for weight gain, hyperglycemia, and diabetes mellitus in adults. Little data is available with regard to the adverse event profile in other populations including children and adolescents.

Presubmission Regulatory Activity

This summary was taken from the note to reviewer document contained in the Sponsor's submission.

On June 11, 1999, Eli Lilly and Company (Lilly) submitted a Proposed Pediatric Study Request to FDA related to the conduct of pediatric studies of Zyprexa.

In response to Lilly's proposed pediatric study request, the FDA issued to Lilly a Written Request for Pediatric Studies dated November 30, 2001 (reissued under the Best Pharmaceuticals for Children Act (BPCA) on July 3, 2002) and amended on April 9, 2002, May 7, 2004, and June 29, 2005. FDA's Written Request (WR) as amended, included a request for clinical data on the use of Zyprexa to treat adolescents with schizophrenia and adolescents with acute bipolar mania in order to make Zyprexa eligible for the pediatric exclusivity extension under Section 505A of the Federal Food, Drug, and Cosmetic Act. More details regarding FDA's WR, and Lilly's response, are provided in Item 20 of this submission.

FDA granted an indication for olanzapine for the treatment of bipolar mania in adults (NDA 20-592/S006) on March 17, 2000. As part of the approval, the FDA requested a study in pediatric patients with bipolar mania as a post-marketing commitment. Study F1D-MC-HGIU is included in this submission to fulfill this post-marketing commitment.

On January 15, 2004, the FDA met with Lilly to discuss the PK package proposed by Lilly to fulfill FDA's Written Request for Pediatric Studies. At this meeting, Lilly provided an overview of the available PK data. FDA requested additional justification of

the utility of the data from Study LOAY in order to make a final decision on whether or not the data is acceptable to sufficiently meet the PK aspects of the Written Request.

On March 22, 2004 Lilly submitted to IND 28,705 additional information regarding study LOAY and requested a meeting to further discuss fulfillment of the PK aspects of the WR. In response to questions from FDA sent to Lilly on July 7, 2004, Lilly submitted additional information to IND 28,705 on July 13, 2004.

Lilly met with FDA on July 21, 2004 to again discuss the PK information needed to fulfill the WR. At that meeting, FDA agreed with Lilly's proposal to provide PK data in adolescents from Studies HGCS, HGCR, HGGC, and LOAY to address the PK requirements outlined in the Written Request.

In discussions with FDA, it was noted that information about the exact sampling time relative to the dose were not collected as part of the protocol in Study LOAY; however, extensive simulations showed that lack of data regarding timing of samples in Study LOAY should not adversely affect the ability to perform a meaningful population analysis. Nonetheless, to assure the robustness of the PK data, Lilly collected additional population PK data in adolescent patients with schizophrenia or bipolar disorder by conducting Study HGMF. Inclusion of data from Study HGMF in this submission was discussed at a pre-NDA meeting on March 17, 2006. At that meeting, FDA requested that Lilly conduct the population PK analysis both with and without the data from Study LOAY. Both analyses were conducted by Lilly and are included with this submission. The population PK analysis also includes a comparison of pediatric olanzapine PK data with the adult olanzapine PK data from Study HGAJ.

The format and content of the submission were also discussed and agreed to at the March 17, 2006 pre-sNDA meeting. The FDA indicated that, based on the pre-sNDA package and discussions, the proposed submission content appeared to be adequate to respond to FDA's Written Request and that Study HGIU appeared to be adequate to fulfill the post-marketing commitment which was part of the bipolar mania in adults approval.

In the 11/30/01 written request, the Division stated "We strongly recommend that the trial be a fixed dose study including at least two fixed doses of the study drug". The Division also recommended that a relapse prevention trial should follow the acute treatment trial. The Sponsor did not follow either recommendation and neither was required in order to fulfill the pediatric written request.

