# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

# 20-592/S-019

***Trade Name:*** Zyprexa 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg

***Generic Name:*** olanzapine tablets

***Sponsor:*** Eli Lilly and Company

***Approval Date:*** January 14, 2004

***Indications:*** For the benefit of maintaining bipolar patients on monotherapy with Zyprexa after achieving a responder status for an average duration of two weeks was demonstrated in a controlled trial. The physician who elects to use Zyprexa for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 20-592/S-019

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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-592/S-019**

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592 / S-019

Eli Lilly and Co., Inc.
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, Indiana 46285
USA

Dear Dr. Brophy:

Please refer to your supplemental new drug application (NDA) dated November 20, 2002, received November 21, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) Tablets, 2.5, 5, 7.5, 10, 15, and 20 mg. This supplemental NDA provides for the use of olanzapine in the long-term treatment of bipolar I disorder.

We also acknowledge receipt of your amendments dated November 4, 2003 and November 13, 2003. Your submission of November 13, 2003 constituted a complete response to our September 22, 2003 action letter.

**Application approved.** We have completed the review of this application as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text, per our discussions of January 13, 2004.

**Final Printed Labeling.** The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Please submit the FPL electronically, according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-592/S-019". Approval of this submission by FDA is not required before the labeling is used.

**Waiver of Requirement for Pediatric Studies.** All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for the use of olanzapine in the long-term treatment of bipolar I disorder.

**No Postmarketing Commitments Required.** We note that there are no postmarketing commitments for this supplemental application.

**Promotional Materials.** In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising and Communications (DDMAC), HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

**Dear Healthcare Professional Letters.** If you issue a letter communicating important information about this drug product (i.e., a "Dear Healthcare Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-594-2850, or via e-mail at batesd@cder.fda.gov.

Sincerely,

*(See appended electronic signature page)*

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure (Agreed-Upon Labeling) [The electronic signature page will follow the labeling.]

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

/s/

Russell Katz
1/14/04 12:48:23 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-592/S-019**

# APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592 / S-019

Eli Lilly and Co., Inc.
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, Indiana 46285
USA

Dear Dr. Brophy:

Please refer to your supplemental new drug application (NDA) dated November 20, 2002, received November 21, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) Tablets, 2.5, 5, 7.5, 10, 15, and 20 mg. This supplemental NDA provides for the use of olanzapine in the long-term treatment of bipolar I disorder.

We also acknowledge receipt of your amendments dated December 12, 2002, January 21, 2003, March 19, 2003, July 10, 2003, and August 7, 2003.

We have completed the review of this application as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following comments and requests.

**CMC: Categorical Exclusion**
We have completed our review of the information provided by your firm, and we agree with your request for a Categorical Exclusion from the requirement to perform a full Environmental Assessment for this application.

**Clinical**

1. We have completed our review of the clinical, statistical, clinical safety, and clinical pharmacology / biopharmaceutics information submitted in this supplement. We have incorporated a number of comments into the revised labeling appended to this letter, as bracketed comments, text insertions [underlined], or deletions [strikethrough]. Please address these changes specifically in your complete response.

   In particular, because patients in the open-label phase of the trial (the phase in which we believe the duration of the treatment effect is best determined) had met "responder" criteria for only about two weeks on average, and about half of the patients in the controlled portion of the trial had left the study in less than two months, we believe it would be very difficult to determine, from this trial, the duration of the effect of the treatment as maintenance.

   [ b(4) ]

2. As you know, we have observed cases of hyperglycemia / diabetes mellitus in patients treated with atypical antipsychotics. We are addressing this as a class labeling issue. We have

therefore incorporated the desired labeling language for the diabetes mellitus / hyperglycemia warning into the labeling at this time.

3. As part of your complete response to this approvable letter, please also provide the following information for Study HGHL:

a) A formal analysis of time-to-event, excluding sites 34 [ ] b(4)

b) An exploration and analysis of treatment-emergent suicidality and an analysis of the HAM-D scores for items 1 and 3 as a separate analysis to examine possible precipitation of depression in this population. Included as part of this analysis we would like to see a comparison of the incidence of patients who start with a HAM-D item 1 or item 3 score of 0 to 2 and then progress to a score of 3 or 4.

c) Re-coded patient disposition table HGHL.10.3 (which is also table ISS.6.1). We have noted apparent discrepancies between the data in this table, the data found in some of the other tables in the submission (see page 3207 of study report HGHL), and the data in [ ] files b(4) such as SUMMARY.xpt and/or COMMENTS.xpt (specifically, the coding categories of lack of efficacy, patient decision, and physician decision). Please explain these discrepancies.

d) With respect to Point (c) above, we also note that Patient 212 is listed as a discontinuation secondary to an adverse event at Visit 110. However, this patient met relapse criteria at Visit 101. Please explain this discrepancy in coding.

e) A definition for the term "Reporting Interval Completed" as used in the disposition tables in Study HGHL.

f) A definition of the term "Days in Remission" as seen in Table HGHL.14.11. Please also clarify when patients were randomized, as the protocol-specified randomization criteria do not appear to have been met in all cases (see patient 455).

g) Table HGHL.14.12 presents symptomatic relapse as estimated percentages stratified by time intervals (see Table HGHL.14.11). Please provide the percentage of patients relapsing, as per Table HGHL.14.11, for the interval 21-28 days and the interval = 35 days. Please also provide an analysis of time in 'remission' compared to time to 'relapse' and an analysis of time in 'remission' compared to time-to-event.

h) A re-analysis of cholesterol laboratory values using a high of 250 mg/dL after a normal baseline measurement, or a change of 50 mg/dL from baseline, with the analysis performed as outlined in point (i) below.

i) A presentation of the laboratory values for eosinophils, uric acid, urine ketones, and cholesterol, stratified from the beginning of the open-label period to the last visit in the double-blind period for study HGHL and, separately, for all other studies with double-blind extensions.

j) A detailed description, including results of any tests performed or consultation received, of the convulsive event seen in the open-label period of study HGHL.

k) Within the active and placebo-controlled databases, for any potentially clinically significant EKG or syncopal events, SAEs related to EKG findings or syncope, or discontinuations secondary to either EKG findings or syncope, please provide vital signs for each patient, including orthostatics and EKG data taken at the time of the event. If none are available, this should be stated.

l) Although this point is not essential for approval of your submission, we would also like an explanation for those patients whose time in study was greater than 365 days, given that the

protocol required both Study Periods III and IV to have a combined maximum duration of 12 months.

**Labeling (Package Insert)**
In addition to responding to the points listed above, it will be necessary for you to submit draft labeling revised as shown in the attachment to this letter (see also point 1 under Clinical, above). We believe the attached draft labeling presents a fair summary of the information available on the benefits and risks of ZYPREXA (olanzapine) as long-term therapy in the treatment of bipolar I disorder.

Please use the proposed text verbatim. You will see that we have proposed a number of changes to the draft labeling submitted in your November 20, 2002 submission, and explanations for these changes are provided in the bracketed comments embedded within the proposed text. Division staff are willing to discuss these proposed changes in detail and to meet with you to discuss any disagreements you might have with any part of the proposed labeling format or content.

**Promotional Materials**
In your complete response to this letter, please also submit three copies of the introductory promotional materials that you propose to use for this product. Please submit all material in draft or mock-up form rather than final printed format. Please send one copy to this Division and two copies of both the promotional material and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

**Options Under 21 CFR 314.110**
Within 10 (ten) days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw this application as provided for under 21 CFR 314.65. Any amendment should respond to all of the comments and requests in this letter, including those incorporated by reference. We will not process a partial reply as a major amendment, nor will the review clock be reactivated, until all deficiencies have been addressed.

**Opportunity for Informal Meeting Under 21 CFR 314.102(d)**
Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Neuropharmacological Drug Products, to discuss what further steps need to be taken before the application may be approved.

This drug product may not be legally marketed until you have been notified in writing that this application has been approved.

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-594-2850.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure (Revised Draft Labeling) [The electronic signature page will follow the labeling.]

25 Page(s) Withheld

Approvable Letter

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Russell Katz
9/22/03 12:30:06 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-592/S-019**

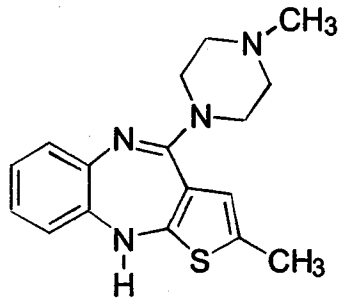
# LABELING

# ZYPREXA®
## (Olanzapine) Tablets

# ZYPREXA® ZYDIS®
## (Olanzapine) Orally Disintegrating Tablets

## DESCRIPTION

ZYPREXA (olanzapine) is a psychotropic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. The chemical structure is:



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 µmol), 5 mg (16 µmol), 7.5 mg (24 µmol), 10 mg (32 µmol), 15 mg (48 µmol), or 20 mg (64 µmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5.0, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 µmol), 10 mg (32 µmol), 15 mg (48 µmol) or 20 mg (64 µmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben and sodium propyl paraben.

## CLINICAL PHARMACOLOGY

### Pharmacodynamics

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$ ($K_i$=4 and 11 nM, respectively), dopamine $D_{1\text{-}4}$ ($K_i$=11-31 nM), muscarinic $M_{1\text{-}5}$ ($K_i$=1.9-25 nM), histamine $H_1$ ($K_i$=7 nM), and adrenergic $\alpha_1$ receptors ($K_i$=19 nM). Olanzapine binds weakly to $GABA_A$, BZD, and β adrenergic receptors ($K_i$>10 µM).

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism. The mechanism of action of olanzapine in the treatment of acute manic episodes associated with Bipolar I Disorder is unknown.

Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic $M_{1\text{-}5}$ receptors may explain its anticholinergic effects. Olanzapine's antagonism of histamine $H_1$ receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic $\alpha_1$ receptors may explain the orthostatic hypotension observed with this drug.

## Pharmacokinetics

Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about one week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age (*see* Special Populations).

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and $\alpha_1$-acid glycoprotein.

Metabolism and Elimination — Following a single oral dose of $^{14}C$ labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4′-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

## Special Populations

Renal Impairment — Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment — Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Age — In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (>65 years) than in non-elderly subjects (≤65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity (*see* DOSAGE AND ADMINISTRATION).

Gender — Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status — Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race — No specific pharmacokinetic study was conducted to investigate the effects of race. A cross-study comparison between data obtained in Japan and data obtained in the US suggests that exposure to olanzapine may be about 2-fold greater in the Japanese when equivalent doses are administered. Clinical trial safety and efficacy data, however, did not suggest clinically significant differences among Caucasian patients, patients of African descent, and a third pooled category including Asian and Hispanic patients. Dosage modifications for race are, therefore, not recommended.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine (*see* DOSAGE AND ADMINISTRATION).

For specific information about the pharmacology of lithium or valproate, refer to the CLINICAL PHARMACOLOGY section of the package inserts for these other products.

## Clinical Efficacy Data

### Schizophrenia

The efficacy of olanzapine in the treatment of schizophrenia was established in 2 short-term (6-week) controlled trials of inpatients who met DSM III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in one of the two trials, but this trial did not compare these two drugs on the full range of clinically relevant doses for both.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed but less well evaluated scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which is embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving two fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5.0 ± 2.5 mg/day, 10.0 ± 2.5 mg/day, and 15.0 ± 2.5 mg/day) on a once daily schedule, the

two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high dose group over the medium dose group.

Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open label treatment for at least 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however, criteria were met for stopping the trial early due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months.

## Bipolar Disorder

Monotherapy — The efficacy of olanzapine in the treatment of acute manic or mixed episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar disorder who had responded during an initial open-label treatment phase for about two weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n = 225) or to placebo (n = 136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open label phase was defined by having a decrease of the YMRS total score to = 12 and HAM-D 21 to = 8. Relapse during the double-blind phase was defined as an increase of the YMRS or HAM-D 21 total score to = 15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Combination Therapy — The efficacy of olanzapine with concomitant lithium or valproate in the treatment of acute manic episodes was established in two controlled trials in patients who met the

DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course. The results of the trials follow:

(1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 μg/mL to 125 μg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 μg/mL to 125 μg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

## INDICATIONS AND USAGE

### Schizophrenia

ZYPREXA is indicated for the treatment of schizophrenia.

The efficacy of ZYPREXA was established in short-term (6-week) controlled trials of schizophrenic inpatients (*see* CLINICAL PHARMACOLOGY).

The effectiveness of oral ZYPREXA at maintaining a treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo-controlled trial (*see* CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

### Bipolar Disorder

Acute Monotherapy — ZYPREXA is indicated for the treatment of acute mixed or manic episodes associated with Bipolar I Disorder.

The efficacy of ZYPREXA was established in two placebo-controlled trials (one 3-week and one 4-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (*see* CLINICAL PHARMACOLOGY).

Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with ZYPREXA after achieving a responder status for an average duration of two weeks was demonstrated in a controlled trial (*see* Clincal Efficacy Data, under CLINICAL PHARMACOLOGY). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Combination Therapy — The combination of ZYPREXA with lithium or valproate is indicated for the short-term treatment of acute manic episodes associated with Bipolar I Disorder.

The efficacy of ZYPREXA in combination with lithium or valproate was established in two placebo-controlled (6-week) trials with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (*see* CLINICAL PHARMACOLOGY).

## CONTRAINDICATIONS

ZYPREXA is contraindicated in patients with a known hypersensitivity to the product.

For specific information about the contraindications of lithium or valproate, refer to the CONTRAINDICATIONS section of the package inserts for these other products.

## WARNINGS

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS) — A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia — A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

For specific information about the warnings of lithium or valproate, refer to the WARNINGS section of the package inserts for these other products.

## PRECAUTIONS

### General

Orthostatic Hypotension — Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its $\alpha_1$-adrenergic antagonistic properties. Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD (*see* DOSAGE AND ADMINISTRATION). A more gradual titration to the target dose should be considered if hypotension occurs. Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures — During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hyperprolactinemia — As with other drugs that antagonize dopamine $D_2$ receptors, olanzapine elevates prolactin levels, and a modest elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats (*see* Carcinogenesis). However, neither clinical studies nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

Transaminase Elevations — In placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. In two of these patients, liver enzymes decreased toward normal despite continued treatment and in two others, enzymes decreased upon discontinuation of olanzapine. In the remaining two patients, one, seropositive for hepatitis C, had persistent enzyme elevation for four months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger premarketing database of about 2400 patients with baseline SGPT ≤90 IU/L, the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

Among all 2500 patients in clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see* Laboratory Tests).

Potential for Cognitive and Motor Impairment — Somnolence was a commonly reported adverse event associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse event was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

Body Temperature Regulation — Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia — Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Two olanzapine-treated patients (2/407) in two studies in patients with Alzheimer's disease died from aspiration pneumonia during or within 30 days of the termination of the double-blind portion of their respective studies; there were no deaths in the placebo-treated patients. One of these patients had experienced dysphagia prior to the development of aspiration pneumonia. Aspiration pneumonia is a common cause of morbidity and mortality in patients with

advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide — The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness — Clinical experience with olanzapine in patients with certain concomitant systemic illnesses (*see* Renal Impairment and Hepatic Impairment *under* CLINICAL PHARMACOLOGY, Special Populations) is limited.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events were not often the basis for discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus.

In a fixed-dose study of olanzapine (olanzapine at doses of 5, 10, and 15 mg/day) and placebo in nursing home patients (mean age: 83 years, range: 61-97; median Mini-Mental State Examination (MMSE): 5, range: 0-22) having various psychiatric symptoms in association with Alzheimer's disease, the following treatment-emergent adverse events were reported in all (each and every) olanzapine-treated groups at an incidence of either (1) two-fold or more in excess of the placebo-treated group, where at least 1 placebo-treated patient was reported to have experienced the event, or (2) at least 2 cases if no placebo-treated patient was reported to have experienced the event: somnolence, abnormal gait, fever, dehydration, and back pain. The rate of discontinuation in this study for olanzapine was 12% vs 4% with placebo. Discontinuations due to abnormal gait (1% for olanzapine vs 0% for placebo), accidental injury (1% for olanzapine vs 0% for placebo), and somnolence (3% for olanzapine vs 0% for placebo) were considered to be drug related. As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia (*see* PRECAUTIONS).

Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients (*see* Orthostatic Hypotension).

For specific information about the precautions of lithium or valproate, refer to the PRECAUTIONS section of the package inserts for these other products.

## Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe olanzapine:

Orthostatic Hypotension — Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol (*see* Drug Interactions).

Interference with Cognitive and Motor Performance — Because olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

Pregnancy — Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with olanzapine.

Nursing — Patients should be advised not to breast-feed an infant if they are taking olanzapine.

Concomitant Medication — Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol — Patients should be advised to avoid alcohol while taking olanzapine.

Heat Exposure and Dehydration — Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Phenylketonurics — ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively).

## Laboratory Tests

Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see* Transaminase Elevations).

## Drug Interactions

The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents.

Olanzapine may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Olanzapine — Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 could potentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

Charcoal — The administration of activated charcoal (1 g) reduced the Cmax and AUC of olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

Cimetidine and Antacids — Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Carbamazepine — Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Ethanol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics.

Fluoxetine — Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended.

Fluvoxamine — Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine Cmax following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

Warfarin — Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics.

Effect of Olanzapine on Other Drugs — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and

CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium.

Valproate — Studies in vitro using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. In vivo administration of olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam and its active metabolite N-desmethyldiazepam, ethanol, or biperiden. However, the co-administration of either diazepam or ethanol with olanzapine potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

## Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily dose on a mg/m$^2$ basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily dose on a mg/m$^2$ basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily dose on a mg/m$^2$ basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily dose on a mg/m$^2$ basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily dose on a mg/m$^2$ basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the maximum recommended human daily dose on a mg/m$^2$ basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown (*see* Hyperprolactinemia *under* PRECAUTIONS, General).

Mutagenesis — No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Impairment of Fertility — In a fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended human daily dose on a mg/m$^2$ basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily dose on a mg/m$^2$

basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily dose on a mg/m$^2$ basis); therefore olanzapine may produce a delay in ovulation.

### Pregnancy

Pregnancy Category C — In reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily dose on a mg/m$^2$ basis, respectively) no evidence of teratogenicity was observed. In a rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily dose on a mg/m$^2$ basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily dose on a mg/m$^2$ basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the maximum recommended human daily dose on a mg/m$^2$ basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Labor and Delivery

Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery in humans is unknown.

### Nursing Mothers

Olanzapine was excreted in milk of treated rats during lactation. It is not known if olanzapine is excreted in human milk. It is recommended that women receiving olanzapine should not breast-feed.

### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

### Geriatric Use

Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in patients with various psychiatric symptoms in association with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient (*see* PRECAUTIONS and DOSAGE AND ADMINISTRATION).

## ADVERSE REACTIONS

The information below is derived from a clinical trial database for olanzapine consisting of 8661 patients with approximately 4165 patient-years of exposure. This database includes: (1) 2500 patients who participated in multiple-dose premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in premarketing bipolar mania trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in a trial of patients having various psychiatric symptoms in association with Alzheimer's disease

representing approximately 29 patient-years of exposure; and (4) 5788 patients from 88 additional clinical trials as of December 31, 2001. In addition, information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar mania trials with approximately 22 patient-years of exposure, is included below.

The conditions and duration of treatment with olanzapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar mania. However, this information is also generally applicable to bipolar mania.

Adverse events during exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used initially to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported events do not include those event terms which were so general as to be uninformative. Events listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the events occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

## Incidence of Adverse Events in Short-Term, Placebo-Controlled and Combination Trials

The following findings are based on premarketing trials for schizophrenia, bipolar mania, a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease, and premarketing combination trials.

### Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Schizophrenia — Overall, there was no difference in the incidence of discontinuation due to adverse events (5% for olanzapine vs 6% for placebo). However, discontinuations due to increases in SGPT were considered to be drug related (2% for olanzapine vs 0% for placebo) (*see* PRECAUTIONS).

Bipolar Mania Monotherapy — Overall, there was no difference in the incidence of discontinuation due to adverse events (2% for olanzapine vs 2% for placebo).

### Adverse Events Associated with Discontinuation of Treatment in Short-Term Combination Trials

Bipolar Mania Combination Therapy — In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse events were 11% for the combination of olanzapine with lithium or valproate compared to 2% for patients who remained on lithium or valproate monotherapy. Discontinuations with the combination of olanzapine and lithium or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and peripheral edema (1%).

### Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials

The most commonly observed adverse events associated with the use of olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

| Common Treatment-Emergent Adverse Events Associated with the Use of Olanzapine in 6-Week Trials — SCHIZOPHRENIA | | |
|---|---|---|
| Adverse Event | Percentage of Patients Reporting Event | |
| | Olanzapine (N=248) | Placebo (N=118) |
| Postural hypotension | 5 | 2 |
| Constipation | 9 | 3 |
| Weight gain | 6 | 1 |
| Dizziness | 11 | 4 |
| Personality disorder[1] | 8 | 4 |
| Akathisia | 5 | 1 |

[1] Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

| Common Treatment-Emergent Adverse Events Associated with the Use of Olanzapine in 3-Week and 4-Week Trials — BIPOLAR MANIA | | |
|---|---|---|
| Adverse Event | Percentage of Patients Reporting Event | |
| | Olanzapine (N=125) | Placebo (N=129) |
| Asthenia | 15 | 6 |
| Dry mouth | 22 | 7 |
| Constipation | 11 | 5 |
| Dyspepsia | 11 | 5 |
| Increased appetite | 6 | 3 |
| Somnolence | 35 | 13 |
| Dizziness | 18 | 6 |
| Tremor | 6 | 3 |

### Adverse Events Occurring at an Incidence of 2% or More Among Olanzapine-Treated Patients in Short-Term, Placebo-Controlled Trials

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 2% or more of patients treated with olanzapine (doses ≥2.5 mg/day) and

with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

**Table 1**
**Treatment-Emergent Adverse Events:**
**Incidence in Short-Term, Placebo-Controlled Clinical Trials[1]**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Body System/Adverse Event** | **Olanzapine (N=532)** | **Placebo (N=294)** |
| **Body as a Whole** | | |
| Accidental injury | 12 | 8 |
| Asthenia | 10 | 9 |
| Fever | 6 | 2 |
| Back pain | 5 | 2 |
| Chest pain | 3 | 1 |
| **Cardiovascular System** | | |
| Postural hypotension | 3 | 1 |
| Tachycardia | 3 | 1 |
| Hypertension | 2 | 1 |
| **Digestive System** | | |
| Dry mouth | 9 | 5 |
| Constipation | 9 | 4 |
| Dyspepsia | 7 | 5 |
| Vomiting | 4 | 3 |
| Increased appetite | 3 | 2 |
| **Hemic and Lymphatic System** | | |
| Ecchymosis | 5 | 3 |
| **Metabolic and Nutritional Disorders** | | |
| Weight gain | 5 | 3 |
| Peripheral edema | 3 | 1 |
| **Musculoskeletal System** | | |
| Extremity pain (other than joint) | 5 | 3 |
| Joint pain | 5 | 3 |
| **Nervous System** | | |
| Somnolence | 29 | 13 |
| Insomnia | 12 | 11 |
| Dizziness | 11 | 4 |
| Abnormal gait | 6 | 1 |
| Tremor | 4 | 3 |
| Akathisia | 3 | 2 |
| Hypertonia | 3 | 2 |
| Articulation impairment | 2 | 1 |
| **Respiratory System** | | |
| Rhinitis | 7 | 6 |

| | | |
|---|---|---|
| Cough increased | 6 | 3 |
| Pharyngitis | 4 | 3 |
| **Special Senses** | | |
| Amblyopia | 3 | 2 |
| **Urogenital System** | | |
| Urinary incontinence | 2 | 1 |
| Urinary tract infection | 2 | 1 |

[1] Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion, depression, diarrhea, dysmenorrhea[2], hallucinations, headache, hostility, hyperkinesia, myalgia, nausea, nervousness, paranoid reaction, personality disorder[3], rash, thinking abnormal, weight loss.
[2] Denominator used was for females only (olanzapine, N=201; placebo, N=114).
[3] Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

### Commonly Observed Adverse Events in Short-Term Combination Trials

In the bipolar mania combination placebo-controlled trials, the most commonly observed adverse events associated with the combination of olanzapine and lithium or valproate (incidence of ≥5% and at least twice placebo) were:

| Common Treatment-Emergent Adverse Events Associated with the Use of Olanzapine in 6-Week Combination Trials — BIPOLAR MANIA | | |
|---|---|---|
| Adverse Event | Percentage of Patients Reporting Event | |
| | Olanzapine with lithium or valproate (N=229) | Placebo with lithium or valproate (N=115) |
| Dry mouth | 32 | 9 |
| Weight gain | 26 | 7 |
| Increased appetite | 24 | 8 |
| Dizziness | 14 | 7 |
| Back pain | 8 | 4 |
| Constipation | 8 | 4 |
| Speech disorder | 7 | 1 |
| Increased salivation | 6 | 2 |
| Amnesia | 5 | 2 |
| Paresthesia | 5 | 2 |

### Adverse Events Occurring at an Incidence of 2% or More Among Olanzapine-Treated Patients in Short-Term Combination Trials

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

**Table 2**
**Treatment-Emergent Adverse Events:**
**Incidence in Short-Term, Placebo-Controlled Combination Clinical Trials[1]**

| Body System/Adverse Event | Percentage of Patients Reporting Event<br>Olanzapine with lithium or valproate (N=229) | Placebo with lithium or valproate (N=115) |
|---|---|---|
| **Body as a Whole** | | |
| Asthenia | 18 | 13 |
| Back pain | 8 | 4 |
| Accidental injury | 4 | 2 |
| Chest pain | 3 | 2 |
| **Cardiovascular System** | | |
| Hypertension | 2 | 1 |
| **Digestive System** | | |
| Dry mouth | 32 | 9 |
| Increased appetite | 24 | 8 |
| Thirst | 10 | 6 |
| Constipation | 8 | 4 |
| Increased salivation | 6 | 2 |
| **Metabolic and Nutritional Disorders** | | |
| Weight gain | 26 | 7 |
| Peripheral edema | 6 | 4 |
| Edema | 2 | 1 |
| **Nervous System** | | |
| Somnolence | 52 | 27 |
| Tremor | 23 | 13 |
| Depression | 18 | 17 |
| Dizziness | 14 | 7 |
| Speech disorder | 7 | 1 |
| Amnesia | 5 | 2 |
| Paresthesia | 5 | 2 |
| Apathy | 4 | 3 |
| Confusion | 4 | 1 |
| Euphoria | 3 | 2 |
| Incoordination | 2 | 0 |
| **Respiratory System** | | |
| Pharyngitis | 4 | 1 |
| Dyspnea | 3 | 1 |
| **Skin and Appendages** | | |
| Sweating | 3 | 1 |
| Acne | 2 | 0 |
| Dry skin | 2 | 0 |
| **Special Senses** | | |
| Amblyopia | 9 | 5 |
| Abnormal vision | 2 | 0 |
| **Urogenital System** | | |

| | | |
|---|---|---|
| Dysmenorrhea[2] | 2 | 0 |
| Vaginitis[2] | 2 | 0 |

[1] Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, abnormal dreams, abnormal ejaculation, agitation, akathisia, anorexia, anxiety, arthralgia, cough increased, diarrhea, dyspepsia, emotional lability, fever, flatulence, flu syndrome, headache, hostility, insomnia, libido decreased, libido increased, menstrual disorder[2], myalgia, nausea, nervousness, pain, paranoid reaction, personality disorder, rash, rhinitis, sleep disorder, thinking abnormal, vomiting.

[2] Denominator used was for females only (olanzapine, N=128; placebo, N=51).

For specific information about the adverse reactions observed with lithium or valproate, refer to the ADVERSE REACTIONS section of the package inserts for these other products.

## Additional Findings Observed in Clinical Trials

The following findings are based on clinical trials.

### Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Extrapyramidal Symptoms — The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia.

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY RATING SCALES INCIDENCE IN A FIXED DOSAGE RANGE, PLACEBO-CONTROLLED CLINICAL TRIAL — ACUTE PHASE*

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | Placebo | Olanzapine 5 ± 2.5 mg/day | Olanzapine 10 ± 2.5 mg/day | Olanzapine 15 ± 2.5 mg/day |
| Parkinsonism[1] | 15 | 14 | 12 | 14 |
| Akathisia[2] | 23 | 16 | 19 | 27 |

* No statistically significant differences.

[1] Percentage of patients with a Simpson-Angus Scale total score >3.

[2] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse events during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia.

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY ADVERSE EVENTS INCIDENCE IN A FIXED DOSAGE RANGE, PLACEBO-CONTROLLED CLINICAL TRIAL — ACUTE PHASE

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | Placebo (N=68) | Olanzapine 5 ± 2.5 mg/day (N=65) | Olanzapine 10 ± 2.5 mg/day (N=64) | Olanzapine 15 ± 2.5 mg/day (N=69) |
| Dystonic events[1] | 1 | 3 | 2 | 3 |
| Parkinsonism events[2] | 10 | 8 | 14 | 20 |
| Akathisia events[3] | 1 | 5 | 11* | 10* |

| | | | | |
|---|---|---|---|---|
| Dyskinetic events[4] | 4 | 0 | 2 | 1 |
| Residual events[5] | 1 | 2 | 5 | 1 |
| Any extrapyramidal event | 16 | 15 | 25 | 32* |

* Statistically significantly different from placebo.

[1] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[2] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[3] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[4] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[5] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

Other Adverse Events — The following table addresses dose relatedness for other adverse events using data from a schizophrenia trial involving fixed dosage ranges. It enumerates the percentage of patients with treatment-emergent adverse events for the three fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse events for which there was a statistically significant trend.

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| Adverse Event | Placebo (N=68) | Olanzapine 5 ± 2.5 mg/day (N=65) | Olanzapine 10 ± 2.5 mg/day (N=64) | Olanzapine 15 ± 2.5 mg/day (N=69) |
| Asthenia | 15 | 8 | 9 | 20 |
| Dry mouth | 4 | 3 | 5 | 13 |
| Nausea | 9 | 0 | 2 | 9 |
| Somnolence | 16 | 20 | 30 | 39 |
| Tremor | 3 | 0 | 5 | 7 |

*Vital Sign Changes* — Olanzapine is associated with orthostatic hypotension and tachycardia (*see* PRECAUTIONS).

*Weight Gain* — In placebo-controlled, 6-week studies, weight gain was reported in 5.6% of olanzapine patients compared to 0.8% of placebo patients. Olanzapine patients gained an average of 2.8 kg, compared to an average 0.4 kg weight loss in placebo patients; 29% of olanzapine patients gained greater than 7% of their baseline weight, compared to 3% of placebo patients. A categorization of patients at baseline on the basis of body mass index (BMI) revealed a significantly greater effect in patients with low BMI compared to normal or overweight patients; nevertheless, weight gain was greater in all 3 olanzapine groups compared to the placebo group. During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

*Laboratory Changes* — An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in SGPT, SGOT, and GGT (*see* PRECAUTIONS). Olanzapine administration was also associated with increases in serum prolactin (*see* PRECAUTIONS), with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models (*see* ANIMAL TOXICOLOGY), careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

*ECG Changes* — Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine use was associated with a mean increase in heart rate of 2.4 beats per minute compared to no change among placebo patients. This slight tendency to tachycardia may be related to olanzapine's potential for inducing orthostatic changes (*see* PRECAUTIONS).

## Other Adverse Events Observed During the Clinical Trial Evaluation of Olanzapine

Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with olanzapine (at multiple doses ≥1 mg/day) in clinical trials (8661 patients, 4165 patient-years of exposure). This listing does not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

**Body as a Whole** — *Frequent:* dental pain and flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, and suicide attempt; *Rare:* chills and fever, hangover effect, and sudden death.

**Cardiovascular System**— *Frequent:* hypotension; *Infrequent:* atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, and ventricular extrasystoles; *Rare:* arteritis, heart failure, and pulmonary embolus.

**Digestive System**— *Frequent:* flatulence, increased salivation, and thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, and tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, and tongue discoloration.

**Endocrine System**— *Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis and goiter.

**Hemic and Lymphatic System**— *Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, and thrombocytopenia; *Rare:* normocytic anemia and thrombocythemia.

**Metabolic and Nutritional Disorders** — *Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, and upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, and water intoxication.

**Musculoskeletal System**— *Frequent:* joint stiffness and twitching; *Infrequent:* arthritis, arthrosis, leg cramps, and myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, and rheumatoid arthritis.

**Nervous System**— *Frequent:* abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, and schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, and withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, and tobacco misuse.

**Respiratory System**— *Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, and voice alteration; *Rare:* atelectasis, hiccup, hypoventilation, lung edema, and stridor.

**Skin and Appendages**— *Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, and vesiculobullous rash; *Rare:* hirsutism and pustular rash.

**Special Senses** — *Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, and tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, and pigment deposits lens.

**Urogenital System**— *Frequent:* vaginitis*; *Infrequent:* abnormal ejaculation*, amenorrhea*, breast pain, cystitis, decreased menstruation*, dysuria, female lactation*, glycosuria, gynecomastia, hematuria, impotence*, increased menstruation*, menorrhagia*, metrorrhagia*, polyuria, premenstrual syndrome*, pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged*, and vaginal hemorrhage*; *Rare:* albuminuria, breast enlargement, mastitis, and oliguria.

*Adjusted for gender.

### Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, pancreatitis, and priapism.

## DRUG ABUSE AND DEPENDENCE

### Controlled Substance Class

Olanzapine is not a controlled substance.

### Physical and Psychological Dependence

In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily dose on a $mg/m^2$ basis.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

## OVERDOSAGE

### Human Experience

In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and one patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In one case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

### Overdosage Management

The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

## DOSAGE AND ADMINISTRATION

### Schizophrenia

Usual Dose — Olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical assessment. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations — The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine (*see* CLINICAL PHARMACOLOGY; also *see* Use in Patients with Concomitant Illness and Drug Interactions *under* PRECAUTIONS). When indicated, dose escalation should be performed with caution in these patients.

Maintenance Treatment — While there is no body of evidence available to answer the question of how long the patient treated with olanzapine should remain on it, the effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo-controlled trial (*see* CLINICAL PHARMACOLOGY). Patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

### Bipolar Disorder

Usual Monotherapy Dose — Olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of two weeks, was demonstrated in a controlled trial (*see* Clincal Efficacy Data, under CLINICAL PHARMACOLOGY). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Bipolar Mania Usual Dose in Combination with Lithium or Valproate — When administered in combination with lithium or valproate, olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals.

Short-term (6 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations — *See* Dosing in Special Populations *under* DOSAGE AND ADMINISTRATION, Schizophrenia.

*Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)*

After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

## HOW SUPPLIED

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. The tablets are available as follows:

| TABLET STRENGTH |
|---|

| | 2.5 mg | 5 mg | 7.5 mg | 10 mg | 15 mg | 20 mg |
|---|---|---|---|---|---|---|
| Tablet No. | 4112 | 4115 | 4116 | 4117 | 4415 | 4420 |
| Identification | LILLY 4112 | LILLY 4115 | LILLY 4116 | LILLY 4117 | LILLY 4415 | LILLY 4420 |
| NDC Codes: | | | | | | |
| Bottles 60 | NDC 0002-4112-60 | NDC 0002-4115-60 | NDC 0002-4116-60 | NDC 0002-4117-60 | NDC 0002-4415-60 | NDC 0002-4420-60 |
| Blisters - ID* 100 | NDC 0002-4112-33 | NDC 0002-4115-33 | NDC 0002-4116-33 | NDC 0002-4117-33 | NDC 0002-4415-33 | NDC 0002-4420-33 |
| Bottles 1000 | NDC 0002-4112-04 | NDC 0002-4115-04 | NDC 0002-4116-04 | NDC 0002-4117-04 | NDC 0002-4415-04 | NDC 0002-4420-04 |

* Identi-Dose® (unit dose medication, Lilly).

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:

| ZYPREXA ZYDIS Tablets* | TABLET STRENGTH 5 mg | 10 mg | 15 mg | 20 mg |
|---|---|---|---|---|
| Tablet No. | 4453 | 4454 | 4455 | 4456 |
| Debossed | 5 | 10 | 15 | 20 |
| NDC Codes: | | | | |
| Dose Pack 30 (Child-Resistant) | NDC 0002-4453-85 | NDC 0002-4454-85 | NDC 0002-4455-85 | NDC 0002-4456-85 |

ZYPREXA is a registered trademark of Eli Lilly and Company.
ZYDIS is a registered trademark of R. P. Scherer Corporation.
*ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Scherer DDS Limited, United Kingdom, SN5 8RU.

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect from light and moisture.

## ANIMAL TOXICOLOGY

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily dose on a mg/m$^2$ basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily dose on a mg/m$^2$ basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily dose on a mg/m$^2$ basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily dose on a mg/m$^2$ basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined.

Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

Literature revised Month dd, 2003

**Eli Lilly and Company**
**Indianapolis, IN 46285, USA**

**www.ZYPREXA.com**

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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-592/S-019**

# SUMMARY REVIEW

**MEMORANDUM**

DATE: September 22, 2003

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-592/SE1-019

SUBJECT: Action Memo for NDA 20-592/SE1-019, for the use of Zyprexa (olanzapine) as long-term treatment in patients with Bipolar Mania

NDA 20-592/SE1-019, for the use of Zyprexa (olanzapine) as long-term treatment in patients with Bipolar Mania, was submitted by Eli Lilly and Co., Inc., on 11/20/02. The application contains the results of a single randomized, controlled trial, Study HGHL, in which patients with Bipolar I disorder whose acute episode (manic or mixed) had responded to open-label Zyprexa (in a 6-12 week open label phase) were randomized to continued olanzapine or placebo. In the randomized portion of the trial patients were to be continued under double-blind treatment until they met relapse criteria or received treatment for 52 weeks.

The application has been reviewed by Dr. Teresa Podruchny, medical officer (review dated 9/8/03), Ms. Roswitha Kelly, statistician, Dr. Vaneeta Tandon, Office of Clinical Pharmacology and Biopharmaceutics (review dated 3/17/03), Dr. Sherita McLamore, chemist (review dated 1/10/03), and Dr. Paul Andreason, Psychiatric Drugs Team Leader (memo dated 9/8/03). The review team recommends that the application be considered Approvable.

I agree that Study HGHL demonstrates the activity of olanzapine in this patient population. The design of this study is similar to other studies relied upon to support statements in labeling about maintenance treatment in many other psychiatric indications (e.g., depression, schizophrenia, etc.).

Typically in these randomized withdrawal studies, patients who meet some pre-defined responder criteria while on open-label treatment are continued on this treatment for a given period of time before they are randomized to continue on treatment or placebo. In this design, it is the open-label phase that speaks most directly to the duration of treatment effect. That is, while the double-blind phase is typically 6-12 months long (by protocol), the duration of actual treatment in this phase varies considerably (due to censoring and patients meeting relapse end-points), and it is therefore difficult to draw definitive conclusions about the duration of effect in this phase (of course, if there are few dropouts in this phase, one would be able to conclude something about long-term treatment; however, this is not usually the case). For this reason, we urge sponsors to employ an open-label phase of long duration: ideally, patients should be stable (i.e., have met response criteria) for at least 6 months.

In the study submitted here, the open-label phase lasted 6-12 weeks. However, the mean duration of time that patients had met response criteria prior to randomization was about 16-17 days, with the median duration of responsiveness of 10 days in the drug group (14 days in the placebo group). About 70% of patients in the drug group had been stable for at most 20 days prior to randomization (see Dr. Podruchny's review, page 27, Table HGHL.14.11).

Further, 50% of the drug group had left the study (due either to censoring or having met relapse criteria) by Day 55 of the randomized phase, compared to 20 days for the placebo group. At Day 300 (almost the nominal end of the trial) 50 people (22%) of the drug group were still in the trial, compared to 11 patients (8%) of the placebo group.

These data are difficult to interpret. While the between-treatment contrast in the randomized phase yielded a p-value of $< 0.001$, the question of the duration of effect of the treatment is not easy to answer.

As I noted earlier, we typically consider the duration of response during the open-label phase to determine the duration of effect of the treatment. Here, the mean duration of response is actually shorter than the duration of the acute trials (although in the acute trials, we gain no information about the actual duration over which the patients could be considered to be responsive, or adequately controlled). In addition, also as I noted above, the randomized phase might possibly speak to the duration of effect if there are few dropouts over the nominal duration of the trial. However, in this case, half of the patients have left the drug group in less than two months (and the loss is substantially greater in the placebo group). Therefore, the controlled portion of the trial cannot speak to the duration of effect of the drug.

While it is true that we have little experience with these sorts of trials in bipolar disorder, it is also probably true that in many of these sorts of trials in other indications done to date, the open-label phase is shorter than we would prefer (they are often on the order of 6-12 weeks, as was the case here), and the duration of response in this phase is also relatively short. Further, in the randomized phase of these trials, there are considerable losses at times much earlier than the nominal duration of this phase (as is the case here). In these cases, we ordinarily permit language in labeling, based on these studies, regarding maintenance treatment.

Nonetheless, the relevant durations of treatment in both phases of this trial are quite short. Given this, I find it difficult to celebrate particular durations of effect in labeling, although I believe that some language pertaining to a maintenance effect would be appropriate, because these patients were, presumably, controlled (albeit for a brief period of time) on treatment in the open-label phase, and the

controlled portion of the trial, which is adequately designed to demonstrate the effect of treatment on patients who were controlled (no longer acutely manic), did demonstrate a between-treatment difference; therefore, this trial provides evidence that the acute treatment trial did not.

In addition, Dr. Podruchny has identified several safety issues that the sponsor should address.

Finally, one other issue needs to be addressed.

The current (bipolar) indication for Zyprexa is as treatment of acute manic episodes associated with Bipolar I Disorder.

As noted above, patients in the study which is the subject of the current application could have had either a mixed or manic index episode. Approving the drug now for maintenance treatment of patients with mixed or manic episodes would be problematic, given the current acute bipolar claim (that is, it would be difficult to approve a maintenance claim for a population for whom the drug is not approved as acute treatment). However, the studies that served as the basis for the acute treatment approval also enrolled patients whose index episode was either mixed or manic. For this reason, then, we will amend the current acute indication to include acute mixed as well as manic episodes.

For this reason, I agree with the review team that this application is Approvable, and I will issue the attached draft labeling.

Russell Katz, M.D.

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/s/
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Russell Katz
9/22/03 03:53:48 PM
MEDICAL OFFICER

MEMORANDUM

DATE: January 12, 2004

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-592/SE1-019

SUBJECT: Action Memo for NDA 20-592/SE1-019, for the use of Zyprexa (olanzapine) as long-term treatment in patients with Bipolar Mania

NDA 20-592/SE1-019, for the use of Zyprexa (olanzapine) as long-term treatment in patients with Bipolar Mania, was submitted by Eli Lilly and Co., Inc., on 11/20/02. The submission contained the results of a single randomized controlled trial in patients with Bipolar I disorder who had responded to open-label olanzapine and were then randomized to continued olanzapine or placebo. Such trials typically are submitted in support of a claim for the maintenance of the effect of the drug in question. The division issued an Approvable letter on 9/22/03, which contained numerous requests for additional analyses of various clinical issues. In addition, of course, the letter included draft labeling; in that labeling, the sponsor was granted a maintenance claim, but we had proposed that only the duration of the open label phase be described (we had determined that it is this phase of the trial that best speaks to the duration of "maintenance" of effect; see my memo of 9/22/03).

The sponsor responded to the Approvable letter on 11/13/03. The response has been reviewed by Dr. Teresa Podruchny, medical officer (review dated 1/12/04) and Dr. Paul Andreason, Psychiatric Drugs Team Leader (memo dated 1/12/04). Dr. Podruchny recommends that the sponsor not be granted a claim for maintenance, primarily because the duration of the open-label phase of the study (which was, on average, about 2 weeks) was too short to support a clinically meaningful effect on maintenance of response, and also because the duration of the double-blind phase was also quite short (50% of drug treated patients had discontinued in this phase after about 2 months, and 50% of the placebo patients discontinued after about 20 days). Dr. Andreason disagrees, and concludes that language about a maintenance claim can reasonably be included in labeling.

I agree with Dr. Andreason. As he notes, although the duration of "maintenance" in this study (again, approximately 2 weeks, as determined by the open-label phase) is quite short, we take this study design to address a different question than the question addressed in typical acute studies. That is, in the current study, patients are considered to be not in an acute phase of their illness, but relatively well controlled, and the current study documents that olanzapine provides this control for at least 2 weeks. Therefore, although this duration is shorter than that of the acute studies on which the current claim for acute

treatment is based (about 4 weeks), this study addresses, and answers (at least for durations up to 2 weeks) a different question. Whether or not the demonstration of maintenance of effect for only 2 weeks is clinically meaningful, (as Dr. Podruchny suggests it is not) is, of course, a fair question. It is my understanding that while most clinicians typically treat patients who have responded to treatment for much longer durations, I am also under the impression that at least some experts consider that 2 weeks of maintenance therapy does, in fact, have clinical utility, and that it is not unreasonable to attempt to discontinue treatment in some patients after they have been controlled for such a relatively brief period. As I have noted in my earlier review, it is not obvious to me how to interpret the relatively short duration of the controlled portion of the study, and so I do not find its duration particularly problematic (although I do acknowledge Dr. Podruchny's point that some of the patients might have relapsed so early in the randomized phase because they had not been adequately controlled in the open-label phase, and that the time in study for the drug treated patients in the randomized phase is also quite short. I also recognize the sponsor's conclusion that the median time to relapse in the drug treated patients is 174 days, though this number is potentially misleading, given the large number of other discontinuations).

In any event, I believe the study does demonstrate a maintenance effect of about 2 weeks, and, while this is quite short, it is not extraordinarily different than the duration of response status we have previously seen for other treatments granted a "maintenance" claim. I believe, therefore, that we can fashion a labeling statement that accurately reports the results of this trial, and, though the duration is short, it can reasonably be called "maintenance". It is important to note, as Dr. Andreason does, that maintenance is not necessarily synonymous with "long"; rather it represents a qualitatively different concept than acute treatment, and the term can be reasonably applied in this case.

Finally, Dr. Podruchny has reviewed the sponsor's responses to the specific questions in the Approvable letter, and they do not have a material effect on the final decision.

Therefore, for the reasons given above, I will issue the attached Approval letter, with appended labeling to which the sponsor and we have agreed.

Russell Katz, M.D.

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Russell Katz
1/14/04 01:44:46 PM
MEDICAL OFFICER

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-592/S-019**

# CROSS DISCIPLINE TEAM LEADER REVIEW

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** September 8, 2003

**FROM:** Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

**SUBJECT:** Recommendation for Approvable Action for Extended Efficacy Olanzapine in the treatment of Bipolar Disorder

**TO:** File, NDA 20-592
[Note: This memo should be filed with the original November 20, 2002 submission of this NDA.]

## 1.0 Background

Olanzapine is an "atypical" neuroleptic that was approved September 30, 1996; the approval was based on two adequate and well controlled studies showing olanzapine to be superior to placebo in the treatment of psychosis in patients with schizophrenia.

Olanzapine is also approved for the treatment of acute mania in bipolar affective disorder (NDA 20-592; SE1-006). Studies supporting the claim for the treatment of acute mania were three weeks in duration. The goal of this supplement is to extend the claim of efficacy for up to [ ]. The Sponsor submitted the results of a single study to support this claim. This was study HGHL "Olanzapine versus placebo in the prevention of relapse of Bipolar Disorder". Study HGHL was a randomized, double blind, placebo controlled, flexible dose, parallel group, treatment withdrawal study of time to relapse in patients who had responded clinically to open label olanzapine treatment; however, as shall be discussed, since 50% of the patients in the olanzapine treatment group had dropped out by month two of double blind treatment an extended efficacy claim of [ ] is not appropriate. b(4) b(4)

## 2.0 Chemistry

Olanzapine is a marketed drug product. Only currently marketed forms were used in the clinical trials. There are no CMC related changes in labeling with this supplement.

## 3.0 Pharmacology/Toxicology

Olanzapine is a currently marketed drug product. There were no pre-clinical pharmacology/ toxicology review issues related to this supplement.

## 4.0 Biopharmaceutics

OCPB consultation with this supplement was not necessary.

## 5.0 Clinical Data

The sponsor submits the single study HGHL in support of the extended efficacy of olanzapine in the treatment of Bipolar Disorder. It should be noted that on May 30, 2002 a Pre-sNDA meeting was held with the Sponsor to discuss overall content and format issues of the proposed NDA submission such as labeling issues, statistical analysis, and safety data. Meeting minutes reflect the Sponsor estimated around 50% of the patients would be expected to remain in the study for 12 months. The Division indicated that the study would fail to be a 12-month study if patient attrition was sufficiently significant prior to this time point. The primary clinical reviewer for supplement 019 was Teresa Podruchny, MD.

**Efficacy**

Study HGHL is a double blind, placebo controlled, randomized, treatment withdrawal protocol that was preceded by a 4-week open label stabilization phase. Stated more clearly, patients who met criteria for bipolar disorder mania were treated with olanzapine monotherapy 5-20-mg/day in an open-label fashion. Patients who went on to meet criteria for a positive treatment response for 4-weeks were then randomized to double-blind treatment where they would either continue on olanzapine monotherapy at their previous open-label dose or placebo.

The primary efficacy measure of the double blind period was the time-to-symptomatic relapse of bipolar disorder, mania or depression, defined as follows:

- **Symptomatic remission** was defined as having a YMRS total score $\leq$ 12 and a HAMD-21 total score $\leq$ 8 at two consecutive visits.
- **Symptomatic relapse of mania** was defined as achievement of a YMRS total score $\geq$ 15 after having met the criterion for symptomatic remission or being hospitalized for mania.
- **Symptomatic relapse of depression** was defined as achievement of a HAMD-21 total score $\geq$ 15 after having met the criterion for symptomatic remission or being hospitalized for depression.
- **Symptomatic relapse of bipolar disorder** was defined as having symptomatic relapse of either mania or depression.

Kaplan-Meier plots and log-rank tests were used to compare treatment groups for time to event data. 80.15% of the placebo group and 46.67% of the olanzapine group were considered to have met criteria for symptomatic relapse as defined by the protocol. This is statistically significant at p<.001. Using data from the [ ] tables (RELAPSE.xpt files) provided by the Sponsor, Dr Podruchny found and I concur that the time at which 50% of the group was no longer in the study due to relapse or censorship, or therefore, the time to discontinuation for any event, was 20 days for the placebo group and 55-56 days for the olanzapine group. This creates a slightly steeper slope than that seen in the Kaplan-Meier curve produced in the Sponsor's submission and disagrees with their statement that the median time to discontinuation was 83 days for olanzapine and 26 for placebo. At day 300 or greater, there were 50 people (22.2%) from the olanzapine group remaining in the study and 11 (8%) in the placebo group. b(4)

b(7) [ ]
b(4) [ ] [ ] Site 34 was identified by the Sponsor as failing in Good Clinical Practice protocols. [ ]
and the median time to discontinuation without sites [ ] 34 was 58 days for olanzapine treated b(4)

patients and 22 days for placebo treated patients. Therefore, reanalysis produces results that are nearly identical both with and without the data from sites [ ] 34. b(4)

In conclusion, an indication for extended efficacy is approvable, but labeling that suggests that olanzapine is effective as maintenance treatment for periods up to [ ] is misleading and should be modified to reflect the limits of the study. b(4)

**Safety**
Study HGHL adds little controlled to the already accumulated safety data on olanzapine that is provided in the initial Schizophrenia treatment development program and short-term treatment of Bipolar Disorder-Mania. The short-term safety of olanzapine was characterized in the 3-week placebo controlled trials of Bipolar Mania submitted in supplement SE1-006. 50% of the placebo patients had dropped out of the study at 20 days after randomization (the 20 day figure here includes sites 20 and 34 for purposes of safety review).

**Depression and Suicidality**
There were no deaths in the double-blind treatment phase of the study. Two patients died within 30 days of completion or discontinuation of the study. One completed suicide 3 weeks after withdrawing consent to return to his doctor. A second died from cardiac arrest after experiencing a stroke 28 days after discontinuation from the study. Neither of these deaths was likely to be drug related.

Dr Podruchny noted that patients treated with olanzapine relapsed to depression more often than mania.

| Type of Relapse Seen in Study HGHL | | |
|---|---|---|
| | Placebo (n=109) | Olanzapine (n=105) |
| Depression | 53 (48.63%) | 68 (64.76%) |
| Mania | 44 (40.37%) | 27 (25.71%) |
| Mixed | 12 (11.01%) | 10 (9.52%) |

An inter-group comparison of incidence rates of significant change in items 1 and 3 of the HAM-D is a means by which a drug's potential for inducing suicidal ideation and behavior is commonly explored in the Division. Mean differences in change in items 1 and 3 of the HAM-D were not significant; however, this was not the usual analysis of the incidence of patients who started with a score of 0-2 and then achieved a score of 3 or 4 on items 1 or 3 of the HAM-D that is usually performed. Given the disparity in the types of relapse between the two groups this analysis needs to be performed as part of the safety work up prior to approval.

[ ] the slow accumulation of case reports of severe metabolic dysregulation, [ ] b(5)

[ ] The Division's Safety Team shall be issuing labeling recommendations based on data not contained in this submission for multiple drugs in the atypical antipsychotic drug group that will subsume my specific recommendation for olanzapine.

Current US labeling mentions weight gain in the adverse events section under Additional Findings Observed in Clinical Trials. Various types of glucose dysregulation are mentioned in the Other

Adverse Events Observed During the Clinical Trial Evaluation of Olanzapine section. The Japanese counterpart to the FDA instituted a red boxed warning that contraindicates the use of olanzapine in patients with diabetes or a history of diabetes.

In a June 20, 2003 General Correspondence the Sponsor analyzed treatment emergent diabetes in sample of bipolar patients enrolled in olanzapine clinical trials. They found that regardless of treatment assignment all patients (n=18) who developed treatment emergent diabetes had at least one diabetes risk factor. Cases of olanzapine treated patients with diabetic ketoacidosis (DKA) or hyperosmolar coma have resolved with supportive care, insulin and with the discontinuation of olanzapine many of these patients have gone on to not require insulin.

In study HGHL, olanzapine treated patients showed a significantly different change in weight from baseline of the double-blind treatment period to endpoint. From the beginning of the open-label period at which the mean weight was 83.18 kg to the end of open label, the mean change to endpoint was 3.05 kg (p168/17467). The mean weight of patients entering the double blind period was 85.94kg. Additionally, 29.1% of patients in the open-label acute treatment phase experienced potentially clinically significant changes in weight.

Weight gain is clinically correlated with deterioration in diabetic control for patients with Type II Diabetes. DKA and hyperosmolar coma are rare in Type II Diabetes and it is striking that there are cases where they have occurred in concert with olanzapine treatment and resolved with the discontinuation of olanzapine. Therefore it is reasonable to strengthen the labeling with a statement in the WARNINGS section that patients with risk factors for diabetes should be monitored more closely for changes in glucose control while taking olanzapine. A frank contraindication is not necessary in my opinion because blood glucose and weight gain are easily monitored and the majority of the most serious cases were reversible when they were identified and treated.

**6.0 WORLD LITERATURE**

Dr. Podruchny examined the published literature for Zyprexa included in the NDA and did not discover any previously unrecognized important safety concerns for this drug.

**7.0 FOREIGN REGULATORY ACTIONS**

To my knowledge, Zyprexa is not approved beyond acute therapy for the treatment of mania anywhere at this time.

**8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING**

We decided not to take this supplement to the PDAC.

**9.0 DSI INSPECTIONS**

Inspections were conducted at US sites: [ ] Hartford (site #22). The Clinical Inspection Summary by FDA reviewer Dr. Ni Khin, dated July 25, 2003 notes that subsequent to [ ] b(4) b(7) [ ] Although there were some deficiencies noted at site 22, overall the data appeared acceptable for use in support of this supplemental NDA.

## 10.0 APPROVABLE LETTER

An approvable letter acknowledging our decision to proceed with an approval action pending agreement on labeling has been included with the approvable package and an analysis of incidence of potentially clinically significant changes in HAM-D items 1 and 3 along with the incidence of treatment emergent depression and suicidal ideation/behavior.

## 11.0 CONCLUSIONS AND RECOMMENDATIONS

I recommend that the Division issue the attached Approvable Action (AE) letter for NDA 20-592 supplement 19 with the conditions for approval being the following:

- A change in labeling removing the implication that olanzapine is effective for up to [ ] b(4)
- [ ] b(5)
  This shall be addressed under a separate class-labeling action letter that shall be initiated by the Division Safety Team
- Analysis of incidence of potentially clinically significant changes in HAM-D items 1 and 3 along with the incidence of treatment emergent depression and suicidal ideation/behavior

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Paul Andreason
9/8/03 12:22:08 PM
MEDICAL OFFICER

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** January 12, 2004

**FROM:** Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

**SUBJECT:** Recommendation for Approvable Action for supplement 19: Olanzapine in the maintenance treatment of Bipolar Disorder

**TO:** File, NDA 20-592
[Note: This memo should be filed with the original November 13, 2003 submission of this NDA.]

## 1.0 Background

Olanzapine is an "atypical" neuroleptic that was approved September 30, 1996; the approval was based on two adequate and well controlled studies showing olanzapine to be superior to placebo in the treatment of psychosis in patients with schizophrenia.

The Division issued an Approvable Action letter on September 22, 2003 for NDA 20-592 supplement 19. The sponsor submitted a complete response to the Approvable Action on November 11, 2003.

## 2.0 Chemistry

There is one CMC related change in labeling with this supplement. The sponsor changed , hydroxypropyl methylcellulose to hypromellose in the description section.

## 3.0 Pharmacology/Toxicology

Olanzapine is a currently marketed drug product. There were no pre-clinical pharmacology/ toxicology review issues related to this supplement.

## 4.0 Biopharmaceutics

OCPB consultation with this supplement was not necessary.

## 5.0 Clinical Data

The sponsor submitted re-analyses of time-to-relapse, analysis of HAM-D items 1 and 3 as an exploration of potential for drug related induction of suicidality, re-analysis of laboratory, ECG and vital sign data of interest from baseline to end of treatment, a re-analysis of efficacy data excluding sites 34[ ], and a re-coded patient disposition table. Along with this the Sponsor submitted an amended version of draft labeling. b(4)

The analysis of HAM-D items 1 and 3 did not reveal a signal for drug induced suicidality. There were no other new safety signals that required immediate changes to labeling or that had not been

explored in larger and more dependable databases. These were reviewed by Teresa Podruchny, MD the Primary Clinical Reviewer. Study HGHL added little controlled to the already accumulated safety data on olanzapine that is provided in the initial Schizophrenia treatment development program and short-term treatment of Bipolar Disorder-Mania. The short-term safety of olanzapine was characterized in the 3-week placebo controlled trials of Bipolar Mania submitted in supplement SE1-006. 50% of the placebo patients had dropped out of the study at 20 days after randomization.

**6.0 FOREIGN REGULATORY ACTIONS**

To my knowledge, Zyprexa is not approved beyond acute therapy for the treatment of mania anywhere at this time.

**7.0 APPROVABLE LETTER and LABELING**

An approvable letter acknowledging our decision to proceed with an approval action pending agreement on labeling is attached to this action package.

Dr Podruchny recommends that the Division take a Not Approved action on S-019. The basis of her decision is that she believes that a maintenance monotherapy sub-section in labeling for Zyprexa under the section on the treatment of bipolar disorder implies a claim of efficacy in long-term treatment [ ] She believes that if the Division grants a maintenance claim of any duration then this will imply approval for what is considered a long-term treatment for bipolar disorder. Patients with a bona fide diagnosis of bipolar disorder should be treated in many instances life long. What those treatments should be and how long they should last remain an unknown that is driven by necessity and drug response. b(4)

I disagree with Dr. Podruchny's recommended action; however, I harbor similar concerns about the labeling being potentially false and misleading when it comes to claims of maintenance treatment of bipolar disorder. Unlike Dr. Podruchny I am making a distinction between maintenance treatment and long-term maintenance treatment. Study HGHL does study patients in a phase of treatment where they meet a priori criteria for response; therefore, they may be considered in a maintenance phase of their illness. I must note that this is an arbitrary research definition and that the true length of time it takes to resolve an acute exacerbation of bipolar disorder is unknown; therefore, when acute treatment ends and maintenance begins is a difficult question to answer. If one considers a maintenance treatment one that begins when an response criteria is met, then study HGHL provides evidence that olanzapine helps maintain this effect at the two week mark and shortly thereafter. It is unknown however if this maintenance of effect will be adequate in monotherapy at any time in the clinically useful future because so many of the comparator group dropped out so soon after randomization. This rendered the study un-interpretable after about 20 days. [ ]

[ ] b(4)

Draft labeling is attached to the package with my comments in brackets. Generally speaking I do not agree with the Sponsor's proposed changes to draft labeling from the Approvable Action letter of September 22, 2003. [ ] 50% of the patients in the olanzapine group had dropped out by day 59 of double blind treatment, though they claim that the median time to relapse was 174 days. 50% of the placebo patients had dropped out by day 20 and the reported median time to relapse was reported as b(4)

22-days. Once 50% each of the treatment groups have dropped out of a relapse-prevention-design-study, it is no longer interpretable. Though the discrepancy in the median-times-to-relapse may be attributed to patients in the olanzapine group dropping out for adverse events and other reasons instead of relapse, it is difficult to accept that the reported duration of effect outstrips what we could reasonably call the duration of the study.

The Sponsor's simple claim that olanzapine is "[ ] maintenance monotherapy", [ ]

b(4)

The Division's views on how to describe studies on maintenance-of-effect have changed and the application of these changes in the draft labeling of 9/22/2003 was in large part catalyzed by the results of this study. The results of this study show clearly that bipolar patients should be treated for periods of longer than two weeks, but they are also clear that olanzapine as maintenance monotherapy is not particularly successful for more than half the patients after two months. A maintenance therapy that seems to fail after two months is not particularly useful in this setting. Little can be said about the comparative efficacy of olanzapine at time points after more than 50% of the placebo group has dropped out of the study.

b(4)

The Division now therefore describes positive results from maintenance treatment studies that employ the "relapse prevention" design by the duration of the treatment prior to double blind randomization. The value of this method of interpreting relapse prevention studies' lengths is that it limits the amount of time patients are taking placebo in long-term treatment studies, it provides a clear definition of the study length that is not effected by the study outcome, and it allows for sponsors to plan to end studies early due to overwhelming efficacy without jeopardizing their commitment or desire to perform a long-term study.

By this new standard this data supports a maintenance claim of two weeks. Though this regulatory interpretation of the study is probably more conservative than represents the true value of olanzapine monotherapy in the maintenance treatment of bipolar disorder, it is in practical reality not far from accurate. There is no good way to tell where efficacy for olanzapine monotherapy ends based on this study.

## 11.0 CONCLUSIONS AND RECOMMENDATIONS

I recommend that the Division issue the attached Approvable Action (AE) letter for NDA 20-592 supplement 19 with the conditions for approval being agreement to acceptable product labeling.

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Paul Andreason
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MEDICAL OFFICER

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-592/S-019**

# MEDICAL REVIEW(S)

CLINICAL REVIEW

# NDA 20-592/S-019

**Sponsor: Eli Lilly and Company**

**Drug Name: Zyprexa® (olanzapine)**

**Proposed Indication: Long-term treatment of Bipolar I disorder**

**Date Submitted: November 20, 2002**

**User Fee Date: September 21, 2003**

**Reviewer: Teresa A. Podruchny, M.D.**

# *Table of Contents*

# Clinical Review for NDA 20592/S-019

## *Executive Summary*

## I. Recommendations

### A. Recommendation on Approvability

The indication of long term treatment of bipolar I disorder, for up to [ ], with olanzapine monotherapy is not supported by the data from the pivotal trial. I recommend the Division consider an approvable action on supplemental NDA 20-592 for the use of olanzapine for the treatment of bipolar I disorder with an index manic or mixed episode for up to approximately [ ]. The rapid attrition and "relapse" rates of the olanzapine and placebo groups respectively make it difficult to interpret the data in the pivotal study and do not allow this reviewer to conclude olanzapine is efficacious for up to [ ] as implied in the proposed label or long-term treatment as stated in the proposed label. b(4) b(5) b(4)

The data show that by approximately day 56 (two-protocol months) of double-blind treatment, 50 % of the olanzapine-treated patients (and 74% of the placebo-treated patients), are no longer in the study. If one assumes time at symptomatic remission, as defined by the protocol, is equivalent to stabilization, this would mean that once stabilized, most patients will have either relapsed or discontinued the medication within three months.

This reviewer does not argue the fact that olanzapine clearly statistically separates from placebo on time to "relapse" as defined in the study. Additionally, there are approximately 25% of the olanzapine treated patients and 8.8% of the placebo treated patients in the study at 273 days. The clinical interpretation of this group is difficult secondary to the high attrition rates and the suggestion from the data that patients perhaps are not clinically stable before randomization occurs.

An indication for total treatment duration of up to approximately [ ] in bipolar I patients with manic or mixed episodes possibly is supported by the data in the pivotal study and is an approvable action. Taken in its entirety, the results of the pivotal trial suggest that the stabilization period in the pivotal study is too short. The rapid "relapse" seen in the placebo group may reflect, in part, the withdrawal of treatment in patients who are not fully clinically remitted. Conversely, the treatment group continues to stabilize more fully. However, within a few months, the treatment group suffers high attrition through either relapse or discontinuation. b(5)

### B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The Sponsor should provide additional data, as outlined in Section X.B. to support the safety data supplied in this submission and included in proposed labeling text.

## II. Summary of Clinical Findings

### A. Brief Overview of Clinical Program

One double-blind, placebo controlled study, F1D-MC-HGHL (HGHL) "Olanzapine versus placebo in the prevention of relapse of Bipolar Disorder" was submitted as the key efficacy study to support the use of olanzapine for the long-term treatment of bipolar I disorder. This study enrolled 731 patients in an open-label period in order to obtain a population of patients who achieved remission with olanzapine. This yielded 361 patients who were considered to be in remission of a manic or mixed episode of Bipolar I disorder. These patients were then randomized to receive either Zyprexa or a placebo. Patients could remain in the group to which they were assigned for up to 12 months. Pre-defined criteria for relapse was used to measure time-to-relapse. Patients who relapsed may have entered a separate part of the study in which they would be treated with olanzapine and other drugs as clinically needed.

Two active comparator studies, F1D-MC-HGHT (HGHT), "Olanzapine versus Lithium in Relapse Prevention in Bipolar Disorder" and F1D-MC-HGHQ (HGHQ) "Olanzapine versus Divalproex in the treatment of Acute Mania" were submitted as was F1D-MC-HGFU (HGFU), "Olanzapine added to mood stabilizers in the treatment of bipolar disorder." F1D-MC-HGHD (HGHD) and F1D-MC-HGEH (HGEH), safety updates from study F1D-MC-HGGY (HGGY) and ISS safety information from F1D-MC-HGGW (HGGW) also were submitted as part of safety information.

### B. Efficacy

Study HGHL does not support the claim that olanzapine is effective as monotherapy for up to b(4) [ ] maintenance treatment of bipolar I disorder in patients who have "remitted" from an index manic or mixed episode with treatment of olanzapine. The data do support an extension or continuation of the efficacy for acute mania or mixed episodes. The time period of this is somewhat uncertain. However, a range of approximately [ ] from the beginning of b(5) treatment may be reasonable.

The primary objective of the study was to assess the efficacy of the drug compared to placebo in the prevention of "relapse" into a manic, mixed, or depressed episode among the population of bipolar I patients who responded and "remitted" with open-label treatment of olanzapine from an index manic or mixed episode.