Other Relevant Background Information

The Pediatric Exclusivity Board met on January 10, 2007 to determine whether the Sponsor had fulfilled the requirements in the written request. It was determined that the requirements had been met and exclusivity was granted.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Statistics

The statistician (Fanhui Kong) reviewed the efficacy data from the pivotal trial, HGIU. In general, the data submitted by the Sponsor provide evidence for efficacy per his review (see Statistical review).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Tables of Clinical Studies

The Sponsor included study reports for 9 pediatric studies in this submission. HGIN is the pivotal study for adolescent schizophrenia and HGIU is the pivotal study for adolescent bipolar I disorder. HGMF is the primary study for determining pharmacokinetic parameters in the adolescent population. The other studies are supportive and provide safety and pharmacokinetic data.

Table 4.1.1 Summary of Clinical Studies

Study	Description	Length	Age Range (years)	Number of Patients
HGIN	MC, DB, PC study in adolescent patients with schizophrenia. Flexible dose olanzapine (2.5 – 20 mg) U.S. and Russia sites	6 weeks DB 26 weeks OL extension	13 to 17	107 (n = 72 olanzapine, n = 35 placebo)
HGIU	MC, DB, PC study in adolescent patients with mixed/manic episode of bipolar I disorder. Flexible dose olanzapine (2.5 – 20 mg) U.S., Puerto Rico	3 weeks DB 26 weeks OL extension	13 – 17	161 (n = 107 olanzapine, n = 54 placebo)
LOAY	OL study in patients with schizophrenia, schizoaffective, and schizophreniform disorders Flexible dose olanzapine (5 – 20 mg) German sites	24 weeks	12 – 21	96 (n = 89, 13-17 years)
HGMF	OL study in adolescent patients with schizophrenia or bipolar I disorder Flexible dose olanzapine (2.5 – 20 mg) U.S., Puerto Rico, Russia	4.5 weeks	13 – 17	107 (n = 37 schizophrenia, n = 70 bipolar)

HGCS	OL study in adolescent patients with schizophrenia Dosing: 2.5 to 20 mg/day Single site	8 weeks	10 – 18	8
HGCR	DB study in adolescent patients with schizophrenia, haloperidol as active comparator Dosing: 2.5 qod – 20 mg/day Single site	8 weeks	12 – 16	2
HGGC	OL study in children and adolescents with bipolar disorder Dosing: 2.5 to 20 mg/day Single site (U.S.)	8 weeks	5 – 14	23

Modified from Sponsor Table 2.5.1.1 clinical-overview.
 MC = multicenter, DB = double-blind, PC = placebo-controlled, OL = open-label

Data Quality and Integrity

The Division of Scientific Investigations was asked to inspect a number of sites for studies HGIN and HGIU – some sites enrolled patients for both studies. DSI was asked to audit one site in Georgia (n = 7 HGIU, n = 5 HGIN) and one site in Ohio (n = 15 HGIU, n = 6 HGIN). The final DSI report was not available at the time this review was completed, but preliminary comments from the investigator did not indicate any major issues thought to effect efficacy.

Compliance with Good Clinical Practices

Per protocols, the studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Of note, one clinical trial site was omitted from the primary efficacy analyses due to significant GCP issues. This site enrolled patients in both HGIU (site 028) and HGIN (site 021). Details regarding the GCP issues are in Section 6.1.3 (Efficacy Findings) of this review.

Financial Disclosures

Financial disclosure information was provided for the study (b) (6). Two investigators received ~\$40,000 in honoraria or other grant monies (sites (b) (6)), a (b) (6) number of patients were randomized from these sites (n = (b) (6)).

5 CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of oral olanzapine were evaluated primarily in study HGMF (see Table 4.1.1 in Section 4.1 Tables of Clinical Studies) via population pharmacokinetic analyses. These data have been extensively reviewed by the biopharmaceutical reviewer (see Biopharm review).

6 INTEGRATED REVIEW OF EFFICACY

One pivotal trial, FID-MC-HGIU, was submitted to support the efficacy of olanzapine in the treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents.