A total of 731 patients received open-label treatment with olanzapine. During this phase of the study, other drugs for the symptoms of bipolar illness were tapered. 361 patients completed this period and met protocol prescribed criteria for symptomatic remission. (Remission and relapse

criteria are discussed in section VI C page 28 of this document.) These patients were then randomly assigned to receive double-blind treatment with either continued olanzapine (225 patients) or placebo (136 patients). The double-blind portion of the study could last up to 12 months. Additionally, patients who relapsed could transition into an open-label rescue period in which olanzapine and other drugs were used as clinically appropriate. The primary objective of the study was to assess the efficacy of olanzapine compared to placebo in the prevention of relapse into a manic, mixed, or depressed episode among the population of bipolar I patients who responded and remitted with open-label treatment of olanzapine from an index manic or mixed episode.

The primary efficacy measure of the study was the time- to-symptomatic relapse of bipolar disorder as defined by Young Mania Rating Scale (YMRS) criteria, Hamilton Depression Scale criteria (HAMD), or hospitalization. The Sponsor's analysis indicates that olanzapine was superior to placebo in time-to-symptomatic relapse of bipolar disorder ($p<.001$) with time-to-relapse at 174 days for the olanzapine group and 22 days for the placebo group. However, this superiority is driven by the quick relapse of the placebo group (~ 59% relapsed by day 30) and diminishes the fact that on day 174 there are only 71 patients left in the study in the treatment group. Stated another way, almost 68% of the 225 patients in the olanzapine treatment group are no longer in the study after day 174. Additionally, 50% of the olanzapine treatment group is no longer in the study at the end of two calendar months (approximately).

### C. Safety

Olanzapine was first marketed in 1996 for schizophrenia. The updated overall integrated database used in the ISS included studies HGHL, HGHT, HGHQ, HGHD, and HGEH. Additionally, a four month update of the open-label extension of HGGY and information in the ISS regarding deaths, serious adverse events, and discontinuations due to adverse events for study HGGW also were submitted. This provided data for 2001 bipolar I disorder patients with a cumulative of 592.1 patient-years of exposure to olanzapine.

Including the pivotal study, seven olanzapine treated patients died either during the clinical trials or within 30 days of discontinuation. There were deaths in placebo and lithium treated patients also. Most of the olanzapine and (known) placebo deaths and one of the (known) lithium deaths were due to suicide. One of the suicides in the olanzapine group was rated as possibly related to study medication by the Investigator. This reviewer believes this possibility cannot be ruled out. However, this patient had experienced the death of a parent three weeks earlier. Cardiac arrest/stroke and "arteriosclerotic cardiovascular disease with myocardial fibrosis and diabetes mellitus" account for two patient deaths in the olanzapine group. (Narratives of these deaths may be found in the appendix.) Rates of suicide attempt and suicidal ideation for the integrated databases (HGHL, HGHT, HGHQ, HGHD, and HGEH) are 0.8% and 2.9% respectively (as listed in the treatment emergent adverse events section).

Weight gain was seen throughout all studies. In a number of patients, this gain was at levels which over long-term, likely will impact general health. Although the issue is complex, treatment emergent adverse events related to glucose in the overall database occurred in 1.4% of patients

(as provided by the Sponsor Table ISS.11.10, please see appendix). Within the pivotal study, when relapse occurred in the olanzapine treated patients, it was more likely to be due to depression than when relapse occurred in the placebo treated patients. Given the primary disorder, interpretation of the increased frequency of depressive relapse versus manic or mixed with olanzapine is unclear.

QTcF prolongation was seen in more olanzapine than placebo treated patients and treatment emergent EPS was seen at a higher rate in the olanzapine treated patients. Other safety related findings such as hyperuricemia, hypercholesterolemia, and elevated eosinophil counts are not unique to this patient population and are in current labeling.

With regard to subgroups, patients under the age of 40 were more likely to relapse into depression than patients greater than the age of 40. Weight loss occurred more frequently in "Causian" than "Other" olanzapine treated patients. Patients of "Caucasian" origin represented the large majority of this study and "Other" represented a heterogeneous group. Therefore, interpretation is unclear.

Although these studies were not designed to produce data that was useful to make judgements about long-term comparative safety, the controlled clinical trials did not reveal, uncommon, unexpected, or previously unreported serious events likely to be drug-related.

**D. Dosing**

Based on the pivotal study data, the dosing schedule can speak only to dosing for a period of two-three months or so for most patients and for the 22 % of patients that might remain in treatment at 10 months. For this time period or population, the dosing schedule would appear to be adequate.

**E. Special Populations**

With regard to safety, subgroup analysis was performed as a secondary analysis to examine treatment consistency effects across demographic groups such as age, gender, and ethnicity for adverse events, laboratory analytes, vital signs, and EKG data. This analysis was performed if there were enough patients as defined by at least 10% of patients included in each subgroup strata. In general, age was stratified as <40 or >40 years old and ethnic origin as Caucasian or other. The pivotal study suggest that when depression occurs with the use of olanzapine in this population, it more frequently occurs in patients under 40 years old than in those over 40 years old. The pivotal study suggest, without statistical significance, that "Caucasian" patients using olanzapine may experience weight loss more easily than "Other" . To some degree, this may reflect weight loss after initial weight gain in the open-label phase.

With regard to efficacy, in the pivotal study, analyses of symptomatic relapse incidence and time to relapse were performed for the subgroups of age, gender, ethnicity, mixed episode versus pure mania, rapid cycling versus a nonrapid cycling course, and psychotic versus non-psychotic when

there was an adequate patient number. The Sponsor notes there were no statistically significant differences in efficacy based on subgroup analyses

## *Clinical Review*

## I. Introduction and Background

### A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Zyprexa® (olanzapine), an antipsychotic agent in the thienobenzodiazepine family, currently is available in two oral forms, tablets and orally dis-integrating tablets, and is indicated for the treatment of schizophrenia, the short-term treatment of acute manic episodes associated with Bipolar I Disorder, and most recently, for bipolar mania combination therapy in the treatment of acute mania. Recommended dosing for the treatment of schizophrenia is 10 mg QD single dose to be started as a single daily dose of 5-10 mg with escalation up to the 10 mg within several days. Dosing changes are to be made in 5 mg QD increments and to occur at intervals of not less than 1 week.

For the short-term treatment of acute manic episodes (3-4 weeks) associated with Bipolar I Disorder, the Sponsor recommends single daily doses with initial doses of 10-15 mg, dosage adjustments at intervals of not less than 24 hours, and changes to be made in increases/decreases of 5 mg QD. A dose range of 5-20 mg/d is recommended based on clinical trial data. In combination therapy with lithium or valproate in the treatment of acute manic episodes, the recommended starting dose is 10 mg a day without regard to meals. Clinical trial data demonstrated efficacy in a dose range of 5-20 mg/d.

The recommended starting dose is 5 mg in patients "who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female $\geq$ 65 years of age), or who may be more pharmacodynamically sensitive to olanzapine". Caution is advised in dosing elderly patients especially those with psychiatric symptoms and Alzheimer's disease. Caution is advised or caution should be exercised in patients with a history of seizures or conditions that may lower the seizure threshold, clinically significant prostatic hypertrophy, narrow angle glaucoma, a history of paralytic ileus, cardiac patients (secondary to orthostatic hypotension), and in patients with signs and symptoms of hepatic impairment.

The safety and efficacy of olanzapine have not been established in pediatric populations. Olanzapine is a category C pregnancy drug. The effect on labor and delivery in humans is unknown and breast feeding is not recommended.

This supplement proposes an indication for olanzapine in the long-term treatment of bipolar I disorder. Specifically, the indication would be for those patients with an index mixed or manic episode and who "symptomatic remission" of this episode with olanzapine. For these patients,

the proposed recommended initial dose of olanzapine is 10 mg QD as a single dose with or without food, with further dosing in the range of 5-20 mg per day.

### B. State of Armamentarium for Indication(s)

Although Depakote® and Zyprexa® are labeled for the treatment of acute mania in bipolar episodes, they are not approved for maintenance therapy. Lithium is the primary maintenance therapy for Bipolar Disorder. Until the recent approval of Lamictal®, it was the only FDA approved drug for this indication. The long term use of lithium presents clinical challenges such as a narrow therapeutic index and toxicity, hypothyroidism, and nephrogenic diabetes insipidus. Additionally, as with most pharmaceuticals, there is not a 100% response rate. In the search for treatment options, clinicians use other medications such as divalproex sodium, carbamazepine, and other antileptics, off-label, for maintenance treatment. Lamictal® carries a box warning for the possibility of serious rashes including Stevens-Johnson Syndrome. Rare cases of toxic epidermal necrolysis have occurred. The rate of serious rash development is greater in pediatric populations and there is evidence that the risk increases with the concomitant use of valproic acid. Dosing recommendations are made and should be followed closely. Common adverse experiences associated with the use of Lamictal® are headache and asthenia.

Valproate is used as an alternative to lithium in patients who either do not respond or who are intolerant to lithium's adverse event profile. The side effects of valproate include hepatotoxicity and hyponatremia. Laboratory testing of liver function tests should be performed during the first three months of treatment. Other adverse effects of valproate include, tremor and weight gain.

Although not approved, carbamazepine is used off label for the treatment of bipolar disorder. Use of carbamazepine necessitates periodic hematologic monitoring as aplastic anemia is a rare possibility.

Other off-label use includes antipsychotics. Typical antipsychotics have a higher risk of inducing extrapyramidal side effects than the atypicals. Olanzapine is one of four approved "atypical" antipsychotic agents. Other atypicals include risperidone, clozapine, and ziprasidone. Unlike more traditional antipsychotics, in which the mechanism is presumed to be through $D_2$ antagonism, the mechanism for the atypical antipsychotics is felt to be due to antagonism of both $D_2$ and $5HT_2$ receptors. With regard to the treatment of acute mania in Bipolar I Disorder, the mechanism of action of olanzapine is unknown.

### C. Important Milestones in Product Development

October 27, 1998
A briefing document summarizing protocol HGHL was submitted to NDA 20-592 to address issues of the October 2, 1998 not approvable letter for NDA 20592_S006 (olanzapine monotherapy for the treatment of manic or mixed episodes associated with bipolar disorder)

August 20, 1999
FDA communication to Sponsor requesting patient enrollment in HGHL be limited to those in acute manic or mixed state and not acute depressive state.

September 10, 1999
Protocol amendment a to F1D-MC-HGHL approved by Lilly. Changes to the protocol included reporting of serious adverse events and noted that serious adverse events occurring after a subject discontinued from the study would not be reported unless the investigator felt the event may have been caused by the study drug or protocol procedure.

October 22, 1999
Amendment to HGHL submitted to IND 28,705 to enroll as per FDA request of August 20, 1999 to limit enrollment to patients with acute mania or mixed states as the index episode.

February 23, 2000
The Sponsor and the Division met to discuss the plan proposed earlier in the February, 2000 . The Division indicated one positive study evaluating the efficacy of olanzapine compared with placebo in the prevention of relapse in bipolar disorder would be acceptable to obtain a claim for maintenance. In addition, a pediatric waiver was granted.

May 14, 2002
Briefing book in support of the May 30, 2002 pre-sNDA meeting was submitted to IND 28,705.

May 30, 2002
Pre-sNDA meeting to discuss overall content and format issues of the proposed NDA submission such as labeling issues, statistical analysis, and safety data. Meeting minutes reflect the Sponsor estimated around 50% of the patients would be expected to remain in the study for 12 months. The Division indicated that the study would fail to be a 12 month study if patient attrition was sufficiently significant prior to this time point. The Division agreed to grant a pediatric waiver.

June 21, 2002
Agreement with electronic format as proposed in the briefing document of May 14, 2002 e-mailed to Lilly.

August 13, 2002
Financial Disclosure to be for studies F1D-MC-HGHL, F1D-MC-HGHT, and F1D-MC-HGFU as "covered" studies used in the ISE and to establish efficacy in the long-term treatment of bipolar disorder.

**Olanzapine Applicable INDs**

| | |
|---|---|
| 28,705 July 23rd, 1986 | Olanzapine for the treatment of psychiatric disorders |
| 51,457 August 29th, 1996 | Olanzapine for the treatment of behavioral disturbances associated with dementia |
| 55,342 March 4th, 1998 | Olanzapine for short-acting intramuscular administration |

| | | |
|---|---|---|
| 58,225 | April 29th, 1999 | Olanzapine orally disintegrating tablets |
| 58,551 | June 30th, 1999 | Olanzapine for the treatment of cognitive deficits associated associated with dementia |
| 60,701 | August 8th, 2000 | Olanzapine pamoate monohydrate depot formulation for the maintenance treatment of various psychiatric disorders |

**Olanzapine Applicable NDAs**

| | | |
|---|---|---|
| 20-592 | September 21st, 1995 | Olanzapine for the management of the manifestations of psychotic disorders |
| 21-086 | March 1st, 1999 | Olanzapine orally disintegrating tablets |
| 21-253 | June 15th, 2000 | Olanzapine for injection |
| 21-520 | November 4th, 2002 | Combination Olanzapine/fluoxetine for Bipolar Depression |

### D. Other Relevant Information

Olanzapine was first approved in the United States as an antipsychotic on September 27, 1996. Approval for short-term was established in 2 six-week trials of inpatients who met DSMIII-R criteria for schizophrenia. Longer-term maintenance was established in a trial of adult outpatients who predominantly met DSM-IV criteria for schizophrenia, were stabilized on olanzapine for approximately 8 weeks, and then were randomized to either olanzapine or placebo.

In the United States, olanzapine is approved as monotherapy (one 3-week and one 4-week trial) and in combination with either lithium or valproate (two 6-week trials) for use in the treatment of acute manic episodes. The patients in clinical trials supporting these uses met DSMIV criteria for Bipolar I Disorder with mixed or manic episodes. As per the Sponsor, olanzapine is not approved for bipolar maintenance in any country.

### E. Important Issues with Pharmacologically Related Agents

The Sponsor notes that no label changes have been made since the last submission to the FDA (September 16, 2002) in Japan, Canada, or New Zealand. Japan's current label includes a box warning regarding increased blood glucose.

Australia and Europe made label changes in 2002. In Australia, label changes under the Precautions and Adverse Reactions sections were made on August 26, 2002. Additions to the Precautions and Adverse Reactions sections were made and are shown as per the Sponsor below:

There is an increased prevalence of diabetes in patients with schizophrenia. As with some other antipsychotics, exacerbation of pre-existing diabetes has been reported very rarely. Hyperglycemia, diabetic coma and diabetic ketoacidosis have been reported in very rare cases, sometimes in patients with no reported history of hyperglycemia (see ADVERSE REACTIONS). Appropriate clinical monitoring is advisable in diabetic patients.
The following language was added to the Adverse Reaction section:
In clinical trials with olanzapine in over 5000 patients with baseline non-fasting glucose levels 7.8 mmol/L, the incidence of non-fasting plasma glucose levels 11 mmol/L (suggestive of diabetes) was 1.0%, compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels 8.9 mmol/L but <11 mmol/L (suggestive of hyperglycemia) was 2.0%, compared to 1.6% with placebo:
Metabolic - Very rare (< 0.01%): exacerbation of pre-existing diabetes.

On September 09, 2002, the following changes to the safety section of the label were approved for the European label:

**Table 3.1. Changes in the European Summary of Product Characteristics**

| Type of Change | Submission Date | CPMP Opinion | Commission Decision | Description of Change |
|---|---|---|---|---|
| Safety variation to SPC | 12 Feb 02 | 31 May 02 | 09 Sep 02 | Sections 4.4 and 4.8: Parkinson's symptomatology and hallucinations<br>Sections 4.4 and 4.8: Caution in patients receiving medicines known to cause neutropenia<br>Sections 4.4 and 4.8: Acute symptoms associated with stopping olanzapine abruptly<br>Section 4.5: Deletion of ketoconazole as CYP1A2 inhibitor<br>Section 4.6: Adverse events reported in infants born to mothers who used olanzapine in third trimester<br>Section 4.8: Allergic reaction, urinary hesitation |

# II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Completed review from the Division of Biometrics is not available at this time. Recommendations made are pending confirmation of the Sponsor's analysis and/or this reviewer's analysis by the Division of Biometrics.

The Office of Clinical Pharmacology and Biopharmaceutics finds the Sponsor's labeling changes in the Drug Interaction section under PRECAUTIONS acceptable. Chemistry Review indicates the supplement is adequate as there have been no changes to either the drug product, drug substance, or package insert.

# III. Human Pharmacokinetics and Pharmacodynamics

## A. Pharmacokinetics

No new pharmacokinetic data was submitted with this submission. The reader is referred to the initial submission and review of NDA 20-592.

### B. Pharmacodynamics

This is not applicable to this supplement.

## IV. Description of Clinical Data and Sources

### A. Overall Data

The Sponsor submitted one randomized, double-blind, placebo-controlled pivotal study, HGHL, in support of the registration of olanzapine for the long-term treatment of bipolar I disorder. Two comparator studies, HGHT and HGHQ, and one combination study, HGFU, also were submitted. HGHT and HGHQ compared olanzapine with lithium or divalproex respectively. Neither study had a placebo arm and HGHT underwent an unplanned interim analysis. A brief synopsis of each of these studies is included within this document. However, neither study is reviewed in detail for efficacy. HGFU was a combination study using olanzapine + either lithium or valproate versus placebo + either lithium or valproate. With regard to long term efficacy, this study design was not directly comparable to the pivotal study and is not reviewed in detail.

HGHL, HGHT, HGHQ, HGFU*, HGHD, HGEH, a four month updated safety report for study HGGY with an updated ISS, and deaths and serious adverse events for a four week study, HGGW were submitted to support safety. Integrated analyses of the comparator studies and of the open-label studies are presented in the ISS. All original safety and efficacy data were generated by the Sponsor. A publication bibliography was submitted by the Sponsor. A brief literature review for safety was conducted by this reviewer.

* included in the original ISS list of studies comprising the ISS database, not included in the overall integrated databases as this study combined olanzapine with a mood stabilizer.

### B. Table Listing the Clinical Trials

The table below lists all studies presented by the Sponsor in support of any component of this application or as background information for the use of olanzapine in the treatment of bipolar disorder. Table information is taken from Sponsor- provided tables/sources.

Table IV.B.1: The controlled clinical studies in this submission for bipolar maintenance.

| Principal Clinical Trials in NDA 20-592, s_019 | | | | |
|---|---|---|---|---|
| **Trial** | **Study Title** | **Study Design** | **Treatment/Duration** | **Number of Patients** |
| HGHL<br>Prevention of relapse, bipolar mania and depression | Olanzapine Versus Placebo in the Prevention of Relapse of Bipolar Disorder | DB, R, PC, parallel, multicenter in patients who remitted from a manic or mixed episode after acute OL treatment with olanzapine | OL:5-20 mg/day olanzapine, 6-12 weeks<br>DB: 5-20 mg/day olanzapine or placebo, up to 12 months<br>OL rescue period | N=731 in OL<br>N=361 in DB<br>• 225 O<br>• 136 P<br>Bipolar I, manic and mixed ( 8 with depressive episodes) |

| | | | | |
|---|---|---|---|---|
| HGHT<br>Prevention of relapse, bipolar mania and depression | Olanzapine Versus Lithium in Relapse Prevention in Bipolar Disorder | DB, R, parallel, mulicenter study in bipolar patients remitted from a manic or mixed episode after OL treatment with olanzapine and lithium | **OL:5-20 mg/day Olanzapine plus lithium, 61-12 weeks DB: 5-20 mg/day olanzapine or lithium in range of 300-1800 mg/day titrated to therapeutic serum level of 0.6-1.2mEq/L, up to 48 weeks.** | N=543 in OL<br>N=431 in DB taper period<br>N=385 DB therapy<br>Bipolar I, Manic and Mixed |
| HGHQ<br>Acute bipolar mania | Olanzapine Versus Divalproex in the Treatment of Acute Mania. | DB, R, parallel, multicenter in bipolar patient, mixed and manic to demonstrate non-inferiority | DB acute: 5-20 mg/day olanzapine or 500-2500 mg/day divalproex, 3 weeks<br>DB extension: Continued same, 11months | N=251 Bipolar I, Manic and Mixed<br>N=167 in DB extension:<br>O=86<br>Dival=81 |
| HGFU<br>Acute bipolar mania, bipolar mania and depression | Olanzapine Added to Mood Stabilizers in the Treatment of Bipolar Disorder. | Two DB, R, parallel, multicenter olanzapine or placebo added to either lithium or valproate in bipolar patients, manic and mixed. | DB acute: 5-20 mg/day olanzapine or placebo, 6 weeks<br>DB extension: responders re-randomized to 5-20 mg/day of olanzapine or placebo, 18 months | N=344 Bipolar I patients, manic and mixed<br>N=99 re-randomized to 18 month |
| HGHD<br>Acute bipolar mania | Olanzapine Versus Haloperidol in the Treatment of Acute Mania | DB, R, parallel multicenter in bipolar patients, manic or mixed | DB acute: 5-20 mg/day olanzapine or 3-15 mg/day haloperidol, 6 weeks<br>DB extension: responders continued the same, 6 weeks<br>OL extension: 5-20 mg/day olanzapine, 6 months | N=453 Bipolar I, Manic and Mixed |
| HGEH<br>Acute bipolar mania | Olanzapine Versus Placebo in the Treatment of Mania Associated with Bipolar I Disorder | Two, DB, R, parallel, multicenter in bipolar patients, manic or mixed | DB acute: 5-20 mg/day olanzapine or placebo, 3 weeks<br>OL extension: 5-20 mg/day olanzapine, 12 months | N=139 Bipolar I, Manic and Mixed |
| HGGY<br>Treatment of Bipolar I Depression | Placebo-Controlled Olanzapine Monotherapy in the Treatment of Bipolar I Depression | Two DB, R, PC, parallel multicenter OL Extension | OL Safety phase: 5-20 mg/day, 6 months | N=562 in OL, safety |
| HGGW<br>Acute bipolar mania<br>Short term study | Olanzapine Vs Placebo in the Treatment of Bipolar Disorder, Manic or Mixed | | Deaths, serious adverse events, discontinuation 2nd to adverse events | |

DB=Double-blind, R=randomized, PC=placebo controlled, OL=open-label, N=number, O=olanzapine, P=placebo

### C. Postmarketing Experience

The collection of adverse events for the spontaneous safety database of olanzapine began on September 27, 1996. The Sponsor states that it "collects all reported spontaneous adverse events for patients treated with olanzapine in the Clintrace safety database. Clintrace began as the safety database on 5 March 1998 and replaced the Drug Experience Network (DEN). DEN was the initial safety database used by Eli Lilly and Company and began on 1 March 1983. All the olanzapine data collected in DEN was transferred to the Clintrace database. The adverse events found in the olanzapine spontaneous safety database are coded to terms from the Medical Dictionary for Regulatory Affairs (MedDRA)."

"Spontaneous adverse events are defined as adverse events occurring with a marketed product in a therapeutic setting or from a source other than a clinical trial or post-marketing study."

## ADVERSE EVENT REPORTS IN PATIENTS WITH BIPOLAR DISORDER

In order to stratify adverse events by patient population, the Sponsor electronically searched the Clintrace (Pharmacovigilance) database for spontaneous adverse event reports temporally associated with the use of olanzapine in the treatment of bipolar disorder between September 27, 1996 and June 30, 2002. The "indication for use" field was searched for reports that listed bipolar disorder, mania, depression, and variations of these terms, such as manic. When both mania and depression type terms were used, the assumption of bipolar disorder was made. In addition, a "textstring" search for the word bipolar was performed on all the olanzapine reports with a blank "indication for use" field. Those found were read for medical content. If determined to contain a patient with bipolar disorder, the case was added to the bipolar disorder group of reports. All other reports with a blank "indication for use" field were considered not to be bipolar cases.

Patients with multiple diagnoses, one of which was bipolar disorder, were included regardless of whether the bipolar disorder was considered the primary or secondary disease according to the "indication for use" field in Clintrace.

Subsequent to the search, a list of all adverse event terms in the MedDRA 4.0 dictionary that appeared in spontaneous adverse event reports in bipolar patients was prepared. The Sponsor provided a reporting ratio as the absolute number of cases for each event term and that event term's percentage of the total cases reported. The absolute numbers reflect numbers of cases, not numbers of adverse events.

The olanzapine spontaneous safety database through June 30, 2002 contained 21, 213 cases. Of these, 11.8% (2, 496 case reports) were considered reports that involved bipolar disorder as an indication. The MedDRA term for neuroleptic malignant syndrome was reported in 45/2496 cases; a reporting ratio of 1.8%. The Sponsor notes that, as not all cases in the database have an indication, this may be an underestimate. The Sponsor provided a table (Table 1, appendix) that

lists the 46 MedDra preferred term events that were reported with a reporting ratio for bipolar patients ≥ 2x that reported in non-bipolar patients and in which the absolute number of cases among the patients being treated for bipolar disorder was ≥ 6.

From this table, it is noted that diabetic coma NOS has a reporting rate of 0.24% which is 2.67x higher than in the non-bipolar patients. The Sponsor provides literature indicating that the frequency of diabetes mellitus in hospitalized bipolar patients is significantly higher than in the general population (Cassidy, F. Ahearn E, Carroll BJ, Am J Psychiatry 1999; 156:1417-1420). Other notable findings in Table 1 are ammonia increased at 0.24% versus 0.02%, neutrophil count decreased (0.25% versus 0.11%), acute renal failure (0.28% versus 0.13%), blood pressure increased (0.72% versus 0.25%), congestive heart failure (0.48% versus 0.12%) and short term memory loss (0.36% versus 0.09%). With concomitant medications likely used for many of these patients, it is difficult to discriminate effects solely due to one drug. The Drug Safety team within this Division monitors the atypical anti-psychotics for effects on glucose regulation and the hematologic system.

**D. Literature Review**

The Sponsor provides a clinical bibliography of approximately 180 publications. In an e-mail communication of August 12, 2003, the Sponsor indicated that the literature search conducted did not identify any prospective, randomized, controlled studies of olanzapine as a monotherapy in the long-term treatment of bipolar disorder. Two open-label studies of olanzapine with mood stabilizers were included. The Sponsor notes that the adverse events reported in these studies were consistent with the known safety profile of olanzapine.

During a literature search conducted by this reviewer, several articles or issues of interest were seen. The first is a 47–week, randomized, double-blind, comparator study of olanzapine versus divalproex published recently[1]. This article appears to be based on study HGHQ. The authors conclude that the median time to symptomatic mania remission was significantly shorter for olanzapine although "rates of bipolar relapse did not differ." At week three, "remission" was seen in a larger percentage of divalproex treated patients than in olanzapine treated patients. At the end of the 47-week period, there were approximately equal numbers and proportions of patients in each group remaining. Weight gain (24.8% versus 11.9%), increased appetite (13.6% versus 5.6%), akathisia (9.6% versus 1.6%), somnolence, dry mouth, and high alanine aminotransferase levels occurred significantly more frequently with olanzapine treatment while nausea (31.7% versus 16.0% ) and nervousness (22.0% versus 12.0%) occurred more with divalproex treatment. There was a significantly greater increase in cholesterol level among the olanzapine group. The mean QTc change with Fridericia correction was 7.97 for the olanzapine group and –3.06 for the divalproex group. Approximately 2% of women in each group experienced clinically significant changes defined as an increase from <450msec at baseline to >450msec during the trial. There were no QTc intervals >450msec in men or >470msec in women.

In a 12-week double-blind, parallel group multicenter study of the efficacy, safety, and tolerability of olanzpine versus divalproex[2], one death from diabetic ketoacidosis occurred in an olanzapine treated patient. The patient was a 53 year old man with a baseline glucose level of

86mg/dL and neither past history nor family history of diabetes. The presence or absence of other risk factors is not detailed. Mean changes in body weight were 4.0 kg and 2.5 kg for olanzapine and divalproex treated patients respectively. Somnolence, weight gain, rhinitis, edema, and speech disorder were reported as adverse events in a greater proportion of the olanzapine group while no adverse events were reported in a significantly greater proportion of divalproex patients. Efficacy was measured after the initial inpatient 21 day stay and is reported as "no significant difference in efficacy was found between treatment groups.". The author postulates that study design and dosing practices may explain the difference in the results of this study versus a previous study which demonstrated olanzapine superiority to valproex.

Another report of fatality from olanzapine induced hyperglycemia of a 31-year old schizophrenic patient was found in the recent literature.[3]

Other areas of safety interest are a recent report in an elderly patient of acute hepatocellular-cholestatic liver injury after thirteen days of olanzapine therapy[4]. The authors felt that this was likely drug-induced based on a validation scale to assess drug-induced hepatitis. Hyperlipidemia has been reported in the literature[5] in patients with schizophrenia.

Appears This Way
On Original

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[1] Olanzapine Versus Divalproex Sodium for the Treatment of Acute Mania and Maintenance of Remission: A 47-week study. Tohen M, Ketter TA, Zarate CA, Suppes T, Frye M, Altshuler L, Zajecka J, Schuh LM, Risser RC, Brown E, Baker RW. Am J Psychiatry 2003; 160:1263-1271.

[2] A Comparision of the Efficacy, Safety, and Tolerability of Divalproex Sodium and Olanzapine in the treatment of Bipolar Disorder. Zajecka JM, Weisler R, Sachs, G, Swann AC, Wozniak, P, Sommerville KW. J Clin Psychiatry 2002; 63:1148-1155.

[3] Fatality from olanzapine induced hyperglycemia. Meatherall R, Younes F. J Forensic Sci 2002 Jul:47(4):893-6.

[4] Acute Hepatocellular-Cholestatic Liver Injury after Olanzapine Therapy. Research Letter. Jadallah K, Limauro D, Colatrella A. Annals of Internal Medicine 2003; 138 (4): 357-358.

[5] An Assessment of the Independent Effects of Olanzapine and Risperidone Exposure on the Risk of Hyperlipidemia in schizophrenic patients. Koro CE, Fedder DO, L'Italien GJ, Weiss S, Magder LS, Kreyenbuhl J, Revicki D, Buchanan RW. Arch Gen Psychiatry, 2002 Nov;59 (11):1021-6.

# V. Clinical Review Methods

## A. How the Review was Conducted

This submission contains one pivotal study , HGHL, for efficacy purposes. As this Division typically allows claims of longer- term efficacy based on positive results in one well-designed and adequately controlled study, HGHL was the focus of this review. A brief synopsis of the double-blind olanzapine versus comparator trials, HGHT and HGHQ is included. These studies were not reviewed exhaustively as no efficacy claims are sought based on them. All other studies in support of efficacy received cursory review only and are not detailed. Safety data from all studies submitted including HGGY and ISS information for HGGW were reviewed although studies which were redundant with those reviewed for the acute maintenance indication were not reviewed in detail.

## B. Overview of Materials Consulted in Review

This supplemental NDA was submitted in electronic form as per the "Guidance for Industry Providing Regulatory Submissions in Electronic Format-NDAs", January, 1999. Additionally, a paper copy was submitted to the Division.

Case Report Tabulations were provided electronically only. The electronic version of the supplemental NDA contains the datasets for studies HGHL, HGHT, HGFU, HGHQ, HGHD, and HGEH.

Case Report Forms (CRFs) were provided electronically only in Adobe Portable Document Format as specified by the Electronic Submissions Guidance. CRFs for all patients who died, discontinued due to adverse events, and reported serious and unexpected adverse events were to comprise the CRF section.

A 4-month safety update, an abbreviated clinical study report, case report tabulations, and case report forms were submitted electronically March 19, 2003 for study HGGY.

An addendum to Clinical Study Reports for HGHL and HGHT was submitted electronically on July 10, 2003. For HGHL, this addendum consisted of descriptions of errors found in four data sets. For HGHT, this addendum consisted of descriptions of errors found in two datasets.

Meeting minutes, correspondences filed under IND 28,705, and other olanzapine supplemental NDA reviews were consulted as part of this review. A limited literature review was performed by this reviewer.

### C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Biometrics received raw data via SAS transport files which was a analyzed according to the Sponsor's methods as described in the protocol. Results were compared to the analyses provided by the Sponsor. This reviewer performed random checks to verify internal consistency of the data within datasets, as transferred to tables, and within protocol definitions. Please see the efficacy section for areas of interest.

DSI inspected [ ] domestic sites for protocol F1D-MC-HGHL, the pivotal trial; [ ] site #022, Hartford (n=69 entered, 23 randomized). b(4)

The Clinical Inspection Summary by FDA reviewer Dr. Ni Khin, dated July 25, 2003 notes that subsequent to [ ] b(7)

[ ] b(4)

[ ] Although there were some deficiencies noted at site 22, overall the data appeared acceptable for use in support of this supplemental NDA.

The Sponsor notes that the investigator at site 34 experienced problems which apparently contributed to site closure.

### D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The Sponsor states the pivotal study was conducted in accordance with Good Clinical Practices (GCP). Additionally, the Sponsor notes there were GCP problems at one site (site 34, n=7 entered, 3 randomized) creating an audit. General Correspondence from the Sponsor dated April 24, 2000 states that this investigator was discontinued as an investigator for the pivotal trial based upon non-compliance with GCP. Eventually, the site was closed and "many database queries left unanswered". Therefore the Sponsor notes performance of separate time-to and rate-of-symptomatic relapse excluding this site.

The Division of Biometrics re-analyzed efficacy data [ ] b(7)
[ ] with and without the site that was closed (site 34). Although a separate review of the data will be provided by the Division of Biometrics, it appears that the primary efficacy measure does not lose statistical significance.

### E. Evaluation of Financial Disclosure

Financial disclosure and certifications statement were included. The pivotal study was conducted by a CRO who obtained the financial disclosures. The Sponsor notes there is only one investigator requiring disclosure. This investigator (#✓) received approximately $43, 000 from the Sponsor between late [ ] and late [ ]. This investigator is the [ ] for study HGHL. b(6)

# VI. Integrated Review of Efficacy

## A. Brief Statement of Conclusions

Pivotal study HGHL demonstrates statistical support for the hypothesis that the time to "relapse" is longer in olanzapine treated bipolar I patients who met remission criteria on olanzapine than placebo treated bipolar I patients who met remission criteria on olanzapine. However, clinical efficacy for long-term treatment, the indication the Sponsor seeks, encompasses more than the demonstration of significance on statistical measures of primary efficacy and requires one to consider the clinical implications of the data in its entirety.

Within the pivotal study, given the rapid "relapse" of the placebo group after drug withdrawal and the high attrition rate in the olanzapine treated group, clinical efficacy up to [ ] is not established. Approximately two months post- randomization, 50 % percent of the treatment group is no longer receiving treatment for various reasons. By the last month of the double-blind treatment phase in HGHL, only approximately 22% of the patients who began the olanzapine treatment arm were still on the drug and without relapse. By day 365, there are four-five people left in the study in the treatment arm and one in the placebo group. The attrition rates make the study data difficult to interpret. After two months of double-blind treatment, although statistically interpretable, the clinical significance appears limited. b(4)

## B. General Approach to Review of the Efficacy of the Drug

This submission contains one pivotal efficacy study, two comparator studies, and one combination study to support a long-term claim. Multiple studies are submitted to support safety. HGHL was the focus of this efficacy review as the regulatory requirement, as interpreted by this Division, has been to allow long term efficacy claims based on positive results in one well-designed and adequately controlled study.

This reviewer believes information from the initiation of drug exposure may be useful and therefore, at times, presents data from the open-label period. Interpretation of this type of open-label data is limited as it is without placebo control and is confounded by concomitant medications and medication tapers.

## C. Detailed Review of Trials by Indication

### C-1. F1D-MC-HGHL: "Olanzapine Versus Placebo in the Prevention of Relapse in Bipolar Disorder"

The efficacy of olanzapine compared with placebo for the treatment of (in the "prevention" of "relapse" into a) manic, mixed, or depressive episodes in bipolar I patients who were considered remitted from an index mixed or manic episode on open-label acute olanzapine treatment was studied as the primary objective in this randomized, double-blind, parallel study. The terms used

in the study are somewhat confusing as patients entered the open-label period ill, were treated until meeting criteria, and then randomized. Therefore, the actual period of "remission" may make it difficult to apply terms such as "relapse" and "prevention of relapse". The proposed Indication the Sponsor seeks is Bipolar Disorder "Long-term treatment" (monotherapy). Proposed language descriptions in the label are "[ ] time to relapse" and [ ] b(4)
[ ]

## C-2. INVESTIGATORS AND SITES

Sixty-nine investigators were recruited, 53 of these received study medication, and 47 enrolled patients. 42 sites were in the United States, 5 were in Romania. A listing of the investigators and sites, as provided by the Sponsor, may be found in the appendix, Table F1D-MC-HGHL.

## C-3. PATIENT POPULATION

The patients in this study were males and females, inpatients or outpatients, at least 18 years of age with a diagnosis of bipolar I disorder currently displaying an acute manic or mixed episode, with or without psychotic features, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and confirmed by structured diagnostic interview Structured Clinical Interview for the DSM-IV-TR Axis I disorders, Research Version, Patient Edition (SCID-I/P). This included the diagnostic codes 296.4x, Bipolar I Disorder, Most Recent Episode Manic; 296.6x, Bipolar I Disorder, Most Recent Episode Mixed. A current diagnosis of bipolar I with a single manic episode, most recent episode hypomanic or most recent episode unspecified or bipolar II, as defined by DSM-IV was excluded. As provided by the Sponsor, inclusion and exclusion criteria are in the appendix.

On August 20th, 1999, the Division requested that enrollment be limited to patients with an index mixed or manic bipolar I episode. This request was made secondary to short-term data suggesting an antimanic effect of olanzapine yet an absence of data addressing the short-term antidepressant efficacy of olanzapine. Before this amendment was in effect, 22 patients with an index episode of depression were enrolled in the open-label treatment phase with 8 entering the double-blind period; 3 to placebo (2.2%) and 5 to olanzapine (2.2%).

## C-4. DEMOGRAPHIC/ILLNESS CHARACTERISTICS

In the open-label phase, study period II, there were 57.7% females and 42.3% males. 86.5% were Caucasian and 9.0% were African. The age range was 18.13-84.36 years old with an average age of 39.16 years. With regard to psychiatric characteristics, 51.7% of the patients were rapidly cycling, 41.6% had an index mixed episode, 55.4% had an index manic episode and 3.0% had an index depressive episode. The average length of the current episode was 67.20 days. The range was 1-1783 days.

In the double-blind phase, study period III, patients had a mean age of 39.79 years and 41.13 years for placebo and olanzapine respectively. Overall, 87% of the patients were Caucasian and 61.2% were female. The placebo and olanzapine groups were comparable at baseline with respect to the demographic characteristics of mean age, gender, ethnic origin and illness

characteristics. For the double-blind phase, overall 49.6% were rapid cycling patients with the olanzapine group having a larger proportion of these patients than the placebo group. 18.2% were psychotic, 64.3% manic, 33.5% mixed, and 2.2% depressed. (Please see the Sponsor's table, ISS 6.2 below). The Sponsor notes this percentage of rapid cycling patients is higher than that typically seen in bipolar populations.

**Table ISS.6.2. Patient Characteristics HGHL, Double-Blind Treatment Placebo-Controlled Maintenance Database**

| Variable | Olanzapine (N=225) | Placebo (N=136) | Total (N=361) | p-Value[a] |
|---|---|---|---|---|
| Sex: Number (%) | | | | 1.00 |
| Male | 87 (38.7) | 53 (39.0) | 140 (38.8) | |
| Female | 138 (61.3) | 83 (61.0) | 221 (61.2) | |
| Origin: Number (%) | | | | .376 |
| Caucasian | 195 (86.7) | 120 (88.2) | 315 (87.3) | |
| African descent | 19 (8.4) | 8 (5.9) | 27 (7.5) | |
| East/Southeast Asian | 1 (0.4) | 2 (1.5) | 3 (0.8) | |
| Western Asian | 1 (0.4) | 0 (0) | 1 (0.3) | |
| Hispanic | 8 (3.6) | 3 (2.2) | 11 (3.0) | |
| Other origin | 1 (0.4) | 3 (2.2) | 4 (1.1) | |
| Age: years | | | | .479 |
| Mean | 41.13 | 39.79 | 40.62 | |
| Median | 41.45 | 39.27 | 41.02 | |
| Standard deviation | 12.07 | 11.54 | 11.87 | |
| Range | 19.05-74.61 | 18.13-84.36 | 18.13-84.36 | |
| Bipolar Episode Type (Mixed vs. Manic vs. Depressed[b]) | | | | .974 |
| Mixed | 76 (33.8) | 45 (33.1) | 121 (33.5) | |
| Manic | 144 (64.0) | 88 (64.7) | 232 (64.3) | |
| Depressed | 5 (2.2) | 3 (2.2) | 8 (2.2) | |
| Psychotic Features (Absent vs. Present) | | | | .401 |
| Absent | 187 (83.1) | 108 (79.4) | 295 (81.7) | |
| Present | 38 (16.9) | 28 (20.6) | 66 (18.3) | |
| Course of Disease (Not Rapid Cycling vs. Rapid Cycling) | | | | .190 |
| Not Rapid Cycling | 103 (45.8) | 75 (55.1) | 178 (49.3) | |
| Unknown | 3 (1.3) | 1 (0.7) | 4 (1.1) | |
| Rapid Cycling | 119 (52.9) | 60 (44.1) | 179 (49.6) | |

Abbreviations: N = number of patients; vs. = versus.
[a]P-value for mean age calculated using a Type III sum of squares analysis of variance; p-values for frequencies calculated using Fisher's exact test.
[b]Eight patients entered with depressed episodes before the protocol was amended to exclude such patients.

## C-5. STUDY PROCEDURES ( The Sponsor- provided tables of the study schedule (HGHL.9.2) may be found in the appendix)

HGHL consisted of four study periods as seen in the Sponsor-provided illustration included below.

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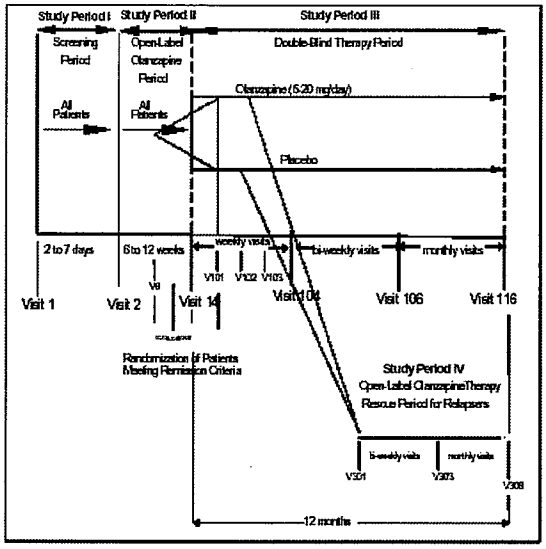


**Figure ISE.6.1. Study design for F1D-MC-HGHL.**

- Study Period I : screening phase of 2-7 days.
- Study Period II: 6-12 weeks (corresponding to visits 8-14) open-label olanzapine treatment (enrichment) phase with dosing from 5-10 mg/day. Initial dosing was 10mg and could be adjusted upward or downward by 5mg within the range of 5-20 mg/day of olanzapine. Medication tapers of prohibited medications were to occur during the first three weeks of study period II (by visit 5). With the exception of benzodiazepines, not allowed medications included psychotropics, concomitant medications used to treat mania and depression, concomitant medications with primarily central nervous system activity and sustained release psychotropics. Fluoxetine was to have been discontinued at least 4 weeks prior to randomization. Sponsor- provided Table HGHL.2 is included in the appendix of this document and details the allowed and prohibited medications.
- Study Period III: double-blind treatment phase, started with visit # 101 and consisted of a maximum of 12 months treatment with 5-20 mg/day of olanzapine versus placebo. The initial dose was equivalent to the final dose from the open-label period. Remission criteria to allow entry into study period are defined below under the REMISSION/RELAPSE DEFINITIONS heading.
- Study Period IV: open-label olanzapine rescue treatment phase for patients who relapsed during Study Period III, not to exceed 6 months. Dosing began with 10 mg per day of olanzapine. Patients could receive concomitant valproate, lithium, and fluoxetine as needed clinically in Study Period IV.
- The cumulative duration of study periods III and IV was not to exceed 12 months.

**C-5. Concomitant Medication Use:**

Benzodiazepine use was allowed in all periods of the study with dose limits as follows:

- Study Periods I & II- maximum of 6 mg lorazepam equivalents/day
- Study Period III- 4 mg lorazepam equivalents/day during the first week and 2 mg lorazepam equivalents/day during the remainder of the period
- Study Period IV- 4 mg lorazepam equivalents/day throughout
- Use during period III was not to exceed 5 consecutive days or 60 cumulative days.

Anticholinergic use was allowed throughout the study for extrapyramidal symptoms (EPS). The use as prophylaxis of EPS was prohibited. Benzotropine mesylate or biperiden could be given up to 6 mg/day or trihexyphenidyl could be given up to 12mg/day throughout the study.

Ibuprofen, lorazepam and paracetamol were concomitant medications reported by $\geq$ 10% of the patients in the double-blind treatment period. 113/136 placebo and 183/225 olanzapine treated patients were taking $\geq$ 1 drug. There were no statistical differences between the groups.

During the double-blind treatment phase, the mean days of benzodiazepine use (mg/day lorazepam equivalent) was 11.2 for the placebo group (n=34, standard deviation of 17.88) and 22.5 for the olanzapine group (n=48, standard deviation of 29.77). Although numerically different, this difference does not reach statistical significance (p=0.57). With regard to dose, the placebo group received mean dose of 1.9 (n= 34, standard deviation of 1.71) and the olanzapine group received a mean dose of 1.8 (n=48, standard deviation 1.50). There is no statistical difference between groups with respect to dose amounts.

During the double-blind period, with regard to anticholinergic use (mg/day benztropine equivalent), four placebo patients had a mean use time of 54.3 days (standard deviation=87.43) while two olanzapine patients had a mean use time of 9 days (standard deviation=0). The mean dose for the placebo and olanzapine patients was 1.8 and 1.3 respectively. There was no statistical difference between groups. In total, 10/225 olanzapine and 6/136 placebo patients used concomitant anticholinergics during the double-blind phase (p=1.00).

The mean daily dose of olanzapine in the open-label acute period was 11.8. The modal dose was 10.0, the median 11.3, and the standard deviation was 7.5. The mean daily dose of olanzapine in the double-blind period was 12.5, the modal was 10.0, the median was 10.9, and the standard deviation was 5.0. Study drug compliance was approximately 93% in both groups during the double-blind treatment phase.

**C-6. REMISSION/RELAPSE DEFINITIONS:**

Symptomatic relapse and remission were assessed based on Y-MRS and HAMD-21 total scores for mania and depression respectively. Symptomatic remission of mania was defined as a Y-MRS total score of $\leq$ 12 at two consecutive visits. Symptomatic remission of depression was defined as a HAMD-21 total score of $\leq$ 8 at two consecutive visits. Symptomatic remission and interim criteria for entry into the double-blind treatment phase was defined as having met criteria

for remission of both manic and depressive symptoms as per HAMD-21 total score of $\leq 8$ and YMRS total score of $\leq 12$ at two consecutive visits.

Symptomatic relapses of mania and/or depression were defined as Y-MRS/HAMD-21 total scores of $\geq 15$ respectively after having met criterion for symptomatic remission **or** hospitalization for either mania or depression. Symptomatic relapse of bipolar disorder was defined as meeting the criteria for relapse of either mania or depression after having met the criteria for remission **or** hospitalization for an affective (manic, mixed, or depressed) episode associated with bipolar disorder.

The Sponsor defined other types of relapse and remission. One was based on DSM-IV criteria and called syndromatic/syndromic. The other, subsyndromal mania or depression, was defined as YMRS total scores 13 or 14 or HAMD-21 total score 9-14 respectively. These definitions were not used for primary efficacy analyses nor for labeling indications and are not reviewed in this document.

## C-7. PRIMARY EFFICACY ANALYSIS

Efficacy analyses were performed by the Sponsor for the open-label lead in, the double-blind treatment period, and the open-label rescue. Only the efficacy analysis of the controlled phase of the study, the double-blind period, received detailed review and the statistical analysis below focuses on this phase. The primary efficacy measure of the double-blind period was the "symptomatic relapse" of bipolar disorder, mania or depression, as defined by the protocol. Primary efficacy analysis of "symptomatic relapse" during the "maintenance" period was performed to include all randomized patients on an intent-to-treat basis. Secondary analyses of "syndromic relapse" were performed by the Sponsor but were not reviewed.

Kaplan-Meier plots and log-rank test were used to compare treatment groups for time- to-event data. Analysis of variance (ANOVA) models were used to evaluate continuous data. Fisher's exact test were used for analysis of proportions. When there were less than two patients per treatment group within an investigative site, the data was pooled with data from other small sites. The main hypothesis of this study was that olanzapine is superior to placebo in time to relapse of bipolar. All hypothesis testing was done at a two-sided $\alpha$ level of 0.05. Treatment-by-investigator interactions and heterogeneity across sites was tested at an $\alpha$ level of 0.10. When LOCF mean change from baseline to endpoint was assessed, patients were included in the analysis only if a patient had a baseline and post baseline measure. For study period II, baseline generally was Visit 2, or Visit 1 if the measure was missing. For study period III, baseline generally was the last observation in study period II. Endpoint was defined as the last measure in the appropriate study period. No patients were excluded from efficacy analysis.

Treatment group comparisons of relapse rate and separate analyses of manic and depressive "relapse" were performed. Treatment groups were compared with respect to LOCF changes from baseline (last visit pre-randomization) to endpoint for the Young Mania Rating Scale (YMRS) and the Hamilton Depression Scale (HAMD-21). Observed case and LOCF visit-wise analyses of YMRS and HAMD-21 total scores were performed. Separate analyses of time-to and rate-of-symptomatic relapse of bipolar disorder were planned to exclude site 34 due to

investigator problems and ultimate closure of the site. Small sites were pooled within the same country. Patients from sites 4, 7, 10, 11, 13, 14, 15, 18, 21, 30, 34, 41, 42, and 50 were pooled from the U.S. sites. The effect of the country on relapse was evaluated using Cochran-Mantel-Haenszel analyses.

## C-8. REMISSION TIMES

Patients considered "remitted" during the open-label treatment phase, as per protocol definitions, were randomized into the double-blind treatment phase. The following Sponsor-provided tables display the time-in-symptomatic "remission" before randomization and the estimated percentage of patients relapsing by time in "remission" prior to randomization. Approximately 41% of the placebo group and 45% of the olanzapine group were stabilized for 7-13 days before randomization. This time period contains the single largest number of patients for each treatment group.

**Table HGHL.14.11. Time-in-Symptomatic Remission Prior to Randomization Double-Blind Treatment**

| Time (Days) in Remission | Pla (%) | Olz (%) |
|---|---|---|
| 0-6 | 10 (7.41) | 19 (8.44) |
| 7-13 | 55 (40.74) | 101 (44.89) |
| 14-20 | 28 (20.74) | 40 (17.78) |
| 21-27 | 12 (8.89) | 23 (10.22) |
| 28-34 | 14 (10.37) | 22 (9.78) |
| ≥35 | 16 (11.85) | 20 (8.89) |
| **Total** | 135 | 225 |
| Mean | 17 | 16 |
| Median | 14 | 10 |

Source: RMP.F1DSHGHL.SASPGM(REMX03SG)

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**Table HGHL.14.12. Symptomatic Relapse Estimated Percentage of Patients Relapsing By Time in Remission Prior to Randomization Double-Blind Treatment**

| Time (Days) | Pla (%) | Olz (%) | p-Value | Therapy Interaction p-Value |
|---|---|---|---|---|
| 7 | 83.8 | 52.1 | <.001 | 0.925 |
| 14 | 81.5 | 47.7 | <.001 | |
| 21 | 78.9 | 43.5 | <.001 | |
| 28 | 76.1 | 39.3 | <.001 | |

Source: RMP.F1DSHGHL.SASPGM(LOGITREL)
Estimated relapse rates and p-values are from a logistic regression model using therapy as a main effect, days in remission as a covariate, and included the therapy-by-days in remission interaction.
Abbreviations: Olz = olanzapine; Pla = placebo.

The Sponsor notes that "The differences in rates of symptomatic relapse between treatment group was similar across time points (interaction p-value=.925), showing that the treatment effect was not dependent upon the amount of time patients had spent in remission." . Visual inspection of table HGHL.14.12 indicates that there is a small decrease in the percentage of "relapsed" patients in both groups as the amount of time in remission lengthens. An analysis of the time in "remission" (as defined in table HGHL.14.11) or total time on treatment to the time to "relapse" may help clarify whether there is a significant relationship between these two factors. Additionally, an analysis of the trajectory of the "remission" to the time of "relapse" may be helpful. For example, a patient with YMRS/HAM-D scores in the 12-20s until visit 8, who then achieves remission criteria for two visits and is randomized may experience a protocol defined "relapse" faster than a patient who, at visit 3 or 4 has achieved lower YRMS/HAM-D scores and is then randomized at visit 8 or 9, as the latter person would actually have been "remitted" for 5 weeks or so versus approximately two for the former. The Sponsor will be asked to define the percentage of "relapse" in each group when remission times, as per Table HGHL.14.11, are 21-28 days and $\geq$ 35 days.

Additionally, symptomatic remission was defined as having a YRMS total score $\leq$ 12 and a HAMD-21 total score $\leq$ 8 at two consecutive visits. The protocol states that once a patient "was determined to be in symptomatic remission, the patient was moved to Study Period III and randomized to a treatment group (olanzapine 5- 20 mg/day or placebo)." (page 42, HGHL Main Report e-version). Based on this criteria, it would appear that all patients should be considered in remission for the length of time of two consecutive visits and randomized after two such consecutive visits. With approximately one week between visits in this period (visits 8-14), this would be roughly two-three weeks. The Sponsor will be asked to clarify how the "remission" times in the above tables were determined as perhaps they represent total time on drug before randomization.

A spot check of the data indicates that patient 455, randomized to placebo had the following HAM-D and YMRS scores.

| Patient # | Therapy | Visit # | **HAMD21 total score** | **YMRS total score** |
|---|---|---|---|---|
| 455 | placebo | 8 | 10 | 2 |
| | | 9 | 5 | 1 |
| | | 10 | 6 | 0 |
| | | 11 | 5 | 2 |
| | | 12 | 5 | 0 |
| | | 101 | 10 | 2 |

For this patient, randomization appears to have happened later than defined by the protocol. Following this patient through .xpt databases (YMRS.xpt, VISIT.xpt, RELAPSE.xpt, PATDISP.xpt, SUMMARY.xpt), checking the Errors to the Locked Database (November 20$^{th}$, 2002 submission sectin 16.1.13), and an electronic search on the patient number in the main study report did not yield an explanation for the time of randomization of this patient. It is possible there were concomitant medications. However, concomitant medications were to be

stopped by visit 5. This reviewer is unsure whether patient 455 is a unique incident and will ask the Sponsor to clarify.

## C-9. DISPOSITION OF THE DOUBLE-BLIND TREATMENT PERIOD

The Sponsor's disposition table is shown below. Three hundred and sixty-one patients began the double-blind period, 225 in the olanzapine group and 136 in the placebo group. The Sponsor notes the most common reasons for discontinuation were adverse events, lack of efficacy as per the perceptions of the patient or physician or both , and patient decision.

Table ISS.6.1. Patient Disposition
HGHL, Double-Blind Treatment
Placebo-Controlled Maintenance Database

| Reason for Discontinuation | Placebo (N=136) n (%) | Olz (N=225) n (%) | p-Value* |
|---|---|---|---|
| Reporting Interval Completed | 13 (9.6) | 53 (23.6) | .001 |
| Adverse Event | 12 (8.8) | 35 (15.6) | .076 |
| Lack of Efficacy | 78 (57.4) | 64 (28.4) | <.001 |
| Lost to Follow-Up | 5 (3.7) | 20 (8.9) | .085 |
| Patient Decision | 12 (8.8) | 30 (13.3) | .237 |
| Criteria not Met/Compliance | 5 (3.7) | 11 (4.9) | .793 |
| Sponsor Decision | 1 (0.7) | 1 (0.4) | 1.00 |
| Physician Decision | 10 (7.4) | 11 (4.9) | .359 |

RMP.PIDP.JCLLIB(HLOF001E)
RMP.PIDP.SASMACRO(SPATOR)
* Frequencies are analysed using a Fisher's Exact test.

There appear to be inconsistencies between the data in this table, the data in the listing of patient disposition (page 3207 of the main study report HGHL), and the data in Sponsor-provided .xpt files. These include the category of lack of efficacy, patient decision, and physician decision. The following examples demonstrate such apparent inconsistency.

- Olanzapine group: patient 005-201-listing of patient disposition (main study report) captured as "physician decision". Datafile (SUMMARY.xpt) sent by the Sponsor indicates this person discontinued at visit 108 with reason listed as "physician decision" and coded as number 22, a distinct code from those of lack of efficacy (codes 8, or 9, or 10). In the section "sumytext" of the .xpt table, "increased depression/relapse of symptoms" is noted for this patient.
- Olanzapine group: Two patients (012-560, 012-563)-listing of patient disposition captures both "patient decision". Datafile (SUMMARY.xpt) shows a code of 13, with the "reason" column indicating "personal conflict or other patient decision", the "sumy text" column stating "feeling very depressed" and "increasing depressive s/s" respectively. Although these may represent only perceptions of depression versus occurrence of protocol-defined depression, it is confusing to this reviewer to have them coded under "personal conflict or other patient decision".
- Placebo group: patient 005-233-listing of patient disposition (page 3197, HGHL main study report) indicates this person is classified as "patient decision". Datafile (SUMMARY.xpt) indicates the patient is coded as 13, "reason" as "personal conflict or other patient decision" with the "sumy text" reading "relapse of mania".

- Patients 021-564 and 013-603 have similar type discrepancies between the "sumy text" description of the discontinuation and the final classification. Both of these patients are coded as 13, "personal conflict or other patient decision". "Sumy text" comments are "became depressed" and "wants antidepressant dyserel" respectively.

With this said, ultimately 5/6 of the patients were considered relapsed for primary efficacy analysis purposes. Patient 012-563 had a HAMD total of 11 and YMRS of 2 at the visit of discontinuation and therefore would not meet protocol defined relapse criteria. From this sample, the patients regardless, of apparent gray terms for coding in the disposition table, are coded correctly in terms of relapse criteria for primary efficacy analysis.

Another type of incident seen in the disposition table is as follows. For patient 005-212, the list of patient disposition (page 3207 of the main study report HGHL) indicates discontinuation at visit 110 secondary to an adverse event (muscle spasms). However, this patient met relapse criteria at visit 101 for mania. With regard to primary efficacy, the days to time-of-event appear to be correctly noted in the RELAPSE.xpt file yet the patient continues to be numbered with the 100 series numbers (versus the 300s as would be the case for open-label treatment, see the study design period figure ISE.6.1 above). The protocol required that a patient meeting relapse criteria during the double-blind treatment phase be discontinued. Therefore, it appears the disposition or discontinuation is secondary to relapse and should not be in the disposition table as discontinued secondary to an adverse event at visit 110. (It appears this patient may have remained in blinded treatment after the relapse.) Additionally, in this case, it should not effect the overall significance of the primary efficacy variable as this patient appears to have been captured correctly for relapse. However, it makes interpretation of the disposition table(s) at face value difficult and uncertain.

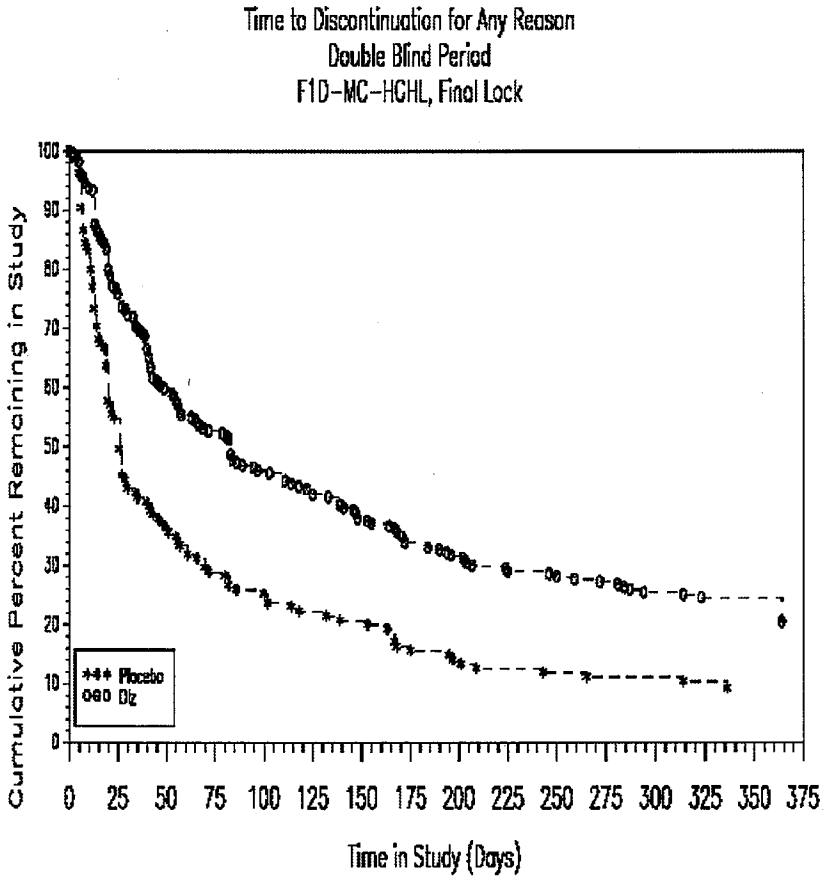
The definition of " Reporting Interval Completed" group is unclear as the numbers displayed in the disposition table are not the number of patients who completed 12 months of treatment in each group. The numbers given for each group indicate the approximate numbers of patients in the double-blind period from approximately day 296 onward. Specifically, as taken from the RELAPSE.xpt file, 12 placebo and 51 olanzapine patients are left in the study at or beyond day 296.

**C-10. RELAPSE RATE/TIME TO DISCONTINUATION FOR ANY EVENT/TIME TO RELAPSE**

With regard to relapse, 80.15% of the placebo group and 46.67% of the olanzapine group were considered to be symptomatic relapsers as defined by the protocol. This is statistically significant at $p<.001$. The overall attrition rates were high for both groups as indicated by the Sponsor-provided Kaplan-Meier survival curve shown below. Using data from the [ ] tables (RELAPSE.xpt files) provided by the Sponsor, the time at which 50% of the group was no longer in the study due to relapse or censorship, or therefore, the time to discontinuation for any event, was 20 days for the placebo group and 55-56 days for the olanzapine group. This creates a slightly steeper slope than seen in the Kaplan-Meier curve below in Figure HGHL.10.2 and does not confirm the Sponsor's statement that the median time to discontinuation was 83 days

b(4)

for olanzapine and 26 for placebo. At day 300 or greater, there were 50 people (22.2%) from the olanzapine group remaining in the study and 11 (8%) in the placebo group.

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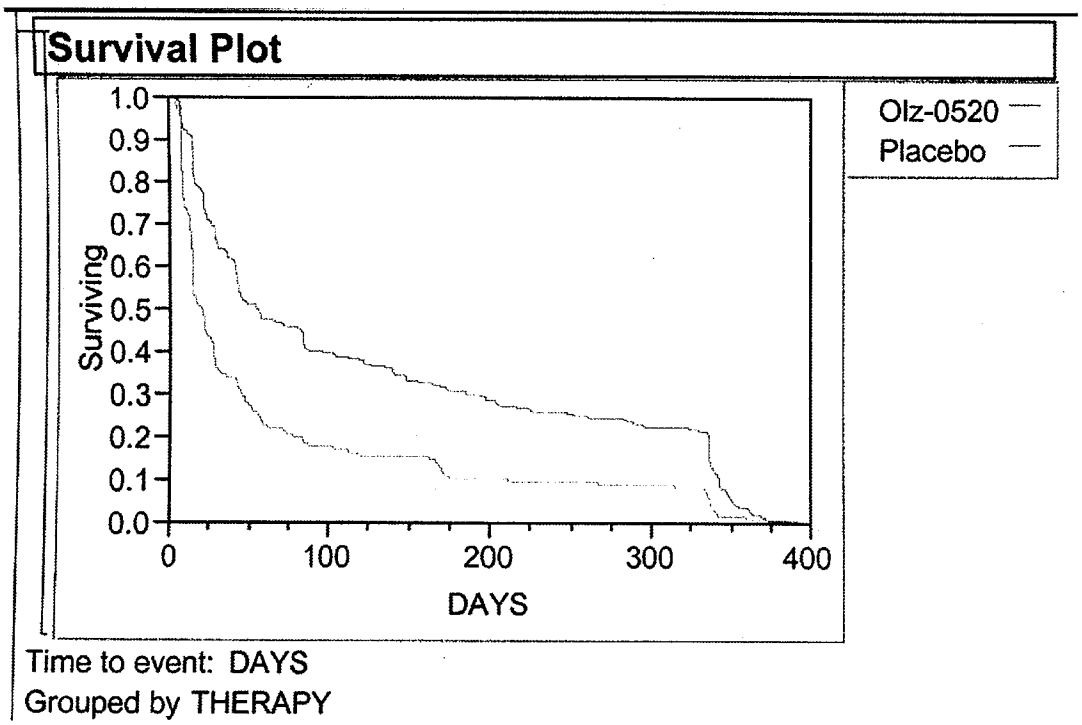
Reviewer's analysis curve: using the data from the datafile RELAPSE.xpt, the survival curve for time to **any** event is as follows.