Indication

The Sponsor proposes the following indication “indicated for the treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents”.

6.1.1 General Discussion of Endpoints

The primary efficacy endpoint for the clinical trial was the change from baseline to endpoint on the YMRS-adolescent structured rating scale total score. The YMRS is a standard rating scale used to evaluate efficacy in adult bipolar populations and is appropriate for evaluating efficacy in this clinical trial.

The Sponsor also included the Clinical Global Impression-Severity rating scale to rate severity of mania, depression and overall severity of bipolar disorder. The Children’s Rating Scale for Depression was also included to assess depressive symptoms. Due to the presence of mania and depression in bipolar illness, inclusion of these endpoints was appropriate.

6.1.2 Study Design

Protocol FID-MC-HGIU is the pivotal study submitted to support the indication “for the treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents”. The other studies submitted as supportive studies in this population are open-label trials and are supportive primarily from a safety and not efficacy perspective. Therefore, only study HGIU is reviewed here.

Protocol HGIN

“Olanzapine versus placebo in the treatment of mania in adolescents with bipolar I disorder”

First patient enrolled 11/18/02, last patient completed 5/9/05.

Investigators and sites

This study enrolled patients at 23 sites in the United States and 2 sites in Puerto Rico. Investigator and site information (including numbers of patients randomized and completing the trial) are included in Appendix 10.1.

Study Objectives

Primary objective: To assess the efficacy of a flexible dose of olanzapine (2.5 to 20 mg/day) compared to placebo in the treatment of mania in bipolar I disorder (manic or mixed episode associated with bipolar I disorder, with or without psychotic features) in adolescents (ages 13 – 17) as measured by the difference between treatment groups in mean change from baseline to endpoint in the Adolescent Structured Young-Mania Rating Scale (YMRS) total score.

Secondary objectives:

To assess secondary efficacy measures 1) YMRS individual items; 2) Clinical Global Impression Scale – Bipolar Version Severity of Illness (Severity of Mania, Severity of Depression, Severity Overall); 3) Children's Depression Rating Scale-Revised; 4) Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version (investigator administered and scored) and 5) Overt Aggression Scale.

To assess the safety of olanzapine compared with placebo for up to 3 weeks of double-blind treatment and for up to an additional 26 weeks of open-label olanzapine treatment.

To assess the health-related quality of life associated with olanzapine compared with placebo for up to 3 weeks of double-blind treatment and for up to an additional 26 weeks of open-label olanzapine treatment.

Compare the frequency of response during the double-blind treatment period (up to 3 weeks), as defined by a $\geq 50\%$ reduction in YMRS total score from baseline to endpoint and a CGI-BP Severity of Mania score of ≤ 3 at endpoint for olanzapine vs. placebo treatment.

Study Population

The study population consisted of generally healthy adolescents, ages 13 to 17 inclusive, with a DSM-IV-TR diagnosis of bipolar I disorder and currently displaying an acute manic or mixed episode (with or without psychotic features). The diagnosis was confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime (K-SADS-PL). The inclusion and exclusion criteria are listed in Appendix 10.2. Patients must have obtained an YMRS total score ≥ 20 at Visit 1 and 2. The patient's parent/authorized legal representative must sign an informed consent document and the patient must sign an informed consent document/assent document as required by local regulations. Exclusion criteria included patients who have been judged clinically to be at serious suicidal risk; patients who have previously not responded to an adequate dose and/or duration of olanzapine treatment; patients currently meeting DSM-IV-TR criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.