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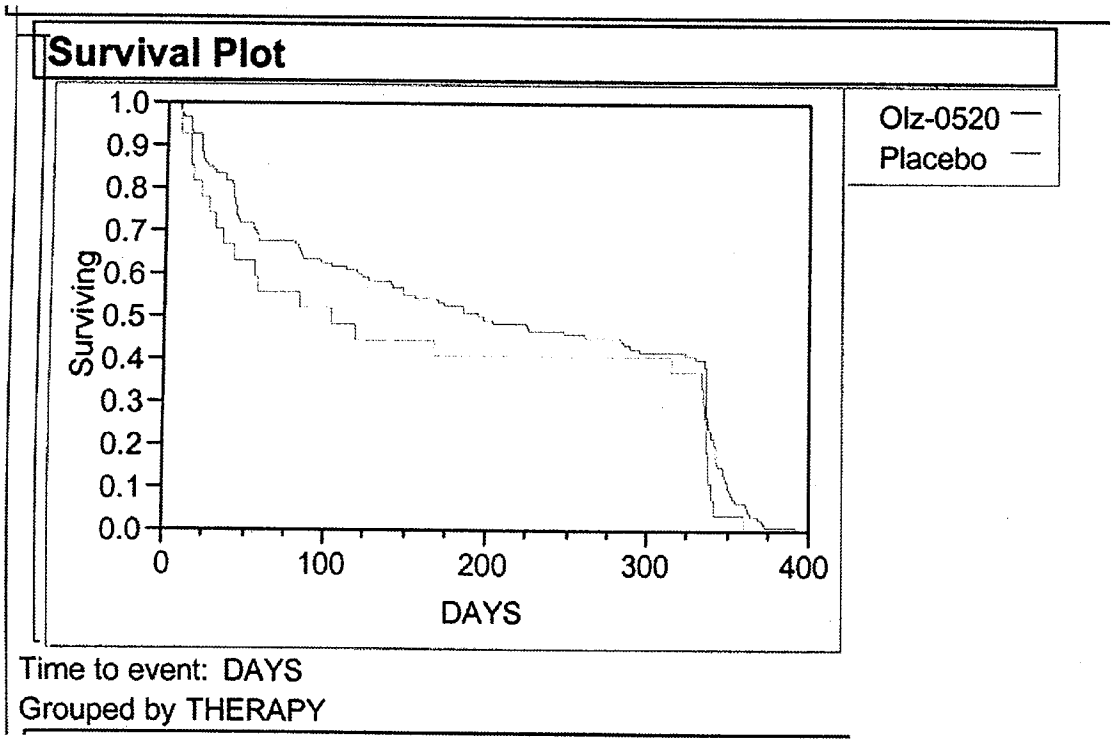
Survival curves created from the Sponsor's E 2 table RELAPSE.xpt for time to relapse=no, which is the time to discontinuation for any reason other than relapse, and time to relapse=yes, which is only those relapsed are shown below. One can see that the curves for each event, censor or relapse, separate. The morphology of the curves in the relapse=yes plot for the treatment group and the placebo group is similar. b(4)

RELAPSE=No

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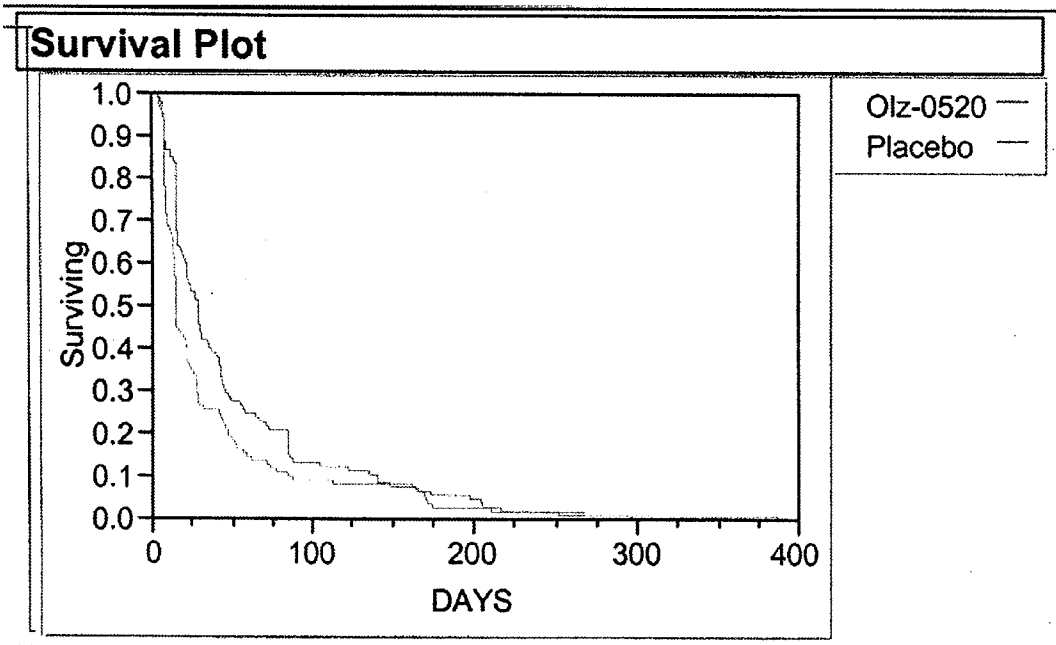
Relapse=Yes

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The Sponsor-provided figure for time-to-relapse is below (Figures ISE.6.2) This reviewer asked for clarification of the Bipolar Relapse group as seen in Table ISE.6.5 (section C-11, page 37 of this document) summarizing the incidence of relapse. Information received from the Sponsor via e-mail on July 31, 2003 indicates that the population captured in the Bipolar Relapse group in that table includes manic, mixed, and depressive episodes. It is presumed this is the same population captured in the figure below. As such, this is the time-to-relapse curve as derived by the Sponsor.

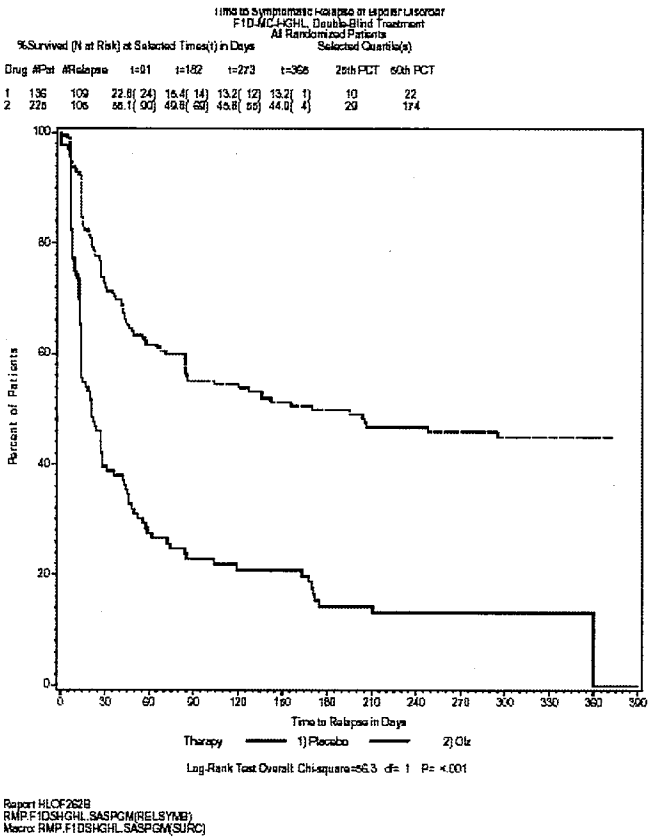


**Figure ISE.6.2.** **Time to protocol-defined symptomatic relapse of bipolar I disorder for the F1D-MC-HGHL double-blind maintenance period from the placebo-controlled maintenance database.**

Numbers for the times given as derived from datafile RELAPSE.xpt differ from the numbers seen in the figure legend for Figure ISE.6.2.

Number of patients relapsed:

| Therapy | <91 days | <182 days | <273days | <296days | ≤364 days | ≥364 days |
|---|---|---|---|---|---|---|
| Olanzapine (n=105) | 91 | +8=99 | +5=104 | +1=105 | +0=105 | +0=105 |
| Placebo (n=109) | 99 | +7=106 | +2=108 | +0=108 | +0=108 | +1=109 |

Number of patients censored:

| Therapy | <91 days | <182 days | <273days | <296days | ≤364 days | ≥364 days |
|---|---|---|---|---|---|---|
| Olanzapine (n=120) | 44 | +13=57 | +9=66 | +4=70 | +46=116 | +4=120 |
| Placebo (n=27) | 13 | +3=16 | +0=16 | +0=16 | +11=27 | +0=27 |

**SUMMARY TABLE OF PATIENT DISPOSITION WHEN CATEGORIZED AS EITHER RELAPSED OR CENSORED FOR THE TREATMENT GROUP (OLANZAPINE) BY DAYS OF THE STUDY:**

Days

| N=225 | ≤55 | <91 | <181 | <273 | <296 | ≤364 | ≥364 |
|---|---|---|---|---|---|---|---|
| Relapsed | 77 | +14=91 | 99 | 104 | 105 | 105 | 105 |
| Censored | 36 | +8=44 | 57 | 66 | 70 | 116 | 120 |
| Total loss | 113 | 135 | 156 | 170 | 175 | 221 | 225 |

When including data from all sites, as indicated in the table above, 50% of the patients in the olanzapine group are out of the study on day 55 or less. There is a group of patients, up to 25% who remain in the study after day 273. Interpreting this data is difficult given that the lead-in or enrichment period was short and it is unclear exactly how long patients were in protocol defined remission before randomization and how stable clinical remission was before randomization. However, a possible interpretation of the 25% remaining in the study after day 273 is that of those patients who were stabilized to a more full clinical remission, meaning those who received olanzapine for several months past the beginning of the double-blind, a subgroup will achieve longer efficacy. Again, this reviewer does not think the extent of this effect, if present, can be adequately evaluated from the study data as analyzed. Additionally, any effect seen cannot be generalized to all bipolar I patients with an index manic or mixed episode as the patients who entered double-blind were an "enriched" or responder population.

## C-11. TYPE OF RELAPSE:

At the beginning of the double-blind, there were no statistical differences between groups with regard to type of bipolar index experience, including depression, and psychosis. Rapid cycling patients were more frequent in the olanzapine group. As indicated from the tables below, there was a difference in the type of relapse with more of the olanzapine group relapsing into depression than the placebo group. The significance of this, if any, is unknown.

The Sponsor's table does not provide an exact comparison to the table created by this reviewer as the Sponsor indicated in an email transmission of July 31, 2003 that the mixed group is included in both the depressive and manic groups.

**Table ISE.6.5. Incidence of Protocol-Defined Symptomatic Relapse F1D-MC-HGHL, Double-Blind Maintenance Period Placebo-Controlled Maintenance Database**

| | Placebo (N=136) | Olz (N=225) | Fisher's Exact P-value |
|---|---|---|---|
| Bipolar Relapse*1 | 109 (80.1%) | 105 (46.7%) | <.001 |
| Depressive Relapse*2 | 65 (47.8%) | 78 (34.7%) | 0.015 |
| Manic Relapse*3 | 56 (41.2%) | 37 (16.4%) | <.001 |

N - Number of patients randomized.
*1 - Bipolar relapse is defined as meeting criteria for either manic or depressive relapse.
*2 - Depressive relapse is defined as a HAMD-21 total score of 15 or greater or hospitalization due to depression at any time during double-blind therapy.
*3 - Manic relapse is defined as a YMRS total score of 15 or greater or hospitalization due to mania at any time during double-blind therapy.

As created by this reviewer from data submitted in the RELAPSE.xpt file of the submission.

| | Relapsers | |
|---|---|---|
| | Placebo (n=109) | Olanzapine (n=105) |
| Depression | 53 (48.63%) | 68 (64.76%) |
| Mania | 44 (40.37%) | 27 (25.71%) |
| Mixed | 12 (11.01%) | 10 (9.52%) |

## C-12. DATA FROM QUESTIONABLE SITES

This reviewer examined the results [ ] without site 34, and without sites 34 [ ] using the [ ] datafile RELAPSE.xpt for HGHL. The median time to discontinuation for any event is 65 days for the olanzapine treated group and 22 days for the placebo group when dropping site /. The median time to event is 55 days for the olanzapine treated group and 20 days for the placebo treated group when site 34 is dropped. Dropping both sites [ ] 34, the median time to discontinuation for any event is 58 days for the olanzapine treated group and 22

b(4)

days for the placebo treated group. [redacted] b(7)

[redacted]

**D. Efficacy Conclusions**

The pivotal study HGHL demonstrates a clear statistical difference in time to an occurrence of either a manic, mixed, or depressive episode between the placebo and olanzapine groups of patients who were considered remitted from an index episode of mania or mixed after 6-12 weeks of olanzapine treatment and a clear separation of placebo and olanzapine groups with regard to initial rate of "relapse". However, clinical efficacy for up to [redacted], as implied in the language of the proposed label, encompasses more than the demonstration of significance on statistical measures of primary efficacy as defined in the pivotal study and requires one to frame the statistical significance within the entire picture the data provide. Therefore, long-term, "up to [redacted]" treatment is not supported by the pivotal trial data given that attrition rates in the olanzapine treatment group are such that at day 56 of double-blind treatment, 50 % percent of the olanzapine-treated patients are no longer in the study. Much of the statistical effect of separation is driven by the rapid relapse of placebo patients after drug withdrawal. Additionally, this trial may suggest that the time in "remission" was too short to adequately assess the long term effect of olanzapine treatment as these patients may have met remission criteria but perhaps were not in a stable clinical remission. b(4) b(4)

The pivotal study data indicate an extension of acute efficacy longer than the three to four weeks for which olanzapine is currently labeled. Determining the length of this efficacy is difficult as this reviewer is unsure when to begin the clock. The open-label period before randomization is considered to have lasted 6-12 weeks (although this is not = to total time on olanzapine alone as medication tapers co-existed with the introduction of olanzapine). Using these time points, a range of 14 weeks to 20 weeks is obtained. If one uses the actual time between the two consecutive visits, this would be approximately 10 weeks total. If one uses the time representing the two larger groups percentage-wise in the Sponsor's table HGHL.14.11 (page 27 of this review)"Days in Remission" , this would be 2 months + 7 to 21 days for a maximum of 3 months. Clarification of the time of protocol defined remission before randomization will be asked of the Sponsor to aid in this assessment.

If an approvable action is granted, in a response to this action, the Sponsor will need to supply clarification and further analysis.

D-1. OTHER STUDIES: SYNOPSES

**STUDY HGHT: Olanzapine Versus Lithium in Relapse Prevention in Bipolar Disorder (Please see the appendix for a Sponsor-provided figure of the study design.)**

This was a randomized, double-blind, parallel study to assess the efficacy of olanzpaine compared with lithium in the "prevention of relapse into a manic, mixed, or depressed episode among bipolar patients who met symptomatic remission criteria of an index manic or mixed episode after 6 to 12 weeks of acute, open-label olanzapine and lithium combination therapy." Remission and relapse criteria were the same as that of HGHL except there was no provision for hospitalization as relapse. Primary efficacy analysis was of symptomatic relapse.

543 patients entered the open-label period. 431 patients entered the double-blind taper period and were randomized 1:1 to either olanzapine or lithium. 101 olanzapine patients and 70 lithium patients were considered as "Reporting Interval Completed". The open-label disposition table reflects that 6.8% discontinued secondary to "patient decision", 6.3% secondary to "adverse event" and 2.9% secondary to "lack of efficacy". The double-blind disposition table indicates that, in the olanzapine group, 18.9% discontinued secondary to an adverse event, 14.3% secondary to "lack of efficacy", and 11.1% secondary to "patient decision". For the lithium group, discontinuations in the double-blind period included, 25.7% for an adverse event, 15.9% for "lack of efficacy", and 12.6% secondary to "patient decision".

As per the Sponsor, olanzapine was noninferior to lithium in the rate of symptomatic relapse of bipolar disorder, with 38.8% of the lithium and 30.0% of the olanzapine-treated patients relapsing. Early in the study, time-to-symptomatic relapse was higher for the olanzapine treated group and statistically significantly more patients relapsed during the 4-week drug taper phase. The Sponsor proposed this may arise from lithium discontinuation effects and noted that time-to-relapse curves favored olanzapine at the end of one year of double-blind treatment.

Using the Sponsor- provided datafile, RELAPSE.xpt for this study, 50% of the lithium group is out of the study at approximately day 193 and 50% of the olanzapine group is out of the study at day 252.

## STUDY HGHQ: OLANZAPINE VERSUS DIVALPROEX IN THE TREATMENT OF ACUTE MANIA **(Please see the appendix for a Sponsor-provided figure of the study design.)**

This was a randomized, double-blind parallel study designed to assess non-inferiority ( measured by reduction from baseline on the YMRS) of olanzapine over divalproex in improving overall manic symptomatology after acute treatment. Patients were in an acute manic or mixed episode at study entry and were to be off all other concomitant CNS active medications, except allowed benzodiazepines, within one day of beginning the double-blind acute phase. Secondary objectives included assessment of continued efficacy in a 44-week double-blind extension phase.

251 patients were randomized into the acute treatment phase and167 were randomized into the double-blind extension phase. These patients continued the drug that was started in the acute phase. A combined double-blind acute and extension disposition table indicates about 15% of each group (n=19/125 olanzapine and 20/126 divalproex) completed the study. Discontinuations in the olanzapine group included 24.8% secondary to an adverse event, 19.2% secondary to "lack of efficacy" and 18.4% due to "patient decision". Discontinuations in the divalproex group included 19.8% secondary to an adverse event, 22.2% secondary to "lack of efficacy" and 15.9% secondary to "patient decision".

The Sponsor reported that the differences between treatment groups at the end of the acute phase, with regard to the percent of patients with response, was not statistically significant although the percent of patients with response was numerically greater in the olanzapine group. The Sponsor reported there was a statistically significant difference between treatment groups in the estimated time-to-clinical response in favor of olanzapine at the end of acute phase therapy. Time-to-

symptomatic "relapse" curves for mania did not show statistical significance (p 177 HGHQ study report). There was an unplanned interim analysis after 117 patients had completed the acute phase of this protocol. It was determined that an α of .0424 would be used for the one-tailed assessment of non-inferiority in the final analysis and a two-tailed assessment of superiority with an α of .0412.

More olanzapine than divalproex patients gained weight (23.6% versus 13.8%).

## VII. Integrated Review of Safety

### A. Brief Statement of Conclusions

As part of the secondary objectives, the placebo controlled study, HGHL, nominally was designed to assess the safety of long-term olanzapine treatment compared with placebo. The placebo group is reduced by 50% within approximately one month or so. Therefore, HGHL did not generate useful comparative safety information. The ISS includes an integrated analysis of several studies with longer term treatment designs. However, these studies are not designed to establish long-term placebo-controlled safety. The two active-comparator controlled trials, HGHT and HGHQ, have no placebo group. HGFU is combination study using lithium or valproate with olanzapine or placebo and therefore is not directly comparable to HGHL.

Seven olanzapine associated deaths occurred during the clinical trials or within 30 days of discontinuation. Most of the olanzapine deaths were due to suicide. One of the suicides in the olanzapine group was rated by the Investigator as possibly related to study medication. This reviewer believes this possibility cannot be ruled out as this patient was experiencing akathisia and, as per the narrative, had no history of suicide attempt. However, this patient had experienced the loss of a parent within three weeks of this suicide. Cardiac arrest and "arteriosclerotic cardiovascular disease with myocardial fibrosis and diabetes mellitus" account for two other patient deaths in the olanzapine group. (Narratives of these two deaths may be found in the appendix).

Several safety findings are of interest from the controlled trial data in the pivotal study. First, QTcF prolongations of >30msec were seen in 5% of olanzapine patients and 0.8% of placebo patients. QTcF prolongations of > 60 msec was seen in 1.1% of olanzapine patients and no placebo patients. However, there were no stated serious adverse events associated with prolongation.

Second, $\geq$ 7% weight gain was seen in 39.9% of patients in the overall integrated database (of November submission, ISS, p365). Within the pivotal study, no patients categorized as "Other" lost weight while some categorized as "Caucasian" did. The clinical significance is uncertain as the "Other" group is heterogeneous and the numbers are small.

Third, treatment emergent, at any time in the double-blind period, parkinsonism and akathisia were seen more frequently in olanzapine treated patients. Tremor was noted as treatment emergent in >5% of the open-label group.

Fourth, in the olanzapine treated patients, relapse was more often due to depression than relapse in the placebo group. Within the olanzapine group, patients under age 40, showed higher rates of depressive relapse than patients over the age of 40.

Safety findings such as hyperuricemia, hypercholesterolemia, and elevated eosinophil were seen in the pivotal study. Although they are not new or distinct to this patient population, further analysis of these analyte findings may elucidate the extent of drug effect. Otherwise, [redacted] b(4) and glucose issues merit stronger language in the label. Further analysis of depression and suicidality will be requested.

## B. Description of Patient Exposure

The review of safety focuses on the controlled trial HGHL. This reviewer calculates that the numbers of patients actually receiving drug in the controlled period for ≥ 180 days is 63 for olanzapine and 11 for placebo group.

As per the exposure table given by the Sponsor and essentially duplicated below, the total exposures to olanzapine and placebo during the double-blind period were 88.0 patient-years and 29.9 patient years respectively. The modal and mean doses of olanzapine were 10.0 and 12.5 mg/d respectively.

| | Placebo | | Olanzapine | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Duration Days | 0 mg | % | <5mg | 5-<10mg | 10-<15mg | 15- <20 mg | >20mg | Total | % |
| <=30 | 74 | 55.2% | 2 | 12 | 15 | 16 | 21 | 66 | 29.3 |
| 30<-60 | 15 | 11.2% | 0 | 8 | 14 | 6 | 9 | 37 | 16.4 |
| 60< -90 | 11 | 8.2% | 0 | 0 | 11 | 3 | 3 | 17 | 7.6 |
| 90<-120 | 4 | 3.0% | 0 | 1 | 4 | 1 | 2 | 8 | 3.6 |
| 120<-180 | 9 | 6.7% | 1 | 3 | 6 | 4 | 8 | 22 | 9.8 |
| 180<240 | 4 | 3.0% | 0 | 1 | 1 | 5 | 3 | 10 | 4.4 |
| 240<-300 | 3 | 2.2% | 0 | 1 | 1 | 3 | 3 | 8 | 3.6 |
| 300<-360 | 13 | 9.7% | 0 | 6 | 25 | 7 | 10 | 48 | 21.3 |
| >360 | 1 | 0.7% | 0 | 5 | 1 | 0 | 3 | 9 | 4 |
| Total | 134 | 99.9% | 3 (1.3%) | 37 (16.4%) | 78 (34.7%) | 45 (20.0%) | 62 (27.6%) | 225 | 100% |

The Integrated Summary of Safety (November) presents six studies as four databases; one

Table ISS.4.2. Exposure to Olanzapine (5 to 20 mg/day) in Safety Databases

| Database: | Patients/Phases Included | Number of Patients | Exposure | |
|---|---|---|---|---|
| | | | Patient-Days | Patient-Years[a] |
| Overall Integrated Database | See Table ISS.5.1 for description of studies and phases included | 1528 | 216269 | 592.1 |
| Placebo-Controlled Maintenance Database (HGHL) | Patients randomized to olanzapine in double-blind | 225 | 32143 | 88.0 |
| Active-Controlled Maintenance Database (Part 1: HGHT) | Patients randomized to olanzapine in double-blind | 216 | 51216 | 140.2 |
| Active-Controlled Maintenance Database (Part 2: HGHQ) | Patients randomized to olanzapine in double-blind | 125 | 13895 | 38.0 |
| Placebo-Controlled Combination Therapy Maintenance Database (HGFU) | Patients randomized to olanzapine in double-blind extension period for remitters | 72 | 15677 | 42.9 |

[a]Patient-years calculated by dividing patient-days by 365.25.

placebo controlled maintenance database (HGHL), lithium (HGHT) and divalproex (HGHQ) active-controlled maintenance databases, a placebo-controlled combination therapy study (HGFU) and the overall integrated database which includes longer-term olanzapine treatment from studies HGHL, HGHT, HGHQ, HGHD, and HGEH. The Sponsor's summary of the numbers of individuals exposed to olanzapine in the ISS databases is provided below. Readers are referred to the appendix for Table ISS.5.1 for definitions of the safety databases as provided by the Sponsor.

The four month update included an ISS update to add data from HGGY. The 456 patients added to the database from HGGY entered with depressive episode, unlike most of the patients in the original ISS of November submission, in which most of the patients entered with a mixed or manic episode (1537/1545). This updated integrated database includes olanzapine treatment group data from the longer phases of HGGY, HGHL, HGHQ, HGHD, and HGEH. As per the Sponsor, exposure to olanzapine from the Overall Integrated Database as supplied with the update of March 19, 2003 shows a total exposure of 674.9 patient-years and includes 2001 patients. (Databases used in the ISS and the update as provided by the Sponsor are included in the appendix.)

### C. Methods and Specific Findings of Safety Review

Olanzapine has been marketed in the United States since September, 1996. This submission seeks an indication for long-term treatment. This review focuses on the placebo-controlled trial HGHL as it is the pivotal study. Although the active comparator and open-label trial data may be valuable as a screen for very rare and unexpected serious adverse events, they are not directly comparable. The ISS of November, 2002 and the updated of March, 2003 were used in this review as an assessment tool of overall safety. Active comparator and open-label trials submitted did not reveal any new obvious safety concerns.

Within this review, open-label information as well as the double-blind information is at times provided for HGHL. As patient exposure to olanzapine started in the open-label phase, this phase may allow one to glean pieces of information that perhaps are minimized if only viewing the double-blind phase. Weight gain is one such example and is detailed below.

### D. Adequacy of Safety Testing

The combined ISS and ISS update include all studies performed with olanzapine in the bipolar population. The other trials of long-term nature do not produce placebo-controlled data. The pivotal study, a placebo-controlled trial, does not produce long-term comparative safety. In most cases, the Sponsor's analyses showing large denominators reflect data carried forward from an earlier time in the study as less than one half of the patients in either group remains two months after randomization. Fasting laboratory measures, specifically glucose and lipid profiles, would be more helpful in assessing the effects of olanzapine on glucose regulation and lipid profiles respectively. Also, the value set as the upper limit for cholesterol measures is high. Formal assessment of suicidality was not performed.

## E. Summary of Critical Safety Findings and Limitations of Data

### E-1. HGHL: DEATHS

There were no deaths in the double-blind treatment phase of the study. Two patients died within 30 days of completion or discontinuation of the study. One completed suicide 3 weeks after withdrawing consent to return to his doctor. A second died from cardiac arrest after experiencing a stroke 28 days after discontinuation from the study. These deaths are not obviously drug-related. Narratives may be found in the appendix.

### E-2. HGHL: SERIOUS ADVERSE EVENTS

There were no unexpected, previously unreported, or unlabeled serious adverse events related to olanzapine treatment.

The Sponsor reports that thirty-eight patients experienced serious adverse events in the open-label treatment phase. Of these, 3 were suicide attempt, 6 were suicidal ideation, 5 were depression or depression aggravated, 6 were mania or mania aggravated, 3 were bipolar disorder or bipolar affective disorder aggravated, and 3 were alcoholism. Akathisia, anxiety aggravated, confusion, convulsion not otherwise specified (NOS), hypersensitivity NOS, homicidal ideation, dyskinesia, overdose NOS, panic attack, paranoia aggravated, pneumonia, and ventral hernia repair accounted for one each.

The event of "convulsion NOS" occurred after approximately 10 weeks of dosing in a patient with no history of seizure disorder and a history of prior alcohol abuse. The patient was experiencing suicidal thoughts, drank a "fifth of vodka, some whiskey, and later had a seizure". The site felt this convulsion was related to alcohol abuse. At the time, it appears the blood alcohol level was high. The patient was treated with two anti-convulsants and was hospitalized for "alcoholism, convulsions NOS, and depression suicidal". The narrative is not detailed, contains possible confounders, and the incidence is not above that for which olanzapine is currently labeled.

In the double-blind period, seven olanzapine treated patients experienced nine different types of serious adverse events. Ten placebo patients experienced 11 serious adverse events (six different types of events). The Sponsor's indicates that 4 patients experienced bipolar I disorder in the placebo group versus none in the olanzapine group. There was one suicide attempt in this period which occurred with an olanzapine treated patient. Two placebo patients experienced suicidal ideation.

Table ISS.6.6. Serious Adverse Events
HGHL, Double-Blind Treatment
Placebo-Controlled Maintenance Database

| | Therapy | | | | | | Fishers Exact Test |
|---|---|---|---|---|---|---|---|
| | | Placebo | | | Olz | | |
| Serious Adverse Events | N | n | % | N | n | % | p-Value |
| Patients who had SAEs | 136 | 10 | 7.4% | 225 | 7 | 3.1% | 0.076 |
| Mania | 136 | 2 | 1.5% | 225 | 1 | 0.4% | 0.559 |
| Bipolar disorder | 136 | 1 | 0.7% | 225 | 1 | 0.4% | 1.000 |
| Aggression | 136 | 0 | 0.0% | 225 | 1 | 0.4% | 1.000 |
| Agitation | 136 | 0 | 0.0% | 225 | 1 | 0.4% | 1.000 |
| Agitation aggravated | 136 | 0 | 0.0% | 225 | 1 | 0.4% | 1.000 |
| Depression aggravated | 136 | 0 | 0.0% | 225 | 1 | 0.4% | 1.000 |
| Non-accidental overdose | 136 | 0 | 0.0% | 225 | 1 | 0.4% | 1.000 |
| Ovarian cancer NOS | 83 | 0 | 0.0% | 138 | 1 | 0.7% | 1.000 |
| Suicide attempt | 136 | 0 | 0.0% | 225 | 1 | 0.4% | 1.000 |
| Bipolar I disorder | 136 | 4 | 2.9% | 225 | 0 | 0.0% | 0.020 |
| Suicidal ideation | 136 | 2 | 1.5% | 225 | 0 | 0.0% | 0.141 |
| Chest pain | 136 | 1 | 0.7% | 225 | 0 | 0.0% | 0.377 |
| Delusion NOS | 136 | 1 | 0.7% | 225 | 0 | 0.0% | 0.377 |

## E-3. HGHL: DISCONTINUATIONS DUE TO ADVERSE EVENTS

In the open-label treatment phase, 75 patients discontinued secondary to adverse events. Ten of these were secondary to weight gain, nine secondary to sedation, seven secondary to fatigue, 11 secondary to either depression or depression aggravated, seven secondary to either liver function tests NOS or hepatic function abnormal NOS or AST increased, three secondary to either mania or mania aggravated, and two each to suicidal ideation or suicide attempt. Of the remaining discontinuations, one was secondary to angioneurotic edema, one to edema, one to peripheral swelling, and one to syncope.

In the double-blind treatment phase, thirty five olanzapine-treated (15.6%) and 12 (8.8%) placebo-treated patients discontinued secondary to an adverse event. In the olanzapine group, the most frequent reasons for adverse event related discontinuations were depression aggravated (9/225), liver function tests NOS abnormal(3/225), weight increased (3/225), depression (2/225), and insomnia (2/225). In the placebo group, the most frequent reasons for adverse event related discontinuations were bipolar I disorder (4/136), mania (2/136), and depression (2/136). Depression + depression aggravated resulted in the discontinuation of 4.88% of the olanzapine treated group

One olanzapine treated patient discontinued due to an EKG related adverse event captured as an EKG abnormality NOS versus no placebo patients.

## E-4. HGHL: TREATMENT EMERGENT ADVERSE EVENTS (TEAEs)

In the open-label phase of the study, the most commonly reported ($\geq$ 5%) treatment emergent adverse events were weight increased (18.6%), dry mouth (16.7%), appetite increased NOS (15.5%), somnolence (15.2%), sedation (12.9%), fatigue (11.5%), dizziness (7.3%), headache NOS (7.1%), and tremor (6.6%).

In the double-blind period, TEAEs reported at $\geq$ 5% and twice the frequency seen in the placebo group were weight increased (8.0%), headache NOS (6.7%), fatigue(6.2%), and depression (5.8%). In the placebo group, the most commonly reported TEAEs and reported at $\geq$ 5% were insomnia, depression aggravated, and anxiety. Depression and depression aggravated occurred in 8.09% of the placebo group and 11.6% of the olanzapine-treated patients. Interpretation of the

depression data is confounded by the fact that although both groups have high attrition rates, the placebo group undergoes a very rapid drop early in the study.

Table ISS.6.8. Treatment-Emergent Adverse Events with Olanzapine Incidence of at Least 2% or with Statistically Significant Treatment Group Difference
HGHL, Double-Blind Treatment
Placebo-Controlled Maintenance Database

| | Therapy | | | | | | Fisher's Exact Test |
|---|---|---|---|---|---|---|---|
| | Placebo | | | Olz | | | |
| Event Classification | N | n | % | N | n | % | p-Value |
| Weight increased | 136 | 2 | 1.5% | 225 | 18 | 8.0% | .008 |
| Headache NOS | 136 | 4 | 2.9% | 225 | 15 | 6.7% | .149 |
| Fatigue | 136 | 2 | 1.5% | 225 | 14 | 6.2% | .036 |
| Depression | 136 | 4 | 2.9% | 225 | 13 | 5.8% | .306 |
| Depression aggravated | 136 | 7 | 5.1% | 225 | 13 | 5.8% | 1.00 |
| Anxiety | 136 | 7 | 5.1% | 225 | 11 | 4.9% | 1.00 |
| Nasopharyngitis | 136 | 3 | 2.2% | 225 | 11 | 4.9% | .266 |
| Irritability | 136 | 5 | 3.7% | 225 | 9 | 4.0% | 1.00 |
| Weight decreased | 136 | 3 | 2.2% | 225 | 9 | 4.0% | .546 |
| Akathisia | 136 | 0 | 0.0% | 225 | 7 | 3.1% | .048 |
| Diarrhoea NOS | 136 | 4 | 2.9% | 225 | 6 | 2.7% | 1.00 |
| Influenza | 136 | 6 | 4.4% | 225 | 6 | 2.7% | .379 |
| Somnolence | 136 | 2 | 1.5% | 225 | 6 | 2.7% | .715 |
| Erectile dysfunction NOS | 53 | 1 | 1.9% | 87 | 2 | 2.3% | 1.00 |
| Hypertension NOS | 136 | 1 | 0.7% | 225 | 5 | 2.2% | .416 |
| Insomnia | 136 | 19 | 14.0% | 225 | 5 | 2.2% | <.001 |
| Rash NOS | 136 | 0 | 0.0% | 225 | 5 | 2.2% | .161 |
| Upper respiratory tract infection NOS | 136 | 4 | 2.9% | 225 | 5 | 2.2% | .734 |
| Amenorrhoea NOS | 83 | 1 | 1.2% | 138 | 3 | 2.2% | 1.00 |
| Bipolar I disorder | 136 | 4 | 2.9% | 225 | 0 | 0.0% | .020 |

Subgroup analysis by age <40 and ≥ 40 indicates that within bipolar patients who responded to olanzapine initially, depression occurs more frequently in patients <40 years old versus patients > 40 years old. Although the overall representation of "Other" is about 13% only of the treatment group and the group "Other" is heterogeneous, "Caucasian" lost weight more frequently than "Other". This weight loss may reflect, in part, loss of weight gained in the open-label phase.

| Event | Age | Placebo N | Placebo n | % | Olanzapine N | Olanzapine N | % | Homogenity Of Odds Ratio | Between group comparison within strata |
|---|---|---|---|---|---|---|---|---|---|
| **Depression** | <40 | 69 | 0 | 0 | 104 | 9 | 8.7 | .009 | .300 |
| | ≥40 | 67 | 4 | 6.0 | 121 | 4 | 3.3 | | .539 |
| **Weight Decreased** | C | 120 | 2 | 1.7 | 195 | 9 | 4.6 | .052 | .216 |
| | O | 16 | 1 | 6.3 | 30 | 0 | | | .348 |

C=Caucasian, O=other

Subgroup analysis of treatment emergent abnormal high or low laboratory values at any time in the double-blind treatment period demonstrated hematologic findings of uncertain clinical significance. For example, decreased lymphocytes were seen more frequently in Other than Caucasian (3/29 versus 2/181).

## E-5. MEASURES OF CENTRAL TENDENCY

The Sponsor reports that the mean laboratory analyte values from baseline to endpoint in the double-blind treatment phase of HGHL demonstrated statistically significant differences but not clinically significant differences in measures from baseline to endpoint for monocytes, cholesterol, uric acid, urine pH, and prolactin. Visual inspection of the analyte data of table

provided by the Sponsor, ISS.6.10, (reader is referred to the appendix), shows that for some analytes, a difference in the direction of the measure for the placebo versus olanzapine groups is seen. In the placebo group, this may reflect the effect of olanzapine withdrawal. For example, uric acid is decreased by 18.76 in the placebo group yet increased by 8.30 in the olanzapine group. In the open-label phase, uric acid mean at baseline is 313.68 and increases by 18.97.