Design

This was a multicenter, randomized, double-blind, parallel, placebo-controlled trial consisting of three periods: screening/washout, 3-week double-blind trial, 26-week open-label olanzapine treatment. The screening/washout period was 2-14 days. Patients were then randomized to olanzapine flexible dose (2.5 to 20 mg/day) or placebo treatment (2:1 randomization) for the 3-week acute double-blind trial. Olanzapine was initiated at 2.5 or 5 mg/day and the dose could be increased by 2.5 or 5 mg/day dose increments at the investigator's discretion. If no tolerability or safety issues were apparent, the dose had to be titrated to at least 10 mg/day by Visit 4 (end of week 1). The investigator could continue to increase the dose by 2.5 or 5 mg/day to the maximum tolerable dose not to exceed 20 mg/day. The investigator could decrease the dose at any time and in any number of dose decrements if patients experienced an adverse event. The minimum allowable olanzapine dose was 2.5 mg/day. During this 3-week acute trial, 3 study visits occurred during the first week and then weekly thereafter.

Patients who did not respond after at least 10 days during the 3-week double-blind trial could participate in the optional 26-week open-label extension study and receive open-label olanzapine therapy (2.5 to 20 mg/day). Response was defined as having a $\geq 20\%$ decrease in the YMRS total score compared to baseline and a CGI-BP Severity of Mania score ≤ 3 . Study visits occurred weekly x 2 visits, biweekly x 4 visits and then monthly until the end of the 26-week study.

Assessments (The Schedule of Events is in Appendix 10.3)

Rating scales – efficacy:

Primary efficacy endpoint: Adolescent Structured Young-Mania Rating Scale (YMRS)

Secondary efficacy endpoints: Clinical Global Impression – Severity of Mania, Severity of Depression, Severity Overall; Children's Depression Rating Scale-Revised; Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version; Overt Aggression Scale (OAS); Child Health Questionnaire (CHQ)

Safety assessments:

Vital signs (blood pressure, pulse, weight, height, temperature) – including orthostatic assessments, ECG, Labs (hematology, clinical chemistry, urinalysis, lipid panel, hepatitis screen and panel, serum pregnancy test, prolactin, thyroid stimulating hormone, HgbA1c, urine drug screen.

Fasting glucose at baseline, end of 3-week study and end of 26-week open-label study.

HbA1c was only obtained for patients with diabetes.

Rating scales: Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BAS), Abnormal Involuntary Movement Scale (AIMS)

Spontaneous reporting of adverse events.

6.1.3 Efficacy Findings

One hundred sixty one patients were randomized, 107 to the olanzapine group and 54 to the placebo group. In the olanzapine group, 22 patients discontinued with lack of efficacy as the primary reason for discontinuation for 54.5% of drop-outs. In the placebo group, 19 patients discontinued with lack of efficacy as the primary reason for discontinuation for 84.2% of drop-outs. Drop-outs due to adverse events were the primary reason for discontinuation for 3 patients in the olanzapine group and 1 patient in the placebo group.

Table 6.1.3.1 Patient Disposition

	Olanzapine N = 107	Placebo N = 54	P-value
Completers	85 (79.4%)	35 (64.8%)	0.056
Drop Outs	22 (20.6%)	19 (35.2%)	
Adverse Event	3 (2.8%)	1 (1.9%)	1.00
Lack of Efficacy	12 (11.2%)	16 (29.6%)	0.007
Lost to Follow-up	0	0	-
Patient Decision	4 (3.7%)	1 (1.9%)	0.665
Criteria Not Met/Compliance	0	1 (1.9%)	0.335
Sponsor Decision	0	0	-
Physician Decision	1 (0.9%)	0	1.00
Other	2 (1.9%)	0	0.551

Modified from Sponsor table HGIU.10.1 in study report

Demographics and Baseline Disease Severity

There were no statistically significant differences between the olanzapine and placebo groups with regard to baseline demographics.

Statistically significant differences indicating a potential imbalance in severity of illness were found for several categories – most indicated that more ill patients were randomized into the olanzapine treatment group (although the YMRS baseline scores, the primary efficacy measure, were not statistically different between the groups). Statistical differences were found for the mean number of previous mania episodes (olanzapine = 2.07, placebo = 4.43), mean number of previous depressive episodes (olanzapine = 1.6, placebo = 3.98), mean number of previous mixed episodes (olanzapine = 1.19, placebo = 3.85), psychiatric hospitalization within the past year (olanzapine = 32.1%, placebo = 16.7%). Scores on most rating scales at baseline did not differ between the two treatment groups with the exception of the CGI-Severity Depression (olanzapine = 3.1, placebo = 2.6).

The groups did not differ with regard to the number of patients with psychotic features (olanzapine = 21%, placebo = 13%) or current episode, manic (olanzapine = 41%, placebo = 54%). The groups did differ with regard to the number of rapid cyclers (olanzapine = 23%, placebo = 9%).

Table 6.1.3.2 Baseline Demographics and Severity of Disease

		Olanzapine N = 107	Placebo N = 54	P-value
Gender	Male	61 (57.0%)	24 (44.4%)	0.137
	Female	46 (43%)	30 (55.6%)	
Age (years)	Mean	15.14	15.38	0.250
	Median	15.12	15.41	
	St. Dev	1.28	1.20	
	Minimum	13.02	13.07	
	Maximum	17.89	17.68	
Origin	African descent	13 (12.1%)	2 (3.7%)	0.247
	Caucasian	71 (66.4%)	41 (75.9%)	
	East/Southeast Asian	0	1 (1.8%)	
	Hispanic	18 (16.8%)	8 (14.8%)	
	Other	5 (4.7%)	2 (3.7%)	
Country	America	95 (88.8%)	48 (88.9%)	1.00
	Puerto Rico	12 (11.2%)	6 (11.1%)	
Age of onset of illness (years)	Mean	10.93	11.46	0.331
	Median	12.00	12.00	
	St. Dev.	3.32	3.13	
	Minimum	1.00*	4.00	
	Maximum	17.00	17.00	
No. of Prev. Mania episodes	Mean	2.07	4.43	0.048
	Median	1.00	1.00	
	St. Dev.	4.97	8.95	
	Minimum	0.00	0.00	
	Maximum	35.00	42.00	
No. of Prev. Depressive episodes	Mean	1.60	3.98	0.014
	Median	1.00	1.50	
	St. Dev.	2.84	8.26	
	Minimum	0.00	0.00	
	Maximum	20.00	50.00	
No. of Prev. mixed episodes	Mean	1.19	3.85	0.027
	Median	0.00	0.00	
	St. Dev.	3.65	9.40	
	Minimum	0.00	0.00	
	Maximum	25.00	42.00	
Total hospitalization for the past year (months)	Mean	0.85	1.43	0.327
	Median	0.50	0.50	
	St. Dev.	1.23	2.53	
	Minimum	0.13	0.10	
	Maximum	6.00	8.00	
Length of current episode (days)	Mean	309.8	237.2	0.521
	Median	45.50	50.50	
	St. Dev.	749.1	542.20	
	Minimum	2.00	4.00	
	Maximum	4441	2902	
Days since last hospitalization	Mean	145.4	361.0	0.072
	Median	8.00	33.00	
	St. Dev.	310.3	540.9	
	Minimum	0.00	0.00	
	Maximum	1688	1651	
Psychiatric	Yes	34 (32.08%)	9 (16.67%)	0.040