**E-6. OUTLIER ANALYSIS:**

- **HGHL: POTENTIALLY CLINICALLY SIGNIFICANT (PCS) ADVERSE EVENTS**

Sponsor-provided tables detailing criteria for PCS adverse events may be found in the appendix as ISS.5.3, ISS 5.4, ISS5.5, and ISS 5.6.

In the open-label phase, three olanzapine treated patients had syncopal episodes, two had diabetes/adult onset diabetes, one had hypercholesterolemia, and one had borderline QTc prolongation. One patient coded as diabetes mellitus in the open-label phase experienced an increase in the non-fasting glucose of >2 fold and glucose in the urine. Another case with baseline high glucose reached levels requiring treatment. Double-blind data is shown below in the Sponsor-provided table HGHL.14.26.

**Table HGHL.14.26. Listing of Treatment-Emergent Adverse Events Considered Potentially Clinically Significant Double-Blind Treatment**

| Patient ID | Visit | Event | Start Date | Stop Date | Severity |
|---|---|---|---|---|---|
| | | | | | |
| **Olanzapine** | | | | | |
| 008-0358 | 107 | Hypercholesterolemia | 09 May 2001 | none | mild |
| 028-1357 | 105 | Diabetes mellitus NOS | Oct 1998 | none | moderate |
| 028-1362 | 107 | Blood cholesterol increased | 27 Sept 2001 | none | moderate |
| 041-2003 | 104 | Diabetes mellitus NOS | 1974 | none | severe |
| 200-8603 | 101 | Diabetes mellitus NOS | 1 Mar 2001 | none | moderate |
| | | | | | |
| **Placebo** | | | | | |
| 015-0703 | 114 | Diabetic retinopathy | 5 April 2001 | none | mild |
| 025-2106 | 108 | Supraventricular tachycardia | Feb 1995 | none | moderate |

Source: RMP.FIDSHGHL.SASPGM(PCSY02DB)

- **POTENTIALLY CLINICALLY SIGNIFICANT CHANGES (PCS)**

Three olanzapine patients demonstated PCS non-fasting glucose levels and two had PCS urine glucose levels (2/155 versus 0/104 placebo). Three olanzapine treated patients and no placebo-treated patients discontinued due to non specific abnormal liver function tests. 3/207 (1.4%) of olanzapine treated patients experienced PCS non-fasting glucose levels versus 0/124 in placebo. Three olanzapine patients discontinued secondary to weight gain compared to no placebo treated patients.

Orthostatic hypotension as defined as 20mmHG decrease in systolic blood pressure concurrent with a 10bpm increase in pulse standing versus supine was seen in 7.9% (13/165)of the olanzapine group and 2.1% (2/97) patients in the placebo group.

- **HGHL: TREATMENT-EMERGENT HIGH OR LOW VALUES AT ANY TIME**

The Sponsor notes there were no statistically significant treatment group differences at any time in the double-blind treatment. Alkaline phosphatase elevations, ALT, Basophils, GGT, Hemoglobin A1C, prolactin (11.5% versus 3.1%), mean hemoglobin concentrations (MCHC) elevations, segmented neutrophils, and urine nitrites occurred at rates greater than 2% and at least twice the frequency as seen in the placebo group. Treatment emergent high eosinophil counts were seen in 1.5% of the open-label patients, of which 0.2 % were PCS, and 1.9% (4/211) of olanzapine treated patients and no placebo treated patients (0/121) in the double-blind period. None of the elevated eosinophil counts in the double-blind period were considered PCS.

Bicarbonate (44/176 olanzapine versus 16/102 placebo), and non-fasting glucose, bilirubin (21/158 olanzapine versus 6/83 placebo) reductions occurred at rates of > 2%. Both high (6.7%olanzapine versus 1.8% placebo) and low segmented neutrophils occurred. Urine ketones and urine protein were seen almost equally between groups (~4.8% and ~4.0%) although given the numbers in the placebo group (n=102), this data is likely to include LOCF from early in the double-blind period and may reflect the effect of olanzapine on both groups. Elevations in AST, uric acid, CPK, leukocyte count also were seen at similar rates in both olanzapine and placebo groups. The placebo group number is high, therefore it is likely this data is from early in randomization.

- **HGHL: TREATMENT EMERGENT HIGH NON-FASTING GLUCOSE OPEN-LABEL ACUTE TREATMENT**

Treatment –emergent nonfasting glucose values of at least 13.875 mmol/L (250 mg/dL) were considered potentially clinically significant and occurred in six patients (6/645). 10/637 patients (1.6%) experienced values considered suggestive of diabetes (≥ 11.1 mmol/L or 200 mg/dL). Additionally, glycosylated hemoglobin (HbA1c) was evaluated in HGHL. (Page 177 HGHL main study report).

The Sponsor notes that three of the10 with values suggestive of diabetes had known pre-existing diabetes. The remaining seven had neither a clinical diagnosis of diabetes nor use of anti-diabetic therapy prior to study entry, although one had a history of hyperglycemia and was overweight with a BMI of 28.6. The Sponsor notes all had one major risk factor for diabetes. Of the six remaining, one patient aged 69 was neither overweight nor with a baseline elevated hemoglobin A1c.

- **TREATMENT EMERGENT GLUCOSE ABNORMALITIES DOUBLE-BLIND**

High non-fasting glucose values considered potentially clinically significant, as defined above, occurred in 3/207 (1.4%) of the olanzapine treated patients and none of the placebo patients. Non-fasting glucose values suggestive of diabetes occurred in 3/206 olanzapine and 2/122 placebo treated patients. Of the two placebo patients, one had only one occurrence of an elevated non-fasting glucose and had risk factors for diabetes including being overweight. The other patient had a pre-existing history of diabetes and was on metformin. Of the three

olanzapine-treated patients, one was not overweight at baseline but became overweight and at had an elevated HbA1C at the beginning of open-label. Both of the other two patients gained weight in the study and had elevated HbA1c measures at the beginning of the open-label period.

**VITAL SIGNS AND WEIGHT** (Sponsor-provided tables ISS.6.15 and ISS 6.16 may be found in the appendix)

Olanzapine treated patients showed a significantly different change in weight from baseline of the double-blind treatment period to endpoint. From the beginning of the open-label period at which the mean weight was 83.18 kg to the end of open-label, the mean change to endpoint was 3.05 kg (p168/17467). The mean weight of patients entering the double-blind period was 85.94kg. Additionally, 29.1% of patients in the open-label acute treatment phase experienced potentially clinically significant changes in weight (increase of at least 10% of body weight as defined in the HGHL study report, p 71).

During the double-blind period, weight gain was seen in 16.1% (36/224) of the olanzapine patients and 3/133 (2.3%) of the placebo patients while weight loss was seen in 7.1% of the olanzapine patients and 12.8% of the placebo patients.

Orthostatic hypotension was seen at ~ 3.5x the rate in olanzapine treated patients than in placebo treated patients (7.9% and 2.1% respectively).

**E-7. HGHL: EKG CHANGES:**

One patient discontinued treatment in the olanzapine group secondary to abnormal EKG NOS (not otherwise specified). No EKG related discontinuation occurred in the placebo group.

QRS prolongation, as defined a priori, was seen at greater than 3 times the rate in the olanzapine treated group versus the placebo group and in 7.8% (12/153) of the olanzapine treated patient versus 2.0% (2/101) of the placebo treated patients (p=.052).

The Sponsor performed additional analyses of QT intervals with criteria as defined in the appendix. A tendency to QT prolongation was seen in the olanzapine treatment group. This was not seen in the placebo group. The Sponsor notes the incidence of potentially significant prolonged QT intervals tended to be numerically higher in the drug treated patients versus the placebo treated patients although incidence was low overall. There was a difference in the incidence of patients with an increase of at least 30ms on the QTcB.

QTcB prolongation was seen in 4.5% (8/179) of the olanzapine treated patients and 0.9% (1/117) of the placebo treated patients. QTc prolongation >60msec by Fridericia's and by Bazett's was seen only in the olanzapine treated group with 2/181 seen with each method.
Corrected QTc Intervals (Taken from Sponsor table HGHL.12.32.)

| | QTcB>= 30msec | p-value | QTcB Male>=450msec/Female>=470 msec | p-value | QTcF Male>=430msec/ Female>=450msec | p-value | QTcF >=30msec | p-value | QTcF >=60 msec | p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| P | 1/118 (0.8%) | .032 | 1/117 (0.9%) | .093 | 3/115 (2.6%) | .535 | 1/118 (0.8%) | .095 | 0/118 | .521 |
| O | 11/181 (6.1%) | | 8/179 (4.5%) | | 8/174 (4.6%) | | 9/181 (5.0%) | | 2/181 (1.1%) | |

Mean changes from baseline to endpoint in QTcB and QTcF are as follows (Sponsor provided Table HGHL.12.30.) As outlined in this table, these changes are unlikely to be clinically significant. Additionally, the high numbers (n) indicate that these are not representative of end of study data.

Table HGHL.12.30. Electrocardiogram Intervals and Heart Rate
Mean Change from Baseline to Endpoint
Double-Blind Treatment

Research Project Code: F1D

| Variables Analysed | Therapy | n | Baseline Mean | Baseline SD | Change to Endpoint Mean | Change to Endpoint SD | p-Values Therapy |
|---|---|---|---|---|---|---|---|
| RCGHR | Placebo | 118 | 74.19 | 12.91 | -2.10 | 11.29 | .113 |
| | Olz | 181 | 75.06 | 12.28 | 0.19 | 12.54 | |
| INTPRSEC | Placebo | 118 | 0.15 | 0.02 | -0.00 | 0.01 | .865 |
| | Olz | 181 | 0.15 | 0.02 | -0.00 | 0.01 | |
| INTQRSEC | Placebo | 118 | 0.08 | 0.01 | -0.00 | 0.01 | .393 |
| | Olz | 181 | 0.08 | 0.01 | 0.00 | 0.01 | |
| QTCB | Placebo | 118 | 422.40 | 18.40 | -5.38 | 16.80 | .001 |
| | Olz | 181 | 421.06 | 19.43 | 1.60 | 17.32 | |
| QTCF | Placebo | 118 | 408.71 | 16.72 | -3.34 | 13.14 | .010 |
| | Olz | 181 | 406.52 | 18.09 | 1.67 | 16.43 | |
| INTQTMSC | Placebo | 118 | 383.64 | 30.86 | 0.38 | 24.55 | .668 |
| | Olz | 181 | 379.78 | 30.13 | 2.01 | 30.25 | |

Note: The following investigators were pooled
004 007 010 011 013 607 610 611 613 614
015 018 021 038 034 036 041 042 050

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On Original

## E-8. EPS

Extrapyramidal symptoms (EPS) were assessed using the Barnes Akathisia Scale, the Simpson-Angus Scale, and the AIMS. Mean change from baseline to endpoint (LOCF) was assessed with ANOVA for between-group comparisons and with Student's t-test for within group comparison. Treatment-emergent parkinsonism was assessed as the proportion of patients with a Simpson-Angus scale total score >3 at any double-blind visit/patients with a total score $\leq 3$ at baseline. Treatment emergent akathisia was assessed similarly with a Barnes Akathisia global score $\geq 2$ at any double-blind visit among those with a baseline <2. Treatment-emergent abnormal dyskinetic movements were assessed using the proportion of patients with a score of $\geq 3$ on any one of the AIMS items 1-7 or a score of $\geq 2$ on any two of the AIMS items 1-7 at any double-blind visit among those without either of these scores at baseline.

The Sponsor's analyses of treatment emergent EPS at anytime in the open-label acute period shows 4.5% of olanzapine treated patients (30/669) demonstrating symptoms of parkinsonism as evidenced by Simpson-Angus scores and 8.2% (52/638) of the patients developing akathisia as noted by Barnes scores. As taken from the Sponsor's table HGHL.12.13, during the open-label acute treatment period, EPS scores mean change from baseline to endpoint were:

| Variable | Therapy | n | Mean baseline | Standard Deviation | Mean endpoint | Standard Deviation | **p-value within group** |
|---|---|---|---|---|---|---|---|
| Simpson Total | OLZ | N=697 | 0.43 | 1.38 | -0.07 | 1.30 | 0.082 |
| Barnes 04 | OLZ | N=698 | 0.27 | 0.59 | -0.14 | 0.61 | <.001 |

Data from the double-blind treatment phase is shown below. Given the numbers in the groups (n) , these may not represent extended treatment as patients were not in the study.

**Table 7.1. EPS Rating Scales Mean Change from Baseline to Endpoint F1D-MC-HGHL**

| | | | Baseline | | Change to Endpoint | | Therapy Effect p-Values | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | **Therapy** | **N** | **Mean** | **SD** | **Mean** | **SD** | **Original** | **Corrected** |
| Simpson-Angus Total | Placebo | 134 | 0.30 | 1.00 | -0.03 | 0.75 | .487 | .811 |
| | Olz | 224 | 0.29 | 1.01 | 0.01 | 0.87 | | |
| Barnes Global | Placebo | 134 | 0.03 | 0.24 | 0.17 | 0.50 | .007 | .066 |
| | Olz | 224 | 0.09 | 0.37 | 0.03 | 0.42 | | |
| AIMS Total | Placebo | 134 | 0.06 | 0.34 | 0.10 | 0.63 | .110 | .091 |
| | Olz | 224 | 0.13 | 0.68 | -0.01 | 0.41 | | |

Abbreviation: AIMS = Abnormal Involuntary Movement Scale; Olz = olanzapine; SD = standard deviation.

Table HGHL.12.34. Extrapyramidal Scale Scores
Categorical Analyses
Double-Blind Treatment

| Treatment Emergent EPS | Therapy | N | n | (%) | Fisher's Exact P-Value |
|---|---|---|---|---|---|
| Parkinsonism (Simpson-Angus)-Anytime | Placebo | 118 | 0 | 0.0% | .163 |
| | Olz | 206 | 5 | 2.4% | |
| Akathisia (Barnes)-Anytime | Placebo | 119 | 1 | 0.8% | .096 |
| | Olz | 194 | 9 | 4.6% | |
| Dyskinesia (AIMS)-Anytime | Placebo | 133 | 1 | 0.8% | .381 |
| | Olz | 216 | 0 | 0.0% | |
| Dyskinesia (AIMS)-End Point | Placebo | 133 | 1 | 0.8% | .381 |
| | Olz | 216 | 0 | 0.0% | |
| Dyskinesia (AIMS)-Last 2 Visits | Placebo | 133 | 0 | 0.0% | |
| | Olz | 216 | 0 | 0.0% | |

## E-9.OTHER STUDIES/INTEGRATED DATABASES

### E-9a. Deaths:

Including the pivotal study, seven olanzapine treated patients died either during the clinical trials or within 30 days of discontinuation. Two lithium and 3 placebo deaths were noted. Most of the olanzapine and placebo deaths and one of the lithium deaths were due to suicide. One of the suicides in the olanzapine group was rated as possibly related to study medication. This patient experienced the death of a parent three weeks earlier, had been experiencing akathisia for several months, and did not have a prior history of suicide attempt. Given the ongoing akathisia, some degree of association with the study drug cannot be ruled out. Cardiac arrest/stroke and "arteriosclerotic cardiovascular disease with myocardial fibrosis and diabetes mellitus" account for two patient deaths in the olanzapine group. These two deaths do not appear likely to be related to the drug.

Rates of suicide attempt and suicidal ideation are listed as .08% and 2.9% for the treatment emergent adverse events in the Integrated Database (HGHL, HGHT, HGHQ, HGHD, and HGEH). No formal assessment of suicidality is presented.

HGHT: No olanzapine patients died. Two lithium treated patients died in the double-blind phase, one by suicide after 8 months of treatment, the other, from injuries sustained subsequent to car versus pedestrian collision nine months into treatment.

HGHQ: One olanzapine treated patient died in the double-blind phase after 13 days of treatment secondary to injuries sustained in a motorcycle accident. Although the narrative does not provide contributory details otherwise, it may be found in the appendix.

HGHD: One olanzapine treated patient completed suicide in the extension phase of the study. This event was thought by the Investigator to be possibly related to the study drug as akathisia was ongoing at the time. Based on the narrative, this possibility cannot be ruled out. However, the patient had experienced the death of a parent three weeks earlier.

HGEH: One olanzapine treated patient was found dead one day after completing the open-label extension. The autopsy report indicated the patient died of "arteriosclerotic cardiovascular disease with myocardial fibrosis and diabetes mellitus as contributing factors". This does not

appear likely to be caused by olanzapine. The narrative may be found in the appendix of this document.

HGFU: OPEN-LABEL EXTENSION: There were no patient deaths during the extension phase.

HGGY: 6 MONTH OPEN-LABEL EXTENSION/ACUTE PHASE UPDATE (Olanzapine monotherapy versus placebo) Five deaths occurred during the study or within 30 days of completion. Two were of olanzapine treated patients. One patient who completed acute treatment with olanzapine and then moved into open-label, committed suicide by hanging approximately two-three weeks after starting open-label. The second patient completed the acute phase randomized to olanzapine and continued into the open-label phase. This patient committed suicide by hanging two days after starting open-label. As suicide is a risk of bipolar illness, it is difficult to determine relatedness to treatment efficacy. Narratives may be found in the appendix. There were two suicides and one homicide in the placebo treated group during the double-blind period.

**E-9b. Serious Adverse Events (SAES):**

**HGHT:** 20 % of the olanzapine treated and 29.4% of the lithium treated patients experienced serious adverse events. The most common serious adverse events in the olanzapine group were mania, depression NOS, hypomania, and anxiety "NEC". The most common serious adverse events in the lithium treated patients were mania, depression NOS, bipolar I disorder, and hypomania. Mania occurred more frequently in the lithium group (15.9% versus 6.9%). Syncope and blood cholesterol increased were reported in two and one patients respectively for olanzapine. One event of syncope was considered PCS. One syncope resulted in discontinuation.

**HGHQ:** The most common serious adverse events that occurred in the double-blind and extension phases of the study for both treatment groups were suicidal ideation and depression NOS. There was no statistical difference between groups for any event. Liver function test abnormalities occurred in two (1.6%) of the olanzapine treated patients and none of the divalproex treated patients.

**HGHD OPEN-LABEL EXTENSION:** It appears that 43 patients experienced adverse events in the open-label extension. Manic reaction was the most common (4.4%). Out of 249 patients, one patient each experienced deep thrombophlebitis and pulmonary embolism, hypotension, grand mal convulsion, myocardial infarction, and septo apical cardiac aneurysm (p 30, HGHD_open.pdf). Three patients experienced treatment emergent diabetes mellitus during the open-label extension per the text (HGHD_OPEN. pdf) although only one is listed in table HGHD.4.17.

**HGEH OPEN-LABEL EXTENSION:** The Sponsor states, "No patients experienced an adverse event that was serious, unexpected, and possibly causally-related to study drug during or within 30 days of discontinuation from the trial."

**HGFU EXTENSION PHASE:** Fourteen patients experienced 19 SAEs of 11 different types, with depression the most common (n=8, 8.1%).

**HGGY ACUTE:** Of adverse events leading to discontinuation, suicidal ideation occurred in 3/370 or 0.8% of the olanzapine treated group, 2/377 or 0.5 % of the placebo treated group, and 1/86 or 1.2% of those on combination olanzapine and fluoxetine. Suicidal depression occurred in 1/370 patient (0.3%) in the olanzapine group and none of the placebo group. Suicide attempt occurred in 2/377 or 0.5% of the placebo patients and 1/370 or 0.3% of the olanzapine patients.

**HGGY OPEN-LABEL EXTENSION:** Twenty-two serious adverse events were reported by 19 patients. The serious adverse event of depression occurred at 4.4% and suicide attempt occurred in 0.7%, two of whom completed. Congestive heart failure and deep venous thrombophlebitis occurred in 1 patient each out of 562 (0.2%).

**Integrated Database Serious Adverse Events/Adverse Events:** As per the March 19, 2003 update, the Sponsor reports that 11.1% or 223 olanzapine-treated patients experienced 127 different types of serious adverse events (333 events in total). Mania occurred in 42/2001(2.4%) patients, depression (1.8%), suicidal ideation (1.5%), suicide attempt (0.7%), completed suicide (0.1%), homicidal ideation (0.1%), depression suicidal (0.1%), depressed mood (0.3%), and depression aggravated (0.2%).

Although depression is expected in bipolar illness, depression as an adverse event is seen throughout the databases. Additionally, the Sponsor notes that there was a statistically greater incidence of depression NOS in olanzapine-treated patients in HGHT (November, ISS p.47). The Sponsor will be asked to consolidate the analysis of depression by clusters of symptoms and/or to analyze HAM-D subscales in order to assess whether olanzapine may be precipitating depression more frequently than placebo in the double-blind period of HGHL. Additionally, the Sponsor will be asked to perform an assessment of suicidality.

**E-9c.DISCONTINUATION SECONDARY TO ADVERSE EVENTS:**

**HGHT:** Forty-one olanzapine-treated (18.9%) and 55 lithium ( 25.7%) treated patients discontinued due to adverse events. The Sponsor states this difference was not statistically significant (p=.105). For olanzapine-treated patients, the most common adverse events causing discontinuation were depression NOS, mania, and depressed mood. For lithium patients, the most common adverse events causing discontinuation were mania and depression NOS. Syncope occurred in one olanzapine patient.

**HGHQ:** 24.8% of the olanzapine group and 19.8 of the divalproex group discontinued secondary to an adverse event. The most common event for both groups was depression NOS. There was no difference between groups for this event. Suicidal ideation leading to discontinuation occurred in 2.4% of both groups. Weight gain occurred in 4 patients on olanzapine and none on divalproex.

**HGHD OPEN-LABEL:** Sixteen patients (6.4%) discontinued secondary to an adverse event. These included two with depression, four with manic reaction, and two with suicide attempts.

**HGEH OPEN-LABEL EXTENSION:** Seven patients discontinued secondary to adverse events. Two of these discontinued secondary to depression and one secondary to hyperglycemia.

**HGGY:** A total of 10.7% discontinued the open-label phase. Somnolence (1.6%), depression (1.4%) and weight gain (1.4%) were the most common events. Suicide attempt occurred in 0.5% and QT interval prolongation in 0.5%.

**E-9d. DISCONTINUATIONS SECONDARY TO LABORATORY ABNORMALITIES/TREATMENT EMERGENT ADVERSE FINDINGS/PCS FINDINGS:**

The Sponsor reports that in the overall integrated database, 20 olanzapine treated patients discontinued due to laboratory measure abnomalities: 12 were secondary to liver function tests NOS abnormality, 2 to hepatic function abnormal NOS, 2 to hypothyroidism (acquired), and one each to increased ALT, AST, blood glucose, blood triglycerides. Based on this information, there is no apparent indication for a label change.

In the ISS, no patient (n=0/1406) experienced PCS changes in cholesterol (page 325, ISS of November). However, the definition of a PCS cholesterol level is fairly high at 15.516 mmol/L or 600 mg/dL. Additionally, the appearance of treatment emergent events of high cholesterol may be artificially diminished in the ISS as the baseline measures appear to be from the baseline of double-blind and, in some of the databases, exposure to olanzapine began in open-label.

**VITAL SIGNS**

As per the Sponsor, there were no discontinuations secondary to vital signs in any of the databases.

**EKG:**

The proportions of patients with QTcB and QTc F abnormalities ($\geq$ 450 for males/470 females) in the overall datases were 3.3 % and 0.4%, respectively. There was one discontinuation secondary to "ECG abnormal NOS". Three potentially clinically significant QT interval prolongations were seen in the open-label extension of HGGY. A QTcB prolongation to 496 msec (QTcF=478.3msec) was seen in HGHD in a patient who was 451.3 QTcB at visit 1. A later visit showed an interval of 408.4msec.

Compared to lithium (double-blind data, HGHT-ISS p 170), QTcF prolongation $\geq$ 60msec (5.3%=9/170 versus 0.5%=1/184) and QTcF prolongation $\geq$ 75msec (2.9% = 5/170 versus 0.5%= 1/184 occurred in a larger proportion of olanzapine treated patients. QTcF $\geq$ 30 msec occurred in 18.2% of olanzapine and 12.0% of lithium treated patients. Compared to divalproex (double-blind and extension, ISS p 277), QTcF prolongations $\geq$ 30msec occurred in 16.3% (17/104) of the olanzapine patients and 10.9% (11/101) of the divalproex patients. QTcF $\geq$ 60 and 75 msec were lower in this study with 2/104 olanzapine treated and 1/101 divalproex treated patients experiencing $\geq$ 60 msec and no patients in either group experiencing $\geq$ 75msec.

**E-9E.GLUCOSE/WEIGHT**

In the November, 2002 submission (ISS, page 371), the Sponsor notes that in the overall integrated database the incidence of treatment-emergent nonfasting glucose ≥200 mg/dL at any time when the baseline was less than 200 mg/dL was 2.5%. Thirty five (7.2%) olanzapine patients had treatment-emergent HbA1c>6.1. Three had baseline diabetes, seven had abnormal "glycemic control" at baseline and 13 were taking other medications that are "associated with increased risk for glucose dysregulation". Thirty-two of these patients and had an average baseline HbA1c of 5.9% but were not known to have diabetes at baseline. One patient had no baseline characteristics suggestive of glucose dysregulation and developed treatment emergent elevated HbA1c and a treatment-emergent nonfasting glucose abnormality. The Sponsor notes risk factors for diabetes for this patient at baseline and weight gain during olanzapine treatment.

The Sponsor indicates that weight gain of at least 7% was seen in almost 40% of the patients in the overall integrated database. Almost half of these reported "weight increased" as an adverse event although the Sponsor notes that only 1.2% of patients discontinued secondary to weight gain. 29.2% of patients gained weight in the open-label extension of HGGY. (Please see the appendix for a Sponsor provided table ISS.11.13. detailing weight gain ≥ 7% across databases)

**E-9F.EPS**

In the overall integrated databases, the incidences of treatment-emergent parkinsonism were 2.4% in HGHL -7.9% in HGHQ, akathisia, 4.6% in HGHL to 18.4% in HGHT, and dyskinesia, 0 % in HGHL to 9.2% in HGHQ. The Sponsor notes the incidence of EPS-related adverse events "was generally low, with no events suggesting cause for concern". The Sponsor notes that there were "no statistically significant differences between olanzapine and comparator groups in the proportions of patients experiencing treatment-emergent EPS, based on predefined changes in EPS scale scores." Information from the November ISS, indicates that akathisia as an adverse event was seen with "statistically significantly greater incidence" in olanzapine-treated patients in HGHL and HGHQ (November ISS, p.47).

## VIII. Dosing, Regimen, and Administration Issues

Modal dose for the HGHL open-label period, in which patients were stabilized, was 10.0mg with a mean of 11.8 mg, median 11.3 mg and standard deviation of 7.5 mg. The double-blind period of HGHL dosed patients between 5 –20 mg day. This is consistent with dosing as recommended for the acute mania indication. The modal dose in the double-blind treatment phase was 10.0 mg, the mean was 12.5, the median was 10.9 and the standard deviation was 5.0. The Sponsor indicates that study compliance was high (>90%) in both the treatment and placebo groups.

**Drug Abuse Potential and Overdose:**

The Sponsor submitted a section of this submission specifically addressing these issues. Based on this information, there is no indication for label changes at this time.

# IX. Use in Special Populations

## A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Subgroup analysis was performed within the pivotal study for both safety and efficacy measures. Given the large attrition rates, the interpretation of the data may be questionable. Subgroup analyses for time-to-symptomatic relapse and incidence-of-symptomatic relapse may be found in the appendix (Sponsor-provided tables).

The Sponsor notes that subgroup analyses of relapse rate based on the psychiatric features of the index episode, such as absence or presence of psychotic features, did not affect the performance of olanzapine.

## B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Efficacy subgroup analyses from the pivotal study are presented above. Excerpts from Sponsor-provided table HGHL.12.19 of treatment emergent adverse events with regard to age, gender, and ethnicity are presented below. With regard to depression, patients under the age of 40 on olanzapine experienced depression at twice the incidence of those ≥ 40 years of age.

| | | | Placebo | | | Olz | | p-Values | |
|---|---|---|---|---|---|---|---|---|---|
| Event | AGE | N | n | (%) | N | n | (%) | Homogeneity of Odds Ratio | Between Group Comparison Within Strata |
| Abdominal pain NOS | < 40 | 69 | 1 | (1.4) | 104 | 0 | | .098 | .399 |
| | >= 40 | 67 | 0 | | 121 | 2 | (1.7) | | .539 |
| Depression | < 40 | 69 | 0 | | 104 | 9 | (8.7) | .009 | .012 |
| | >= 40 | 67 | 4 | (6.0) | 121 | 4 | (3.3) | | .459 |

Nine "Caucasion" patients (4.6%) and no "Other" patients lost weight in the double-blind period.

Table HGHL.12.19. Treatment-Emergent Adverse Events
Subgroups with Significant (p<.1) Difference in Odds Ratio
Double-Blind Treatment (concluded)

| | | | Placebo | | | Olz | | p-Values | |
|---|---|---|---|---|---|---|---|---|---|
| Event | ORIGIN | N | n | (%) | N | n | (%) | Homogeneity of Odds Ratio | Between Group Comparison Within Strata |
| Weight decreased | Caucasian | 110 | 2 | (1.7) | 195 | 9 | (4.6) | .053 | .316 |
| | Other | 32 | 1 | (3.2) | 70 | 0 | | | .365 |

## C. Evaluation of Pediatric Program

A pediatric waiver was granted.

### D. Comments on Data Available or Needed in Other Populations

The Division agreed that one positive well designed and adequately controlled study evaluating the efficacy of olanzapine compared with placebo in the prevention of relapse in bipolar disorder would be acceptable to obtain a claim for maintenance. The pivotal study, while statistically meeting criteria defined for primary efficacy, does not demonstrate clinical efficacy in the long term, up to [ ], treatment of bipolar I disorder in patients who initially responded to treatment. The attrition rate for the olanzapine group is clinically significant, demonstrating a median time-to-discontinuation for any event of approximately 55 days. Therefore, long term efficacy has not been demonstrated. This may, in part, be a result of sub-optimal clinical responses, yet adequate protocol responses, in the "stabilization" phase demonstrating that patients actually require longer stabilization than this trial studied. b(4)

Additionally, as presented, the data from this study support that olanzapine can be used clinically for an extended time in acute mania, beyond the current acute mania indication. As seen in the pivotal study, the data do not support monotherapy for long- term, up to [ ], maintenance in most patients. b(4)

Larger representation of non-Caucasian patients, larger numbers, would be useful in assessing any efficacy or safety differences between races/ethnicities. Specifically, diabetes, weight gain, and cardiac issues need better evaluation in non-white populations.

Otherwise, no specific requirement for testing in other populations was made by the Division before filing of this supplement.

## X. Conclusions and Recommendations

### A. Conclusions

The indication of long term treatment of bipolar I disorder, for up to [ ] with olanzapine monotherapy is not supported by the data from the pivotal trial. I recommend the Division consider an approvable action on supplemental NDA 20-592 for the use of olanzapine for the treatment of bipolar I disorder with an index manic or mixed episode for up to approximately [ ]. The rapid attrition and "relapse" rates of the olanzapine and placebo groups respectively make it difficult to interpret the data in the pivotal study and do not allow this reviewer to conclude olanzapine is efficacious for up to [ ] as implied in the proposed label or long-term treatment as stated in the proposed label. b(4) b(5) b(4)

The data show that by approximately day 56 (two-protocol months) of double-blind treatment, 50 % of the olanzapine-treated patients (and 74% of the placebo-treated patients), are no longer in the study. If one assumes time at symptomatic remission, as defined by the protocol, is equivalent to stabilization, this would mean that once stabilized, most patients will have either relapsed or discontinued the medication within three months. This reviewer does not argue the fact that olanzapine clearly statistically separates from placebo on time to "relapse" as defined in the study. Additionally, there are approximately 25% of the olanzapine treated patients and 8.8%

of the placebo treated patients in the study at 273 days. The clinical interpretation of this is difficult secondary to the high attrition rates and the suggestion from the data that patients perhaps are not clinically stable before randomization occurs.

An indication for treatment duration longer than the present approval for acute mania in bipolar I patients with manic or mixed episodes is supported by the data in the pivotal study. Therefore, this appears to be an approvable action if the Division decides to take such an action. The length of time of this effect is difficult to determine. Therefore, language for labeling is difficult to determine. Taken in its entirety, the results of the pivotal trial suggest that the stabilization period in the pivotal study is too short. The rapid "relapse" seen in the placebo group may reflect, in part, the withdrawal of treatment in patients who are not fully clinically remitted. Conversely, the treatment group continues to stabilize more fully. However, within a few months, the treatment group suffers high attrition through either relapse or discontinuation.

Controlled safety information for a duration longer than three months is not provided in the pivotal study secondary to the high attrition/and or relapse rates. HGHT and HGHQ are not designed to establish long term safety as they have no placebo arms. Open-label studies only provide hints at rare serious adverse events.

Safety areas that are of interest at this time are the [ ] seen across all studies, emergent hyperglycemia, QTcF prolongations as seen in HGHL, treatment-emergent EPS, and orthostatic blood pressure changes. Of these, this reviewer believes that the label should be modified to strengthen the language regarding [ ] potential glucose dysregulation. Other safety areas of interest such as hyperuricemia, hypercholesterolemia, and elevated eosinophil counts are not unique to this patient population. However, further analysis of these findings may elucidate the extent of any drug effect. b(5) b(5)

HGHL data showing olanzapine patients relapsing more often into depression, while not interpretable at this time, is worth further exploration as is the suggestion of a differential effect by origin ("Caucasian" versus "Other") on weight loss. As the bipolar patient population will include younger females, issues of teratogenicity will be important to define more clearly in the future.

### B. Recommendations

Whether the benefits of this drug outweigh the risks of this drug for use beyond [ ] cannot be adequately assessed as clinical long term, up to [ ], efficacy is not supported by the data from this study and the numbers of patients for long term safety analysis are too small. b(5) b(4)

This reviewer recommends that the Division consider granting an approvable action for a claim of either continued acute efficacy or possibly, extended efficacy. The Sponsor will need to supply additional information in support of this potential action as well as new proposed label text. Proposed label text should include stronger language for the potential of treatment-emergent [ ] and possibly for glucose dysregulation. Additional safety analysis is b(5)

requested for several laboratory measures and adverse events to assist in labeling decisions. Treatment emergent depression and suicidality should be assessed as indicated below.

As part of a complete response to a potential approvable action, it is recommended that the Sponsor provide the following:

1) a formal analysis of time- to-event without sites 34 [redacted]. b(4)

2) an exploration and analysis of treatment emergent suicidality and an analysis of the HAM-D scores for items 1 and 3 as a separate analysis to examine possible precipitation of depression in this population.

3) re-coded patient disposition table(s), as discussed in section VI C of this document. If there is/are a reason(s) for the apparent discrepancies noted earlier in this review, please explain.

4) a definition for the phrase "Reporting Interval Completed" as used in the disposition table(s) in the pivotal study.

5) a definition of "Days in Remission" as seen in table HGHL.14.11 and clarification as to when patients were randomized.

6) the percentage of relapse, as per Table HGHL.14.11, for the interval 21-28 days and the interval $\geq$ 35 days and provide an analysis of time in "remission" to time-to-"relapse" and time in "remission" to time-to-event.

7) a re-analysis of cholesterol measures using a high of 250 mg/dL after a normal baseline or a change of 50 mg/dL from baseline with the analysis performed as outlined in #8.

8) a presentation of the laboratory values of eosinophils, uric acid, urine ketones, and cholesterol, stratified from the beginning of the open-label period to the last visit of the double-blind period and from the beginning of double-blind to the last visit of the double-blind period for the pivotal trial and possibly all databases with double-blind extensions.

9) a detailed description, to include results of any tests performed or consultation received, of the convulsive event seen in the open-label period of HGHL is requested.

10) Within the active and placebo controlled databases, for any PCS EKG or syncopal events, SAEs related to EKG findings or syncope, or discontinuations secondary to either EKG findings or syncope, please provide vital signs to include orthostatics and EKG data taken at the time of the event. If none are available, this should be stated clearly.

11) Although not essential to approvability, the Sponsor is asked to explain the patients in the pivotal study for >365 days as the protocol required both SPIII and IV to have a combined maximum duration of 12 months.

# XI. Appendix

## A. Other Relevant Materials

Tables, graphs, and narratives as provided by the Sponsor.

## B. Individual More Detailed Study Reviews (If performed)

NA

**Table 1.** **MedDRA Preferred Terms Reported at a Rate Within Bipolar Patients of ≥ Twice that Reported in Nonbipolar Patients and with an Absolute Number of Bipolar Cases of ≥6**

| MedDRA Preferred Term (MedDRA 4.0 version) | Reporting Ratio (%) Within Bipolar Patients | Reporting Ratio (%) Within Nonbipolar Patients | Proportional Reporting Ratio (PRR) |
|---|---|---|---|
| Mania | 2.08% | 0.68% | 3.06 |
| Depression NOS | 2.00% | 0.79% | 2.53 |
| Disturbance in Attention | 0.68% | 0.28% | 2.43 |
| Bipolar Disorder NEC | 0.48% | 0 (no cases) | 9999 |
| Short Term Memory Loss | 0.36% | 0.09% | 4.0 |
| Depression Suicidal | 0.36% | 0.05% | 7.2 |
| Mental Impairment NOS | 0.32% | 0.15% | 2.13 |
| Road Traffic Accident | 0.28% | 0.06% | 4.67 |
| Abnormal Dreams | 0.24% | 0.11% | 2.18 |
| Drug Screen Positive | 0.28% | 0.10% | 2.8 |
| Sleep Walking | 0.36% | 0.08% | 4.5 |
| Mood Swings | 0.24% | 0.10% | 2.4 |
| **Above 12 terms grouped together (bipolar symptoms)** | **7.75%** | **2.48%** | **3.13** |
| Joint Swelling | 0.60% | 0.28% | 2.14 |
| Peripheral Swelling | 1.88% | 0.81% | 2.32 |
| Fluid Retention | 0.60% | 0.21% | 2.86 |
| Cardiac Failure Congestive | 0.48% | 0.12% | 4.0 |
| Swelling NOS | 0.40% | 0.15% | 2.67 |
| Abdominal Distension | 0.80% | 0.35% | 2.29 |
| Arthritis NOS | 0.24% | 0.05% | 4.8 |
| **Above 7 terms grouped together** | **5.01%** | **1.98%** | **2.53** |

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Table 1. **MedDRA Preferred Terms Reported at a Rate Within Bipolar Patients of ≥ Twice that Reported in Nonbipolar Patients and with an Absolute Number of Bipolar Cases of ≥6 (continued)**

| MedDRA Preferred Term (MedDRA 4.0 version) | Reporting Ratio (%) Within Bipolar Patients | Reporting Ratio (%) Within Nonbipolar Patients | Proportional Reporting Ratio (PRR) |
|---|---|---|---|
| Drug Level NOS Decreased | 0.52% | 0.12% | 4.33 |
| Drug Withdrawal Syndrome | 0.52% | 0.24% | 2.17 |
| Laboratory Test Abnormal NOS | 0.36% | 0.06% | 6.0 |
| Anticonvulsant Drug Level NOS Below Therapeutic | 0.36% | 0.05% | 7.2 |
| Drug Level NOS Decreased | 0.28% | 0.02% | 14.0 |
| **Above 5 terms grouped together** | **2.05%** | **0.49** | **4.18** |
| Blood Pressure Increased | 0.72% | 0.25% | 2.88 |
| Thirst | 0.60% | 0.30% | 2.0 |
| Drooling | 0.56% | 0.26% | 2.15 |
| Hypoglycaemia NOS | 0.48% | 0.19% | 2.53 |
| Anoroxia | 0.48% | 0.19% | 2.53 |
| Hunger | 0.48% | 0.06% | 8.0 |
| Incontinence NOS | 0.40% | 0.18% | 2.22 |
| Jerky Movement NOS | 0.40% | 0.17% | 2.35 |
| Neck Stiffness | 0.36% | 0.17% | 2.12 |
| Cough | 0.36% | 0.14% | 2.57 |
| Sluggishness | 0.36% | 0.07% | 5.14 |
| Blood Creatinine Increased | 0.32% | 0.15% | 2.13 |
| Tinnitus | 0.32% | 0.15% | 2.13 |
| Respiratory Distress | 0.32% | 0.11% | 2.91 |
| Renal Failure Acute | 0.28% | 0.13% | 2.15 |
| Skin Discoloration | 0.28% | 0.10% | 2.8 |
| Blood Thyroid Stimulating Hormone Increased | 0.28% | 0.06% | 4.67 |
| Facial Palsy | 0.25% | 0.11% | 2.27 |
| Neutrophil Count Decreased | 0.25% | 0.11% | 2.27 |
| Coordination Abnormal NOS | 0.24% | 0.10% | 2.4 |
| Diabetic Coma NOS | 0.24% | 0.09% | 2.67 |
| Ammonia Increased | 0.24% | 0.02% | 12.0 |
| | | | |

Abbreviations: NEC = not elsewhere classified; NOS = not otherwise specified.

Investigators/sites HGHL:

F1D-MC-HGHL Investigators and Other Key Individuals

| Site No | Principal Site Investigator | Other Site Investigators |
|---|---|---|
| 001 | George Aiudis, MD<br>Psychiatric Services of Coatesville<br>Building 38 (116A)<br>1400 Black Horse Hill Road<br>Coatesville, PA 19320<br>USA | |
| 004 | Mohammad Bari, MD<br>Synergy Clinical Research Center<br>450 Fourth Avenue, Suite 409<br>Chula Vista, CA 91910<br>USA | |
| 005 | Jason Burns, MD<br>Medfah Research of Houston, Inc<br>6360 Westpark #110<br>Houston, TX 77057<br>USA | |
| 006 | Albert Bayer<br>31700 W 13 Mile Road Suite 107<br>Farmington Hills, MI 48334<br>USA | |

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F1D-MC-HGHL Investigators and Other Key Individuals (continued)

| Site No | Principal Site Investigator | Other Site Investigators |
|---|---|---|
| 007 | Charles L. Bowden, MD<br>University of Texas Health Science<br>Center at San Antonio<br>Department of Psychiatry<br>7703 Floyd Curl Drive<br>San Antonio, TX 78284<br>USA | |
| 008 | Ronald Brenner, MD<br>Neurobehavioral Research, Inc<br>371 Central Avenue<br>Lawrence, NY 11559<br>USA | |
| 009 | John S. Carman, MD<br>Carman Research<br>4015 S Cobb Drive, Suite 245<br>Smyrna, GA 30080<br>USA | |
| 010 | Joachim D. Rasas, MD<br>Dr. Rasas and Associates<br>5987 Brockton Avenue, Suite 200<br>Riverside, CA 92506<br>USA | |

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| Site No | Principal Site Investigator | Other Site Investigators |
|---|---|---|
| 011 | James C. Close, MD<br>Bellevue Hospital, Dept of Psychiatry<br>462 First Avenue, Room 20 West-12A<br>New York, NY 10016<br>USA | |
| 012 | Anne Gilbert, MD<br>Indianapolis Psychiatric Associates<br>6820 Parkdale Place, Suite 115<br>Indianapolis, IN 46254<br>USA | |
| 013 | Andrew Cutler, MD<br>Coordinated Research of Florida, Inc<br>807 W Morse Boulevard, Suite 101<br>Winter Park, FL 32789<br>USA | |

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F1D-MC-HGHL Investigators and Other Key Individuals (continued)

| Site No | Principal Site Investigator | Other Site Investigators |
|---|---|---|
| 019 | William Fuller, MD<br>University Physicians Psychiatry<br>Associates, Room 308<br>1400 W 22nd Street<br>Sioux Falls, SD 57105<br>USA | |
| 020 | John H. Gilliam, MD<br>Health South Hospital<br>Medical Office Building 2 Suite 240<br>7650 E Parham Avenue<br>Richmond, VA 23294<br>USA | |
| 021 | Wayne K. Goodman, MD<br>University of Florida Specialty Clinic<br>1600 SW Archer Road, Room 11-431<br>Gainesville, FL 32610<br>USA | |

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F1D-MC-HGHL Investigators and Other Key Individuals (continued)

| Site No | Principal Site Investigator | Other Site Investigators |
|---|---|---|
| 014 | John M. Downs, MD<br>Clinical Trials of Memphis, Inc<br>707 W Brookhaven Circle<br>Memphis, TN 38117<br>USA | |
| 015 | Rif El-Mallakh, MD<br>University of Louisville School of Medicine<br>Ambulatory Care Building-1st floor<br>Clinical Psychiatry Drug Studies<br>530 S Jackson Street<br>Louisville, KY 40202<br>USA | |
| 016 | Emmett R. Bishop, MD<br>Coastal Clinical Trials, Inc<br>6405 Abercorn Street, Suite 112<br>Savannah, GA 31405<br>USA | |
| 017 | Herman Clements, MD<br>Pharmacotherapy Research Associates<br>750 Princeton Avenue, Suite 2<br>Zanesville, OH 43701<br>USA | |
| 018 | Ronald R. Fawa, MD<br>Fawa Clinical Services<br>236 E 75th Street<br>New York, NY 10021<br>USA | |

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F1D-MC-HGHL Investigators and Other Key Individuals (continued)

| Site No | Principal Site Investigator | Other Site Investigators |
|---|---|---|
| 022 | James T. Hartford, MD<br>Hartford Research Group, Inc<br>10550 Montgomery Road, Suite 20<br>Cincinnati, OH 45242<br>USA | |

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FID-MC-HGHL Investigators and Other Key Individuals (continued)

| Site No | Principal Site Investigator | Other Site Investigators |
|---|---|---|
| 024 | Scott Hoopes, MD<br>315 N Allumbaugh<br>Boise, ID 83704<br>USA | |
| 025 | Arifulla Khan, MD<br>Northwest Clinical Research Center<br>1908 116th Avenue, Northeast #112<br>Bellevue, WA 98004<br>USA | |
| 026 | Robert H. Levine, MD<br>1216 Park Avenue<br>New York, NY 10128<br>USA | |

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FID-MC-HGHL Investigators and Other Key Individuals (continued)

| Site No | Principal Site Investigator | Other Site Investigators |
|---|---|---|
| 027 | Harry E. Legus, MD<br>Birmingham Psychiatry Pharmaceutical Studies, Inc<br>One Independence Plaza, Suite 900<br>Birmingham, AL 35209<br>USA | |
| 028 | Leon Rubenfine, MD<br>Pioneer Pharmaceutical Research<br>Harbor Oaks Hospital<br>35031 23-Mile Road<br>New Baltimore, MI 48047<br>USA | |
| 029 | Norman C. Moore, MD<br>4750 Waters Avenue<br>Savannah, GA 31404<br>USA | |
| 030 | Leon Rosenberg, MD<br>Center for Emotional Fitness<br>Moorestown Office Center, Suite 304<br>110 Marter Avenue<br>Moorestown, NJ 08057<br>USA | |

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FID-MC-HGHL Investigators and Other Key Individuals (continued)

| Site No | Principal Site Investigator | Other Site Investigators |
|---|---|---|
| 031 | George Nurnberg, MD<br>University of New Mexico Department of Psychiatry Research<br>2400 Tucker NE<br>Albuquerque, NM 87131<br>USA | |
| 033 | Michael Lambert, MD<br>Veterans Affairs Medical Center<br>Mental Health, 116A<br>4500 S Lancaster Road<br>Dallas, TX 75216<br>USA | |
| 034 | Dattala Ghula Reddy, MD<br>Clinical Investigators Pool, Ltd<br>340 W Miller<br>Springfield, IL 62702<br>USA | |
| 035 | Frederick W. Reimherr, MD<br>University of Utah School of Medicine<br>Department of Psychiatry Mood Disorders Clinic<br>50 N Medical Drive<br>Salt Lake City, UT 84132<br>USA | |

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FID-MC-HGHL Investigators and Other Key Individuals (continued)

| Site No | Principal Site Investigator | Other Site Investigators |
|---|---|---|
| 036 | Robert A. Rosenberg, MD<br>Atlanta Center of Medical Research<br>811 Juniper Street NE<br>Atlanta, GA 30308<br>USA | |
| 037 | Stephen M. Stahl, MD, PhD<br>Clinical Neuroscience Research Center<br>8899 University Center Lane, Suite 130<br>San Diego, CA 92122<br>USA | |
| 038 | Sidney Lerfald MD<br>415 Morris Street, Suite 306<br>Charleston, WV 25301<br>USA | |
| 039 | Anantha Shekhar, MD, PhD<br>Methodist Hospital-IU Adult Psychiatry<br>Methodist Campus C-2<br>1701 N Capitol Avenue<br>Indianapolis, IN 46202<br>USA | |

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FID-MC-HGHL Investigators and Other Key Individuals (continued)

| Site No | Principal Site Investigator | Other Site Investigators |
|---|---|---|
| 040 | Levi L. Davis<br>Veterans Affairs Medical Center<br>Neurobehavioral Research and Education Advancement Corporation<br>1701 Loop Road East<br>Tuscaloosa, AL 35404<br>USA | |
| 041 | Adam Trevis, MD<br>Langeley Porter Psychiatric Institute<br>401 Parnassus Box 0984<br>San Francisco, CA 94143<br>USA | |
| 042 | Harold David Udelman, MD<br>Biomedical Stress Research Foundation, Inc<br>45 E Osborn Road<br>Phoenix, AZ 85012<br>USA | |
| 045 | Richard I.H. Wang, MD, PhD<br>Medelmann, Inc<br>4608 W Burleigh Street<br>Milwaukee, WI 53210<br>USA | |

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FID-MC-HGHL Investigators and Other Key Individuals (continued)

| Site No | Principal Site Investigator | Other Site Investigators |
|---|---|---|
| 047 | Craig Wrzeski, MD<br>Affiliated Research Institute<br>801 N Tustin Avenue, Suite 101<br>Santa Ana CA 92705<br>USA | |
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| 050 | Anne L. Marek<br>Institute for Advanced Clinical Research<br>7900 High School Road<br>Elkins Park, PA 19027<br>USA | |
| 052 | David A. Slack, MD<br>Institute for Psychopharmacology Research<br>11050 E Artesia Boulevard, Suite G<br>Cerritos, CA 90703<br>USA | |

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FID-MC-HGHL Investigators and Other Key Individuals (continued)

| Site No | Principal Site Investigator | Other Site Investigators |
|---|---|---|
| 053 | Claudia Baldessarini, MD<br>Friends Hospital<br>4641 Roosevelt Boulevard<br>Philadelphia, PA 19124<br>USA | |
| 200 | Prof. Vasile Chiriță<br>Spitalul Clinic De Psihiatrie Socola<br>Șoseaua Bucium Nr. 36<br>Iași<br>6900<br>Romania | |
| 201 | Dr. Iosif Gahn<br>Clinica De Psihiatrie I<br>Clinic I<br>Strada Gheorghe Marinescu, NR. 38<br>Tg. Mures<br>Romania | |
| 202 | Dr. Aurel Nirestean<br>Clinica De Psihiatrie I<br>Clinic II<br>Strada Gheorghe Marinescu, NR. 38<br>Tg. Mures<br>Romania | |
| 203 | Dr. Tudor Udristoiu<br>University Clinic of Psychiatry<br>35, Calea Dorobanti Street<br>1100, Craiova Judet Dolj<br>Craiova<br>Romania | |
| 204 | Prof. Mircea Lucanescu<br>Clinica Psihiatrica Timisoara<br>Strada I. Vacarescu 21<br>Timisoara<br>1900<br>Romania | |

Abbreviations: No = number.

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INCLUSION/EXCLUSION CRITERIA: SPONSOR –PROVIDED TABLES

INCLUSION/EXCLUSION CRITERIA HGHL: (Sponsor provided)

### *9.3.1. Inclusion Criteria*

Patients could be included in the study only if they met all of the following criteria:

[1] Was a male or female inpatient or outpatient, at least 18 years of age.

[2] If female of childbearing potential, was using a medically accepted means of contraception (in the judgment of the primary investigator).

[3] Had a level of understanding sufficient to perform all tests and examinations required by the protocol.

[4] Was considered reliable.

[5] Understood the nature of the study and signed an informed consent document (and/or a patient's authorized legal representative understood the nature of the study and signed an informed consent document).

[6] Had a diagnosis of bipolar I disorder and currently displayed an acute manic or mixed episode (with or without psychotic features) according to the DSM-IV (Attachment HGHL.2 in (Appendix 16.1.1) based on clinical assessment and confirmed by structured diagnostic interview Structured Clinical Interview for the DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). This included the following diagnoses: 296.4x, Bipolar I Disorder, Most Recent Episode Manic; 296.6x, Bipolar I Disorder, Most Recent Episode Mixed.

[7] Must have experienced at least two prior manic or mixed episodes within 6 years prior to study entry.

[8] If had an index manic or mixed episode, must have had a YMRS total score ≥20 at Visit 1 and Visit 2.

### 9.3.2. Exclusion Criteria

Patients were excluded from the study for any of the following reasons:

[9] Investigators and their immediate families, defined as the investigator's spouse, parent, child, grandparent, or grandchild.

[10] Participation in a clinical trial of another investigational drug less than 1 month (30 days) prior to study entry (Visit 1).

[11] Persons who had previously participated in this study or any other study investigating olanzapine, except patients who had participated in other olanzapine short-acting intramuscular (SAIM) studies outside of the United States.

[12] Female patients who were either pregnant or breast-feeding.

[13] Serious, unstable illnesses including hepatic, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic disease such that death was anticipated within 1 year or intensive care unit hospitalization for the nonpsychiatric disease was anticipated within 6 months.

[14] Documented history of intolerance to olanzapine.

[15] Patients entering study receiving olanzapine must have discontinued olanzapine use by Visit 2 (if prescribed olanzapine prior to the study).

[16] DSM-IV substance (except nicotine and caffeine) dependence within the past 30 days.

[17] Treatment with remoxipride less than 6 months (180 days) prior to Visit 2.

[18] Treatment with clozapine less than 4 weeks prior to Visit 2.

[19] Past diagnosis of schizophrenia or other psychotic disorders (including schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, psychotic disorder not otherwise specified) as defined in the DSM-IV.

[20] Current diagnosis of major depressive disorder, dysthymic disorder, depressive disorder not otherwise specified (NOS), substance-induced psychotic disorder, bipolar I disorder (single manic episode), bipolar I disorder (most recent episode hypomanic), bipolar I disorder (most recent episode unspecified), or bipolar II disorder, as defined in the DSM-IV.

[21] Judged clinically to be at serious suicidal risk.

[22] History of allergic reaction to study medication(s).

ALLOWED AND PROHIBITED CONCOMITANT MEDICATIONS DOUBLE-BLIND PERIOD OF HGHL (Sponsor- provided table)

**Table HGHL.2. Drugs Allowed (Y) and Drugs not Allowed (N) as Concomitant Medications**

| Drug Class | Episodic Use | Chronic Use |
|---|---|---|
| Antihypertensives (including ACE inhibitors)[a] | Y | Y |
| Cough/Cold preparations (except loratadine [Claritin]) | N | N |
| Steroids (inhaled, topical, ophthalmic only) | N | N |
| Antiemetics | N | N |
| Amantadine | N | N |
| Anorexics | N | N |
| Antiarrythmics | N | N |
| Anticoagulants | N | N |
| Anticholinergics[b] | N | N |
| Anticonvulsants[b] | N | N |
| Antidepressants[b] | N | N |
| Antipsychotics[b] | N | N |
| Benzodiazepines[b] | N | N |
| Calcium Channel Blockers | N | N |
| Chloramphenicol | N | N |
| Clozapine | N | N |
| Erythromycins | N | N |
| Guanabenz | N | N |
| Guanadrel | N | N |
| Guanethidine | N | N |
| Guanfacine | N | N |
| Ketanserin | N | N |
| Lithium[b] | N | N |
| Methyldopa | N | N |
| Metyrosine | N | N |
| Narcotics | N | N |
| Neuroleptics[b] | N | N |
| Psychostimulants | N | N |
| Reserpine | N | N |
| Tryptophan | N | N |
| Valproate[b] | N | N |
| Zolpidem | N | N |

ACE = angiotensin converting enzyme

[a] Except calcium channel blockers and clonidine

[b] Except as permitted in Section 3.8.

# Sponsor Provided Schedule of Events, TABLE HGHL.9.2.

**Table HGHL.9.2. Study Schedule: F1D-MC-HGHL Study Periods I, II, and III**

| Description of Data | V1 | V2 | V3-4 | V5 | V6-7 | V8-14 | V101 | V102-103 | V104 | V105 | V106 | V107-109 | V110 | V111-115 | V116/Final |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Weeks until next visit | 2-7 days | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 4 | 4 | 4 | 4 | |
| Informed consent | X | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | |
| Study drug compliance | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | |
| Weight and temperature | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood pressure and heart rate | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Psychiatric examination[a] and SCID-I/P | X | | | | | | | | | | | | | | |
| Physical examination[a] | X | | | | | | | | | | | | | | X |
| Electrocardiogram[a] | X | | | | | X[c] | | | | | | | X | | X[c] |
| Preexisting conditions and adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Historical illnesses and previous medications | X | | | | | | | | | | | | | | |
| Study drug dispensed[f] | | X[g] | X[s] | X[s] | X[s] | X[f, g] | X | X | X | X | X | X | X | X | X[s] |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Visit comments | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse event follow-up, if necessary | | | | | | | | | | | | | | | X |
| Patient summary including comments[e] | | | | | | X | | | | | | | | | X |
| **Laboratory Tests[b]** | | | | | | | | | | | | | | | |
| Clinical chemistry[c]/electrolytes | X | X | | X | | X[c] | | | X | | X | X | X | X | X[c] |
| Hematology | X | X | | X | | X[c] | | | X | | X | X | X | X | X[c] |
| Hepatitis screen and pregnancy test[d] | X | | | | | | | | | | | | | | |
| Urinalysis | X | | | | | X[c] | | | | | | | | | X[c] |
| Urine drug screen | X | X | | | | X[c] | | | X | X | X | X | X | X | X[c] |
| TSH | X | | | X | | | | | | | | | | | |
| Prolactin and HbA1c | | X | | | | X[c] | | | | | | | | | X[c] |

continuation of table and footnotes on next page

**Table HGHL.9.2. Study Schedule: F1D-MC-HGHL Study Periods I, II, and III (concluded)**

| Description of Data | V1 | V2 | V3-4 | V5 | V6-7 | V8-14 | V101 | V102-103 | V104 | V105 | V106 | V107-109 | V110 | V111-115 | V116/Final |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| YMRS, MRS, PANSS, HAMD-21, MADRS, CGI-BP | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Barnes Akathisia, Simpson-Angus, AIMS | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| DSM-IV checklist | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Habits | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| SF-36 (US only) | | X | | | | X[c] | | | X | X | X | X | X | X | X |
| SLICE/LIFE (US only) | | X | | | | X[c] | | | X | X | X | X | X | X | X |
| Resource Utilization | | X | | | | X[c] | | | X | X | X | X | X | X | X |
| Hospitalization | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PGWB (US only) | | X | | | | X[c] | | | X | X | X | X | X | X | X |
| Unscheduled visits[h] | | | | | | | | | | | | | | | |

Abbreviations: AIMS = Abnormal Involuntary Movement Scale; CGI-BP = Clinical Global Impression Severity of Illness Scale-Bipolar Version; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HAMD-21 = Hamilton Depression Rating Scale-21 item; HbA1c = hemoglobin A1c; MADRS = Montgomery-Asberg Depression Rating Scale; MRS = Mania Rating Scale; PANSS = Positive and Negative Syndrome Scale; PGWB = Psychological General Well Being Schedule; SCID-I/P = Structured Clinical Interview for the DSM-IV-TR Axis I Disorders, Research Version, Patient Edition; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; SLICE/LIFE = Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation; TSH = thyroid-stimulating hormone; V = Visit; YMRS = Young Mania Rating Scale.

a Electrocardiogram (ECG), physical examination, and psychiatric examination at Visit 1 could be performed within 5 days prior to Visit 1. Subsequent ECG and physical examinations were to be performed on actual visit dates.

b Labs could occur ±1 day relative to the visit, except at baseline visit(s). Labs for baseline visit(s) had to be collected on the day of the visit.

c Any patient who showed an increase from baseline (Visit 2) in AST/SGOT, ALT/SGPT, GGT, total bilirubin, or alkaline phosphatase ≥3 times the upper limit of the laboratory reference range was to have the following tests performed: IgM anti-HAV, HBsAg, and anti-HCVab.

d A pregnancy test was to be performed on all females at Visit 1 and when clinically indicated.

e Electrocardiograms (ECGs) and laboratory samples were completed at Study Period summaries, which occurred at the final visit of Study Periods I, II, and III.
f Double-blind kit assigned at last visit of Study Period II (Visit 8, 9, 10, 11, 12, 13, or 14).
g Open-label olanzapine lot number recorded at all visits in Study Period II and last visit of Study Period III prior to transition to open-label treatment due to relapse.
h Unscheduled visit packets were numbered with the last visit number and then alphabetically, starting with "a" (for example, Visit 3a, 3b).
i Only collected if patient discontinued from Study Period II.

STUDY DESIGNS: All figures are Sponsor-provided.

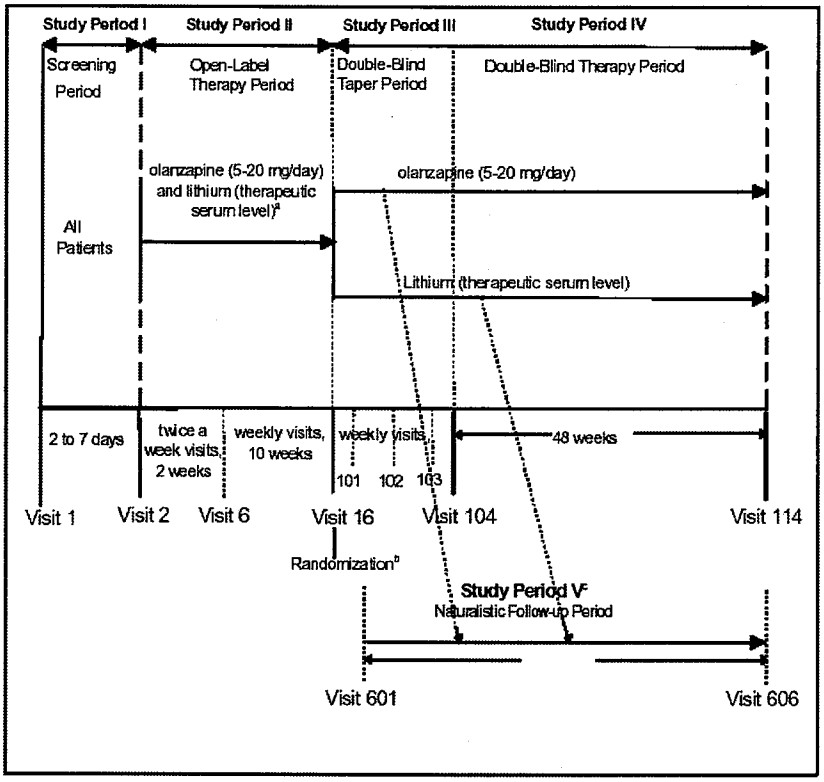


**Figure ISS.4.2. Study design for HGHT.**

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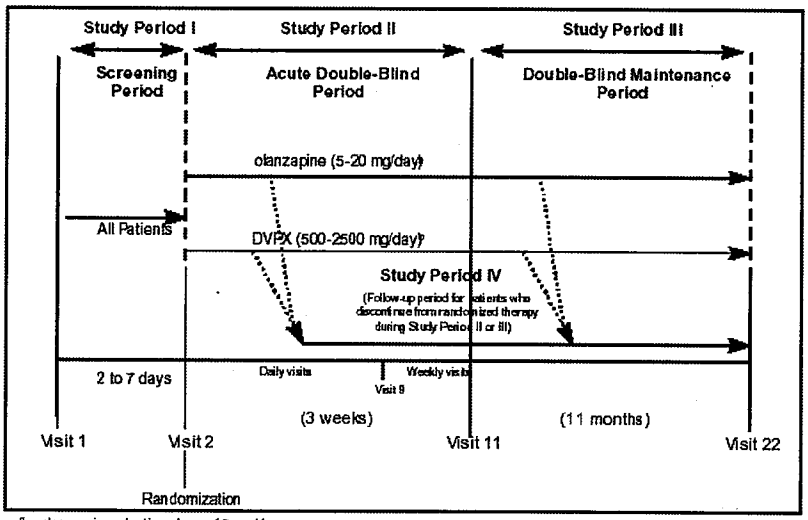


[a] olanzapine starting dose, 15 mg/day
[b] valproate starting dose, 750 mg/day

**Figure ISS.4.3. Study design for HGHQ.**

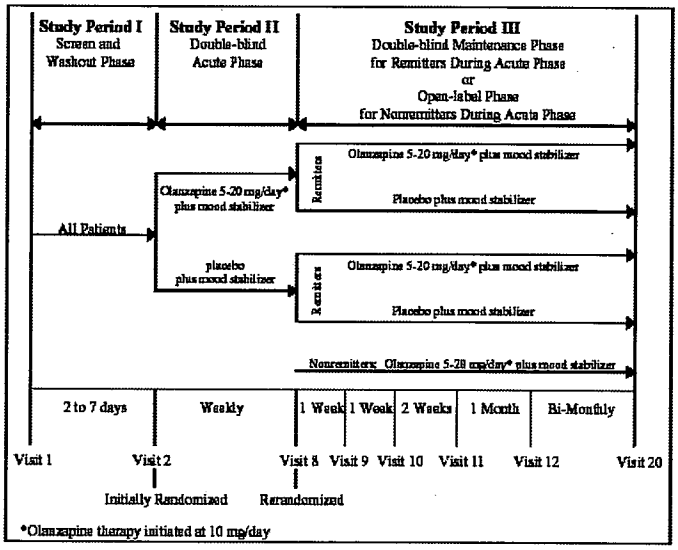


**Figure ISS.4.4. Study design for HGFU.**

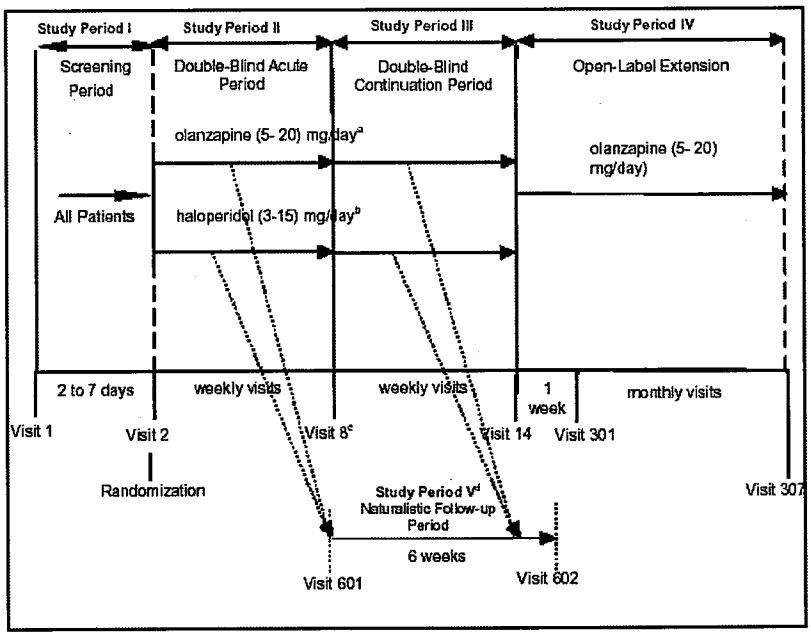


**Figure ISS.4.5. Study design for HGHD.**

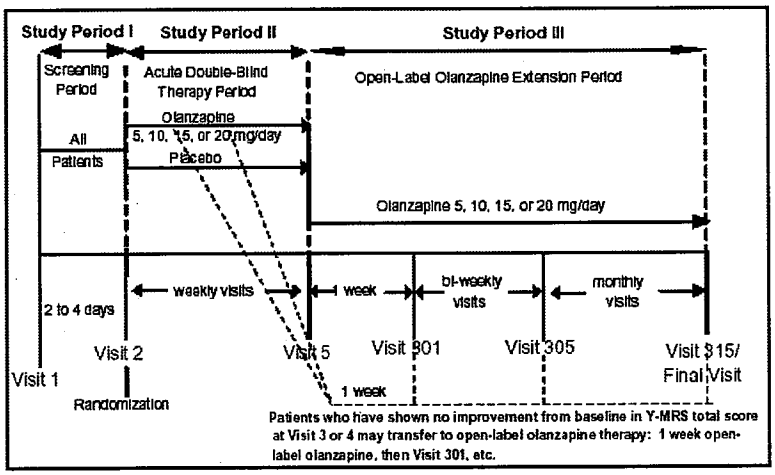


**Figure ISS.4.6. Study design for HGEH.**

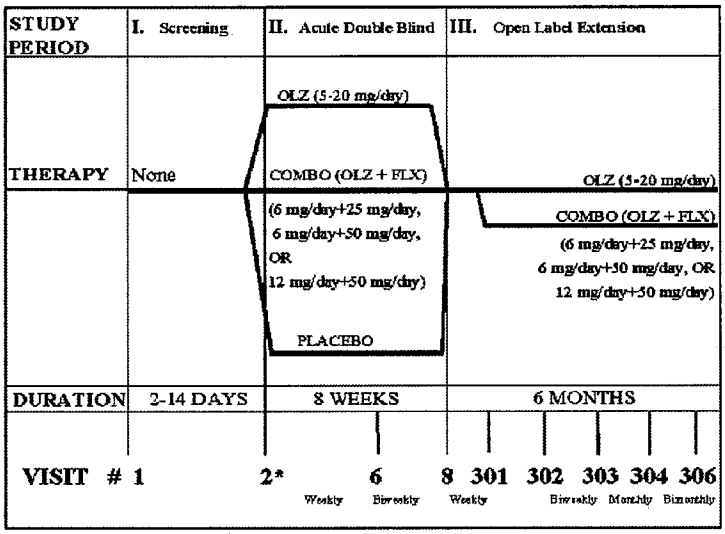


**Figure ISS.4.7. Study design for HGGY.**

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**Table ISS.5.1. Databases Used in Integrated Summary of Safety**

| Placebo-Controlled Maintenance Database | | |
|---|---|---|
| **Studies** | **Phases/Patients Included** | **Definition of Baseline[a] and Comparator Periods** |
| HGHL | The double-blind therapy phase is presented for all remitters. | Baseline: Visits 1-14<br>Comparator: Visits 101-116, 301-308 |
| **Active-Controlled Maintenance Database:** Results for the two studies are presented separately. | | |
| **Studies** | **Phases/Patients Included** | **Definition of Baseline[a] and Comparator Periods** |
| HGHT | The double-blind therapy phase is presented for all remitters. | Baseline: Visits 1-16<br>Comparator: Visits 101-114 |
| HGHQ | The complete double-blind therapy phase is presented for all randomized patients. | Baseline: Visits 1-2<br>Comparator: Visits 3-22 |
| **Placebo-Controlled Combination Therapy Maintenance Database** | | |
| **Studies** | **Phases/Patients Included** | **Definition of Baseline[a] and Comparator Periods** |
| HGFU | The double-blind therapy extension phase is presented for patients who were rerandomized when they remitted after acute phase therapy with olanzapine+mood stabilizers or with placebo+mood stabilizers. | Baseline: Visits 1-8<br>Comparator: Visits 9-22 |

[a]The baseline period is represented by several visits. For quantitative comparisons, the baseline value is the last visit of the baseline period. For analysis of treatment-emergent events, the baseline value is the worst value/event occurring during the baseline period.