hospitalization within the past year	No	72 (67.92%)	45 (83.33%)	
Current episode has concurrent psychotic features	Yes No	22 (20.75%) 84 (79.25%)	7 (12.96%) 47 (87.04%)	0.281
Current episode, manic	Yes No	44 (41.1%) 63 (58.9%)	29 (53.7%) 25 (46.3%)	0.136
Rapid Cyclers	Yes No Unknown	25 (23.4%) 71 (66.4%) 11 (10.3%)	5 (9.3%) 43 (79.6%) 6 (11.1%)	0.031
CDRS Raw Total Score	Mean Median St. Dev. Minimum Maximum	40.2 39 15.3 17 82	36.2 33.5 15.5 17 101	0.096
CGI-Severity of depression	Mean Median St. Dev. Minimum Maximum	3.14 4.00 1.57 1.00 6.00	2.65 2.00 1.60 1.00 6.00	0.043
CGI-Severity of mania	Mean Median St. Dev. Minimum Maximum	4.79 5.00 0.70 4.00 6.00	4.81 5.00 0.75 3.00 6.00	0.852
CGI-Severity overall	Mean Median St. Dev. Minimum Maximum	4.79 5.00 0.71 4.00 6.00	4.83 5.00 0.75 3.00 6.00	0.727
YMRS Total score	Mean Median St. Dev. Minimum Maximum	33.05 33.00 6.53 20.00 48.00	32.04 32.00 6.23 21.00 43.00	0.347

Modified from Sponsor table HGIU.11.1, HGIU.11.2, HGIU.11.3, HGIU.11.4, HGIU.11.6 in study report

*An age of onset of 1 year old is highly suspect.

No statistically significant differences were noted between groups in baseline OAS verbal aggression total, OAS physical aggression toward self total, OAS physical aggression toward objects, OAS total, ADHD total, ADHD inattention subtotal. Baseline ADHD hyperactivity-impulsivity subtotal bordered on significance (olanzapine 13.68 vs. placebo 11.67; $p = 0.051$).

A diagnosis of comorbid ADHD was present in more patients in the olanzapine group compared to the placebo group (42% vs. 24%, $p = 0.024$). Though not common, a diagnosis of comorbid conduct disorder was present in more patients in the olanzapine group compared to the placebo group ($n = 14$, $n = 1$, $p = 0.021$).

Efficacy Analyses

Site Issues

In the efficacy analysis, the sponsor included analyses with and without site 028. Per the sponsor, site 028 had significant GCP issues and patients from this site were dropped from the primary analyses (efficacy analyses were similar with and without this site). The study report did not specify what the GCP issues were with this site. The sponsor was asked to provide details and indicated the following:

Lilly discontinued site 021 (Dr. Robb) from study HGIN, and also discontinued Dr Robb's site (site 028) from study HGIU. Lilly informed FDA of the discontinuation of Dr Robb's site from these studies in a submission to IND 28,705; serial number 953, dated May 21, 2004. In a letter dated May 2, 2004 sent to Dr Robb, Lilly listed the following GCP issues that occurred at this site related to studies HGIN and HGIU:

- Not following the randomization procedures outlined in the protocol
- Not submitting protocol amendment A, approved by Lilly on October 17, 2002, to the Institutional Review Board (IRB) for approval before use
- Not submitting revised informed consent documents to IRB
- Not communicating to patients about safety issues in risk profile of study drug. The risk profile was updated by Lilly on December 4, 2003 and faxed to the site on January 6, 2004 and a reminder fax was sent on January 28, 2004.
- Significant problems with drug accountability
- Not being able to reconstruct the regulatory document in the Clinical Trial Record Binder
- Violation of inter-active voice response system (IVRS) security personal identification number process.

Concomitant Medications

Interestingly, 39.3% (42/107) of patients in the olanzapine group and 46.3% (25/54) of patients in the placebo group had no previous medications for bipolar I disorder. It is not known whether these patients participated in nonpharmacological treatment of their disorder.

The most commonly used concomitant medications (> 5% of patients) included benzodiazepines (see next paragraph) and mixed amphetamine salts in 7.5% (8/107) of patients in the olanzapine group and 5.6% (3/54) patients in the placebo group.

There were no statistically significant differences in the frequency of concomitant benzodiazepine use between the olanzapine and placebo groups. Concomitant lorazepam use occurred in 9.3% (10/107) patients in the olanzapine group and 7.4% (4/54) patients in the placebo group. Concomitant temazepam use occurred in 3.7% (4/107) patients in the olanzapine

group and 1.9% (1/54) patients in the placebo group. A few patients in both groups had concomitant clonazepam, alprazolam and diazepam use. There was a statistically significant difference in the mean number of days of benzodiazepine use between the treatment groups: 2.8 ± 3.5 days in the olanzapine group and 10 ± 7.0 days in the placebo group ($p = 0.019$). The mean dose of benzodiazepines (using equivalent doses) did not differ between the treatment groups: 1.4 ± 0.5 mg in the olanzapine group and 2.0 ± 1.7 mg in the placebo group.

There were no statistically significant differences in the frequency of concomitant anticholinergic medication use between the olanzapine and placebo groups. However, only 5 patients in the study had concomitant use of anticholinergic medications and all 5 were in the olanzapine group: benztropine mesylate ($n = 3$), amantadine ($n = 1$), and diphenhydramine ($n = 1$). The mean number of days on anticholinergic medication was 3 ± 2.6 days. The mean dose of anticholinergic medication was 1.4 ± 0.5 mg.

Primary Endpoint

Primary Analysis - LOCF

The mean modal daily dose of olanzapine was 10.7 mg and the mean daily dose was 8.9 mg.

The primary efficacy analysis is in Table 6.1.3.3 below. The analysis including site 028 was similar, least square mean difference was 7.88 favoring the olanzapine group ($p < 0.001$).

Table 6.1.3.3 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint – LOCF. (Excluding site 028)

Efficacy Variable	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value
			Mean	Std	Mean	Std			
YMRS TOT, Total (1-11)	olanzapine	105	33.08	6.55	-15.90	10.03	-17.65	-7.66	<.001
	Placebo	54	32.04	6.23	-7.72	9.42	-9.99		

Supportive Analyses – OC and MMRM

The findings for the OC analysis (Table 6.1.3.4) and MMRM analysis (Table 6.1.3.5) were similar to the LOCF analysis.

Table 6.1.3.4 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint by Visit- OC.

Efficacy Variable	Visit	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value
				Mean	Std	Mean	Std			
YMRSOT:Total (1-11)	3	olanzapine	105	33.08	6.55	-7.98	7.26	-6.37	-2.24	.048
		Placebo	54	32.04	6.23	-5.37	6.83	-4.13		
	4	olanzapine	104	33.11	6.57	-12.62	9.01	-11.46	-3.97	.002
		Placebo	53	32.17	6.21	-8.06	7.38	-7.49		
	5	olanzapine	103	33.03	6.56	-15.46	9.47	-16.16	-7.40	<.001
		Placebo	53	32.17	6.21	-7.49	10.56	-8.77		
	6	olanzapine	88	33.23	6.48	-17.17	9.71	-19.14	-5.74	.001
		Placebo	37	32.41	6.19	-11.11	9.05	-13.40		

Sponsor's Table HGIU.14.21

Table 6.1.3.5 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint by Visit- MMRM

Efficacy Variable	Visit (week)	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean StdErr	LSMean Difference	Diff StdErr	*P-value
				Mean	Std	Mean	Std					
YMRSOT:Total (1-11)	Combined	olanzapine						-12.41	0.85	-5.19	1.08	<.001
		Placebo						-7.23	1.05			
	3 (0.5)	olanzapine	105	33.08	6.55	-7.98	7.26	-7.27	0.88	-2.14	1.14	.062
		Placebo	54	32.04	6.23	-5.37	6.83	-5.13	1.09			
	4 (1)	olanzapine	104	33.11	6.57	-12.62	9.01	-11.84	0.94	-4.08	1.28	.002
		Placebo	53	32.17	6.21	-8.06	7.38	-7.76	1.19			
	5 (2)	olanzapine	103	33.03	6.56	-15.46	9.47	-14.77	1.06	-7.58	1.53	<.001
		Placebo	53	32.17	6.21	-7.49	10.56	-7.19	1.37			
	6 (3)	olanzapine	88	33.23	6.48	-17.17	9.71	-15.78	1.10	-6.95	1.68	<.001
		Placebo	37	32.41	6.19	-11.11	9.05	-8.83	1.50			

Sponsor's Table HGIU.14.27

U.S. vs. Puerto Rico Sites

The Sponsor did perform an analysis comparing the efficacy between U.S. and Puerto Rico sites. There were, however, very few subjects from the latter sites.

Table 6.1.3.6 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint by Country- U.S. vs. Puerto Rico sites.

Efficacy Variable	Country	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy*Country)
				Mean	Std	Mean	Std				
YMRSOT:Total (1-11)	America	olanzapine	93	32.80	6.65	-15.28	9.89	-15.09	-7.87	<.001	.668
		Placebo	48	31.71	6.38	-6.85	8.63	-7.22			
	Puerto Rico	olanzapine	12	35.25	5.45	-20.75	9.38	-20.71	-5.97	.297	
		Placebo	6	34.67	4.37	-14.67	13.23	-14.74			

Secondary Analyses

Efficacy results from select secondary analyses were reviewed.

YMRS Individual Item Analyses

Mean change from baseline to endpoint (LOCF) for the individual items of the YMRS were analyzed. Statistically significant differences favoring olanzapine were evident for all YMRS items except sexual interest and insight (see Appendix 10.4).

CGI-BP (Severity)

Mean change from baseline to endpoint (LOCF) for CGI-BP Severity of Mania, Depression and Overall were analyzed. Statistically significant differences favoring olanzapine were found for CGI-BP Severity – Mania and CGI-BP Severity-Overall, but not for CGI-BP Severity-Depression (see Table 6.1.3.7). Patients enrolled in this clinical trial were exhibiting acute manic or mixed bipolar symptoms. In the olanzapine group, 42% (44/105) exhibited manic symptoms and 58% (61/105) exhibited mixed symptoms at baseline. In the placebo group, 54% (29/54) exhibited manic symptoms and 46% (25/54) exhibited mixed symptoms at baseline. The CGI-BP Depression mean scores at baseline indicated mildly ill severity while the CGI-BP Mania and Overall mean scores at baseline indicated moderate-markedly ill severity.

Table 6.1.3.7 Sponsor's Table. CGI-BP Severity for Mania, Depression and Overall

Table HGIU.11.23. CGI-BP Severity (Mania, Depression, Overall)
Mean Change from Baseline to Endpoint (LOCF)
Double-Blind Period

Efficacy Variable	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value
			Mean	Std	Mean	Std			
CGI Severity Depression	olanzapine	105	3.12	1.59	-0.86	1.21	-0.89	-0.10	.533
	Placebo	54	2.65	1.60	-0.54	1.04	-0.80		
CGI Severity Mania	olanzapine	105	4.81	0.69	-1.70	1.29	-1.73	-0.67	<.001
	Placebo	54	4.81	0.75	-1.04	1.12	-1.05		
CGI Severity Overall	olanzapine	105	4.81	0.71	-1.60	1.30	-1.63	-0.64	<.001
	Placebo	54	4.83	0.75	-0.98	1.17	-0.99		

Children's Depression Rating Scale - Revised

No statistically significant differences were found between olanzapine and placebo for mean change from baseline to endpoint for CDRS-R Total Score (The CDRS-R contains 17 anchored items, most are rated from 1 to 7 for severity; maximum score = 113). Some statistical differences were found for individual items – one favored olanzapine (sleep disturbance) and three items favored placebo (appetite disturbance, excessive fatigue, and depressed facial affect) [See Appendix 10.5]. Most of these statistical differences on individual items could have been related more to the side effect profile of olanzapine. Of note, the baseline mean score for suicidal ideation¹ was 1.77 in the olanzapine group and 1.42 in the placebo group, mean change

¹ CDRS-R Suicidal ideation item scoring: 1 = understands the word "suicide" but does not apply the term to