**Table ISS.5.1. Databases Used in Integrated Summary of Safety (concluded)**

| Overall Integrated Database | | |
|---|---|---|
| **Studies** | **Phases/Patients Included** | **Definition of Baseline[a] and Comparator Periods** |
| HGHL | All patients exposed to open-label olanzapine during the stabilization phase who were randomized to olanzapine for double-blind therapy are included.<br>and<br>All patients exposed to open-label olanzapine during the stabilization phase who failed to be randomized or were randomized to placebo are included. NOTE: Exposures to olanzapine during open-label rescue subsequent to relapse after randomization to placebo were not included. | Baseline: Visits 1-2<br>Comparator: Visits 3-14, 101-116, 301-308<br><br>Baseline: Visits 1-2<br>Comparator: Visits 3-14 |
| HGHT | All patients randomized to olanzapine were included. (These patients were treated with olanzapine and lithium during baseline and tapered off lithium from Visits 101-104.) | Baseline: Visits 1-16<br>Comparator: Visits 101-114 |
| HGHQ | All patients randomized to olanzapine are included. | Baseline: Visits 1-2<br>Comparator: Visits 3-20 |
| HGHD | All patients randomized to olanzapine are included.<br>and<br>All patients randomized to haloperidol who later entered open-label olanzapine therapy are included. | Baseline: Visits 1-2<br>Comparator: Visits 3-14, 301-307<br><br>Baseline: Visits 1-14/last double-blind visit<br>Comparator: Visits 301-307 |
| HGEH | All patients randomized to olanzapine are included.<br>and<br>All patients randomized to placebo who later entered open-label olanzapine therapy are included. | Baseline: Visits 1-2<br>Comparator: Visits 3-5, 301-315<br><br>Baseline: Visits 1-5/last double-blind visit<br>Comparator: Visits 301-315 |

[a]The baseline period is represented by several visits. For quantitative comparisons, the baseline value is the last visit of the baseline period. For analysis of treatment-emergent events, the baseline value is the worst value/event occurring during the baseline period.

**Table ISS.4.1. Studies Included in the Safety Analysis of Olanzapine for Maintenance Treatment of Bipolar Disorder**

| Protocol Code: Study Design | Primary Study Objective | Phase Duration: | Treatments |
|---|---|---|---|
| **HGHL:** Double-blind, randomized, parallel, multicenter study of olanzapine versus placebo in bipolar patients who had remitted from a manic or mixed episode after acute open-label therapy with olanzapine. | To assess the efficacy of olanzapine compared with placebo in the prevention of relapse into a manic, mixed, or depressed episode among bipolar patients who had remitted from an episode after open-label therapy. | 6 to 12 wks OL:<br>12 mos DB: | 5-20 mg/day olanzapine<br>5-20 mg/day olanzapine or placebo |
| **HGHT:** Double-blind, randomized, parallel, multicenter study of olanzapine versus lithium in bipolar patients who had remitted from a manic or mixed episode after acute open-label combination therapy with olanzapine and lithium. | To assess the efficacy of olanzapine compared with lithium in the prevention of relapse into a manic, mixed, or depressed episode among bipolar patients who had remitted from an episode after open-label therapy. | 6 to 12 wks OL:<br>12 mos DB:<br><br>Lithium was titrated to a therapeutic serum level of 0.6 to 1.2 mEq/L in a dose range of 300 to 1800 mg/day. | 5-20 mg/day olanzapine plus lithium<br>5-20 mg/day olanzapine or lithium |
| **HGHQ:** Double-blind, randomized, parallel, multicenter study of olanzapine versus divalproex in bipolar patients (manic or mixed). | To assess the noninferiority of olanzapine compared with divalproex in improving overall manic symptomatology. | 3 wks DB acute:<br><br>11 mos DB ext: | 5-20 mg/day olanzapine or 500 to 2500 mg/day divalproex<br>Patients continued same treatment |
| **HGFU:** Two double-blind, randomized, parallel, multicenter studies of olanzapine or placebo added to therapy with either lithium or valproate in bipolar patients (manic or mixed) | To assess the acute and long-term efficacy of olanzapine compared with placebo when added to mood stabilizer therapy after both acute and long-term therapy. | 6 wks DB acute:<br>18 mos DB ext: | 5-20 mg/day olanzapine or placebo<br>Responders rerandomized to 5-20 mg/day olanzapine or placebo |
| **HGHD:** Double-blind, randomized, parallel, multicenter study of olanzapine versus haloperidol in bipolar patients (manic or mixed). | To assess the efficacy of flexible dosing of olanzapine compared with haloperidol in improving overall manic symptomatology. | 6 wks DB acute:<br><br>6 wks DB ext:<br>6 mos OL ext: | 5-20 mg/day olanzapine or 3-15 mg/day haloperidol<br>Responders continued same treatment<br>5-20 mg/day olanzapine |

Abbreviations: DB = double-blind; OL = open-label; wks = weeks; mos = months; ext = extension.

**Table ISS.4.1. Studies Included in the Safety Analysis of Olanzapine for Maintenance Treatment of Bipolar Disorder (concluded)**

| Protocol Code: Study Design | Primary Study Objective | Phase Duration: | Treatments |
|---|---|---|---|
| **HGEH:** Two double-blind, randomized, parallel, multicenter studies of olanzapine versus placebo in bipolar patients (manic or mixed). | To assess the efficacy of flexible dosing of olanzapine compared with placebo. | 3 wks DB acute:<br>12 mos OL ext: | 5-20 mg/day olanzapine or placebo<br>5-20 mg/day olanzapine |
| **HGGY** (included in 4-month safety update): Two double-blind, randomized, parallel, multicenter studies of olanzapine versus OFC versus placebo in patients with bipolar depression. | To assess acute olanzapine therapy compared with placebo in improving overall symptomatology. | 8 wks DB acute:<br><br>6 mos OL ext:<br><br>Olanzapine plus fluoxetine dose combinations were 6/25, 6/50, and 12/50 mg/day. | 5-20 mg/day olanzapine, placebo, or OFC<br>5-20 mg/day olanzapine or OFC |

Abbreviations: DB = double-blind; OL = open-label; OFC = olanzapine plus fluoxetine in combination; wks = weeks; mos = months; ext = extension.

**Table SU.5.1. Patients Included from Each Study
Updated Overall Integrated Database**

| Study | Study Title<br>• Patients Included | Definition of Baseline[a] and Comparator Periods |
|---|---|---|
| HGGY | **Placebo-Controlled Olanzapine Monotherapy in the Treatment of Bipolar I Depression** | |
| | • Patients randomized to olanzapine during the acute phase who did not participate in the open-label phase | Baseline: Visits 1-2<br>Comparator: Visits 3-8 |
| | • Patients randomized to olanzapine during the acute phase who later received only olanzapine during the open-label phase (never switching to OFC) | Baseline: Visits 1-2<br>Comparator: Visits 3-306 |
| | • Patients randomized to OFC or placebo during the acute phase who later received only olanzapine during the open-label phase (never switching to OFC) | Baseline: Visits 1-8<br>Comparator: Visits 301-306 |
| | (See the HGGY open-label clinical study report for complete data for the latter two groups of patients, who are referred to as "olanzapine monotherapy patients.") | |

**Table SU.5.1. Patients Included from Each Study
Updated Overall Integrated Database (concluded)**

| Study | Study Title<br>• Patients Included | Definition of Baseline[a] and Comparator Periods |
|---|---|---|
| HGHL | **Olanzapine Versus Placebo in the Prevention of Relapse in Bipolar Disorder** | |
| | • Patients exposed to open-label olanzapine during the stabilization phase who were randomized to olanzapine for double-blind therapy | Baseline: Visits 1-2<br>Comparator: Visits 3-14, 101-116, 301-308 |
| | • Patients exposed to open-label olanzapine during the stabilization phase who failed to be randomized or were randomized to placebo (NOTE: Exposures to olanzapine during open-label rescue subsequent to relapse after randomization to placebo were not included) | Baseline: Visits 1-2<br>Comparator: Visits 3-14 |
| HGHT | **Olanzapine Versus Lithium in Relapse Prevention in Bipolar Disorder** | |
| | • Patients randomized to olanzapine (these patients were treated with olanzapine and lithium during baseline and tapered off lithium from Visits 101-104) | Baseline: Visits 1-16<br>Comparator: Visits 101-114 |
| HGHQ | **Olanzapine Versus Divalproex in the Treatment of Acute Mania** | |
| | • Patients randomized to olanzapine | Baseline: Visits 1-2<br>Comparator: Visits 3-20 |
| HGHD | **Olanzapine Versus Haloperidol in the Treatment of Acute Mania** | |
| | • Patients randomized to olanzapine | Baseline: Visits 1-2<br>Comparator: Visits 3-14, 301-307 |
| | • Patients randomized to haloperidol who later received open-label olanzapine therapy | Baseline: Visits 1-14/last double-blind visit<br>Comparator: Visits 301-307 |
| HGEH | **Olanzapine Versus Placebo in the Treatment of Mania Associated with Bipolar I Disorder** | |
| | • Patients randomized to olanzapine | Baseline: Visits 1-2<br>Comparator: Visits 3-5, 301-315 |
| | • Patients randomized to placebo who later received open-label olanzapine therapy | Baseline: Visits 1-5/last double-blind visit<br>Comparator: Visits 301-315 |

[a] The baseline period is represented by several visits. For quantitative comparisons, the baseline value is the last visit of the baseline period. For analysis of treatment-emergent events, the baseline value is the worst value/event occurring during the baseline period.

## 5.2. Exposure

Table SU.5.2 and Table SU.5.3 summarize patient exposure to olanzapine over long-term treatment, as presented in the original and updated overall integrated databases, respectively. In the original database, the total exposure to olanzapine was 592.1 patient-years. A total of 473 patients had exposures of >183 days, and 129 patients had over a year of exposure. In the updated database, the total exposure to olanzapine was 674.9 patient-years. A total of 512 patients had exposures of >183 days. The total number of patients with over a year of exposure remained constant at 129, since Protocol HGGY was designed to be only 32 weeks long. Note that just one study had a scheduled duration >365 days (HGHL). Some patients in other studies had exposures >365 days because their visits were separated by the maximum visit window.

**Table SU.5.2.** **Patient Exposure to Olanzapine Therapy**
**ISS Overall Integrated Database**
**(HGHL, HGHT, HGHQ, HGHD, HGEH)**

| Duration (Days) | Dosage Range <5 mg | 5 - <10 mg | 10 - <15 mg | 15 - <20 mg | >=20 mg | Total | (%) |
|---|---|---|---|---|---|---|---|
| <=14 | 11 | 14 | 56 | 28 | 32 | 141 | (9.2%) |
| 14< - 31 | 9 | 25 | 60 | 34 | 49 | 177 | (11.6%) |
| 31< - 91 | 8 | 78 | 150 | 118 | 151 | 505 | (33.0%) |
| 91< - 183 | 1 | 68 | 78 | 50 | 35 | 232 | (15.2%) |
| 183< - 270 | 1 | 61 | 47 | 40 | 33 | 182 | (11.9%) |
| 270< - 365 | 0 | 51 | 31 | 36 | 44 | 162 | (10.6%) |
| >365 | 0 | 27 | 49 | 32 | 21 | 129 | (8.4%) |
| Total | 30 | 324 | 471 | 338 | 365 | 1528 | |
| (%) | (2.0%) | (21.2%) | (30.8%) | (22.1%) | (23.9%) | | |

Total patient days of exposure: 216269

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Table ISS.6.10. Laboratory Evaluations Mean Change from Baseline to Endpoint
HGHL, Double-Blind Treatment
Placebo-Controlled Maintenance Database

Research Project Code: 91D

| Lab Test | Lab Unit | Therapy | n | Baseline Mean | Baseline SD | Change to Endpoint Mean | Change to Endpoint SD | p-Values Therapy (Int*1) | p-Values Model |
|---|---|---|---|---|---|---|---|---|---|
| HCT | l | Placebo | 124 | 0.42 | 0.04 | 0.01 | 0.03 | .306 | FULL2 |
| | | Olz | 216 | 0.42 | 0.04 | 0.01 | 0.03 | (.240) | |
| HGB | mml/L-Fe | Placebo | 124 | 8.73 | 0.91 | 0.23 | 0.50 | .281 | FULL2 |
| | | Olz | 216 | 8.69 | 0.86 | 0.18 | 0.50 | (.030) | |
| RBC | TI/L | Placebo | 124 | 4.69 | 0.48 | 0.13 | 0.26 | .188 | FULL2 |
| | | Olz | 216 | 4.70 | 0.46 | 0.11 | 0.27 | (.009) | |
| MCHC | mml/L-Fe | Placebo | 124 | 20.87 | 1.04 | 0.13 | 0.93 | .799 | FULL2 |
| | | Olz | 216 | 20.88 | 1.01 | 0.12 | 0.96 | (.292) | |
| MCH | fmol(Fe) | Placebo | 124 | 1.87 | 0.13 | -0.01 | 0.07 | .298 | FULL2 |
| | | Olz | 216 | 1.86 | 0.13 | -0.01 | 0.06 | (.534) | |
| WBC | GI/L | Placebo | 124 | 7.71 | 2.15 | 0.12 | 1.79 | .928 | FULL2 |
| | | Olz | 216 | 7.76 | 2.38 | 0.17 | 1.70 | (.240) | |
| POLYS | GI/L | Placebo | 124 | 4.83 | 1.86 | 0.17 | 1.68 | .994 | FULL2 |
| | | Olz | 216 | 4.84 | 1.85 | 0.20 | 1.56 | (.364) | |
| LYMPHS | GI/L | Placebo | 124 | 2.24 | 0.66 | -0.02 | 0.51 | .522 | FULL2 |
| | | Olz | 216 | 2.28 | 0.84 | -0.00 | 0.54 | (.863) | |
| MONOS | GI/L | Placebo | 124 | 0.41 | 0.13 | -0.01 | 0.13 | .283 | FULL2 |
| | | Olz | 216 | 0.43 | 0.16 | -0.02 | 0.14 | (.708) | |
| EOSN | GI/L | Placebo | 124 | 0.17 | 0.13 | -0.02 | 0.10 | .944 | FULL2 |
| | | Olz | 216 | 0.16 | 0.13 | -0.01 | 0.11 | (.516) | |
| BASO | GI/L | Placebo | 124 | 0.05 | 0.03 | 0.00 | 0.03 | .423 | FULL2 |
| | | Olz | 216 | 0.06 | 0.03 | -0.00 | 0.03 | (.310) | |
| MCV | fL | Placebo | 124 | 89.79 | 6.01 | -0.83 | 4.08 | .657 | FULL2 |
| | | Olz | 216 | 89.04 | 6.05 | -0.79 | 3.61 | (.036) | |
| PLTCT | GI/L | Placebo | 124 | 266.15 | 59.89 | 2.05 | 50.16 | .519 | FULL2 |
| | | Olz | 213 | 264.71 | 57.76 | 4.37 | 38.31 | (.152) | |
| U-SPGR | NO UNITS | Placebo | 108 | 1.02 | 0.01 | 0.00 | 0.01 | .534 | RDUC2 |
| | | Olz | 161 | 1.02 | 0.01 | -0.00 | 0.01 | (.297) | |
| U-PH | U | Placebo | 108 | 5.73 | 0.68 | 0.06 | 0.92 | .002 | RDUC2 |
| | | Olz | 161 | 5.81 | 0.75 | -0.28 | 0.89 | (.295) | |

XLAS0006

Table ISS.6.10. Laboratory Evaluations Mean Change from Baseline to Endpoint
HGHL, Double-Blind Treatment
Placebo-Controlled Maintenance Database (continued)

Research Project Code: F1D

| Lab Test | Lab Unit | Therapy | n | Baseline Mean | Baseline SD | Change to Endpoint Mean | Change to Endpoint SD | p-Values -- Therapy (Int*1) | Model |
|---|---|---|---|---|---|---|---|---|---|
| AST | U/L | Placebo | 128 | 24.78 | 12.19 | 2.49 | 60.05 | .738 | FULL2 |
| | | Olz | 216 | 26.03 | 23.85 | -0.04 | 13.53 | (.070) | |
| ALT | U/L | Placebo | 128 | 28.48 | 21.83 | -1.63 | 48.85 | .186 | FULL2 |
| | | Olz | 216 | 31.01 | 31.17 | 0.89 | 20.34 | (.126) | |
| CPK | U/L | Placebo | 128 | 114.88 | 105.52 | 12.11 | 179.25 | .253 | FULL2 |
| | | Olz | 216 | 103.37 | 76.20 | -6.59 | 66.39 | (.533) | |
| ALKPH | U/L | Placebo | 128 | 74.33 | 19.11 | 1.67 | 17.40 | .586 | FULL2 |
| | | Olz | 216 | 76.63 | 24.13 | 2.13 | 13.66 | (.539) | |
| GGT | U/L | Placebo | 128 | 28.17 | 21.89 | -2.68 | 18.17 | .671 | FULL2 |
| | | Olz | 216 | 33.72 | 33.66 | -0.64 | 16.96 | (.411) | |
| BUN | mmol/L | Placebo | 128 | 4.60 | 1.47 | -0.09 | 1.26 | .133 | FULL2 |
| | | Olz | 216 | 4.90 | 1.40 | -0.38 | 1.24 | (.973) | |
| CREAT | umol/L | Placebo | 128 | 98.06 | 15.51 | 2.67 | 10.60 | .198 | FULL2 |
| | | Olz | 216 | 96.69 | 15.02 | 3.39 | 10.43 | (.526) | |
| CALC | mmol/L | Placebo | 128 | 2.36 | 0.11 | 0.04 | 0.10 | .159 | FULL2 |
| | | Olz | 216 | 2.35 | 0.11 | 0.03 | 0.11 | (.486) | |
| PHOS | mmol/L | Placebo | 128 | 1.23 | 0.21 | -0.06 | 0.24 | .332 | FULL2 |
| | | Olz | 216 | 1.21 | 0.19 | -0.06 | 0.21 | (.225) | |
| SODIUM | mmol/L | Placebo | 127 | 140.62 | 2.38 | 0.10 | 2.91 | .145 | FULL2 |
| | | Olz | 215 | 140.77 | 2.47 | 0.30 | 2.99 | (.161) | |
| POTAS | mmol/L | Placebo | 127 | 4.24 | 0.37 | 0.04 | 0.41 | .601 | FULL2 |
| | | Olz | 215 | 4.23 | 0.38 | -0.03 | 0.40 | (.606) | |
| CHLOR | mmol/L | Placebo | 127 | 104.61 | 2.83 | -0.22 | 3.04 | .422 | FULL2 |
| | | Olz | 215 | 104.90 | 2.63 | -0.18 | 3.02 | (.536) | |
| TPROT | g/L | Placebo | 128 | 72.77 | 4.18 | 0.87 | 4.35 | .341 | FULL2 |
| | | Olz | 216 | 72.12 | 4.74 | 0.80 | 4.45 | (.049) | |
| ALBUM | g/L | Placebo | 128 | 40.20 | 3.26 | 1.30 | 2.49 | .607 | FULL2 |
| | | Olz | 216 | 40.25 | 3.35 | 1.09 | 2.98 | (.267) | |
| HYGLU | mmol/L | Placebo | 128 | 5.84 | 2.73 | 0.01 | 1.94 | .125 | FULL2 |
| | | Olz | 216 | 5.92 | 3.00 | 0.22 | 1.89 | (.017) | |

Table ISS.6.10. **Laboratory Evaluations Mean Change from Baseline to Endpoint**
**HGHL, Double-Blind Treatment**
**Placebo-Controlled Maintenance Database (continued)**

Research Project Code: F1D

| Lab Test | Lab Unit | Therapy | n | Baseline Mean | Baseline SD | Change to Endpoint Mean | Change to Endpoint SD | p-Values Therapy (Int*1) | p-Values Model |
|---|---|---|---|---|---|---|---|---|---|
| UR AC | umol/L | Placebo | 128 | 342.34 | 75.04 | -18.76 | 53.31 | <.001 | FULL2 |
| | | Olz | 216 | 324.78 | 81.13 | 8.30 | 49.42 | (.107) | |
| CHOL | mmol/L | Placebo | 128 | 5.31 | 0.96 | -0.27 | 0.77 | .106 | FULL2 |
| | | Olz | 216 | 5.43 | 1.18 | -0.04 | 0.79 | (.345) | |
| BICARB | mmol/L | Placebo | 127 | 24.12 | 2.69 | -0.50 | 3.03 | .645 | FULL2 |
| | | Olz | 215 | 23.93 | 2.73 | -0.39 | 2.95 | (.587) | |
| T.BILI | umol/L | Placebo | 128 | 6.38 | 3.77 | 1.12 | 3.43 | .238 | FULL2 |
| | | Olz | 216 | 6.02 | 3.30 | 0.57 | 3.06 | (.022) | |
| PROLAC | nmol/L | Placebo | 111 | 1.04 | 1.17 | -0.33 | 1.19 | .007 | RDUC2 |
| | | Olz | 172 | 0.88 | 0.62 | -0.07 | 0.61 | (.143) | |
| HGBA1C | 1 | Placebo | 111 | 0.06 | 0.01 | -0.00 | 0.00 | .060 | RDUC2 |
| | | Olz | 170 | 0.06 | 0.01 | 0.00 | 0.00 | (.001) | |

Reporting SI units
Note: The following investigators were pooled
004 007 010 011 013 007 010 011 013 014
015 018 021 030 034 036 041 042 050
RMP.F1DP.JCLLIB(HLOF819B)
RMP.F1DP.SASMACRO(SSAFHS8)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL2 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.
RDUC2 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=investigator and treatment for the overall p-Value and model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
Note: At least one investigator does not have patients in every treatment group.

**Table ISS.6.10.** Laboratory Evaluations Mean Change from Baseline to Endpoint
HGHL, Double-Blind Treatment
Placebo-Controlled Maintenance Database (concluded)

Legend of Lab Test Code Abbreviations:

| Abbrev. | Description |
|---|---|
| HCT | HEMATOCRIT |
| HGB | HEMOGLOBIN |
| RBC | ERYTHROCYTE COUNT |
| MCHC | MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC) |
| MCH | MEAN CELL HEMOGLOBIN (MCH) |
| WBC | LEUKOCYTE COUNT |
| POLYS | NEUTROPHILS, SEGMENTED |
| LYMPHS | LYMPHOCYTES |
| MONOS | MONOCYTES |
| EOSN | EOSINOPHILS |
| BASO | BASOPHILS |
| MCV | MEAN CELL VOLUME (MCV) |
| PLTCT | PLATELET COUNT |
| U-SPGR | UA-SPECIFIC GRAVITY |
| U-PH | UA-PH |
| AST | AST/SGOT |
| ALT | ALT/SGPT |
| CPK | CREATINE PHOSPHOKINASE |
| ALKPH | ALKALINE PHOSPHATASE |
| GGT | GGT (GGPT/SGGT/YGGT) |
| BUN | UREA NITROGEN |
| CREAT | CREATININE |
| CALC | CALCIUM |
| PHOS | INORGANIC PHOSPHORUS |
| SODIUM | SODIUM |
| POTAS | POTASSIUM |
| CHLOR | CHLORIDE |
| TPROT | TOTAL PROTEIN |
| ALBUM | ALBUMIN |
| NFGLU | GLUCOSE, NON-FASTING |
| UR AC | URIC ACID |
| CHOL | CHOLESTEROL |
| BICARB | BICARBONATE, HCO3 |
| T.BILI | BILIRUBIN, TOTAL |

Legend of Lab Test Code Abbreviations:

| Abbrev. | Description |
|---|---|
| PROLAC | PROLACTIN |
| HGBA1C | HEMOGLOBIN A1C |

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# CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT LABORTORY/EKG/VITAL SIGNS

**Table ISS.5.3. Criteria for Identifying Patients with Potentially Clinically Significant Laboratory Abnormalities**

| Analytes With Units | SI Units | | | Conventional US Units | | |
|---|---|---|---|---|---|---|
| | Units | Low Limit | High Limit | Units | Low Limit | High Limit |
| Albumin | G/L | 25 | -- | g/dL | 2.5 | -- |
| Alkaline Phosphatase | U/L | -- | 420 | IU/L | -- | 420 |
| ALT/SGPT | U/L | -- | 168 | IU/L | -- | 168 |
| AST/SGOT | U/L | -- | 150 | IU/L | -- | 150 |
| Calcium | Mmol/L | 1.7465 | 2.994 | mg/dL | 7 | 12 |
| CK: Female | U/L | -- | 507 | IU/L | -- | 507 |
| Male | U/L | -- | 594 | IU/L | -- | 594 |
| Creatinine | µmol/L | -- | 176.8 | mg/dL | -- | 2 |
| Eosinophils | % WBC | -- | 10 | % WBC | -- | 10 |
| GGT: Female | U/L | -- | 135 | IU/L | -- | 135 |
| Male | U/L | -- | 195 | IU/L | -- | 195 |
| Glucose (non fasting) | mmol/L | 2.4975 | 13.875 | mg/dL | 45 | 250 |
| Hematocrit: Female | l | 0.32 | 0.50 | % | 32 | 50 |
| Male | l | 0.37 | 0.55 | % | 37 | 55 |
| Hemoglobin: Female | mmol/L (Fe) | 5.8957 | 10.2599 | g/dL | 9.5 | 16.5 |
| Male | mmol/L (Fe) | 7.1369 | 11.4811 | g/dL | 11.5 | 18.5 |
| Neutrophils | % WBC | 15 | -- | % WBC | 15 | -- |
| Platelet Count | Gi/L | 75 | 700 | 1000/µ L | 75 | 700 |
| Phosphorous | mmol/L | 0.48435 | 1.77595 | mmol/L | 0.48435 | 1.77595 |
| RBC | Ti/L | 3 | 6 | million/µ L | 3 | 6 |
| Sodium | mmol/L | 129 | 160 | mEq/L | 129 | 160 |
| Total Cholesterol | mmol/L | -- | 15.516 | mg/dL | -- | 600 |
| Total Bilirubin | µmol/L | -- | 34.2 | mg/dL | -- | 2 |
| Total Protein | G/L | 50 | -- | g/dL | 5 | -- |
| Urea Nitrogen | mmol/L | -- | 10.71 | mg/dL | -- | 30 |
| Uric Acid: Female | µmol/L | -- | 505.58 | mg/dL | -- | 8.5 |
| Male | µmol/L | -- | 624.54 | mg/dL | -- | 10.5 |
| WBC | Gi/L | 2.8 | 16.0 | 1000/µ L | 2.8 | 16.0 |

| Analytes Without Units | Low Limit | High Limit |
|---|---|---|
| UA-Casts | -- | increase ≥2 and score ≥3 |
| UA-Glucose | -- | increase ≥2 and score ≥3 |
| UA-Ketones | -- | increase ≥2 and score ≥3 |
| UA-pH | 4.6 | 8.0 |
| UA-Protein | -- | increase ≥2 and score ≥3 |
| UA-RBC | -- | increase ≥2 and score ≥3 |
| UA-Specific Gravity | 1.001 | 1.035 |
| UA-WBC | -- | increase ≥2 and score ≥3 |

Abbreviations: ALT/SGPT = alanine transaminase/serum glutamic pyruvic transaminase; AST/SGOT = aspartate transaminase/serum glutamic oxaloacetic transaminase; GGT = gamma-glutamyl transferase; CK = creatine kinase; Fe = iron; RBC = red blood cell; UA = urinalysis; WBC = white blood cell; SI = International System of Units.

**Table ISS.5.4. Criteria for Identifying Patients with Potentially Clinically Significant Changes in Vital Signs and Weight**

| Parameter | Low | High |
|---|---|---|
| Orthostatic systolic BP (mm Hg) | ≥30 mm Hg decrease in systolic BP (supine to standing) | -- |
| Orthostatic hypotension | ≥20 mm Hg decrease in systolic BP and ≥ 10 bpm increase in pulse (supine to standing) | -- |
| Supine systolic BP (mm Hg) | ≤90 and decrease ≥20 | ≥180 and increase ≥20 |
| Standing systolic BP (mm Hg) | ≤90 and decrease ≥20 | ≥180 and increase ≥20 |
| Supine diastolic BP (mm Hg) | ≤50 and decrease ≥15 | ≥105 and increase ≥15 |
| Standing diastolic BP (mm Hg) | ≤50 and decrease ≥15 | ≥105 and increase ≥15 |
| Supine pulse (bpm) | <50 and decrease ≥15 | >120 and increase ≥15 |
| Standing pulse (bpm) | <50 and decrease ≥15 | >120 and increase ≥15 |
| Temperature (°F)* | -- | ≥101 °F and increase ≥2 |
| Weight (kg) | decrease ≥7% | increase ≥7% |

Abbreviations: BP= blood pressure; bpm = beats per minute.
*Converted to Celsius for analysis

**Table ISS.5.5. Criteria for Identifying Patients with Potentially Clinically Significant Change in Electrocardiogram Intervals and Heart Rate**

| Interval | Low | High |
|---|---|---|
| PR | -- | 200 ms |
| QRS | -- | 100 ms |
| QT | -- | 450 ms |
| QTc | -- | 450 ms for males; 470 ms for females |
| Heart Rate | 40 bpm | 120 bpm |

Abbreviations: bpm = beats per minute; ms = millisecond.

**Table ISS.5.6. Additional Criteria for Identifying Patients with a Potentially Clinically Significant Prolonged Electrocardiogram QTc Interval**

| Criterion Number | Criterion |
|---|---|
| 1 | In adult males, QTc ≥430 ms; in adult females, QTc ≥450 ms |
| 2 | In adult males, QTc ≥450 ms; in adult females, QTc ≥470 ms |
| 3 | QTc ≥500 ms |
| 4 | Increase ≥30 ms relative to baseline |
| 5 | Increase ≥60 ms relative to baseline |
| 6 | Increase ≥75 ms relative to baseline |

Table ISS.6.15. **Vital Signs and Weight Mean Change from Baseline to Endpoint**
**HGHL, Double-Blind Treatment**
**Placebo-Controlled Maintenance Database**

Research Project Code: F1D

| Variables Analyzed | Therapy | n | Baseline Mean | Baseline SD | Change to Endpoint Mean | Change to Endpoint SD | p-Values Therapy (Int*1) |
|---|---|---|---|---|---|---|---|
| WEICHTKG | Placebo | 133 | 87.01 | 19.62 | -2.03 | 4.44 | <.001 |
| | Olz | 224 | 84.86 | 21.31 | 0.98 | 5.18 | (.853) |
| TEMPC90 | Placebo | 133 | 36.77 | 0.44 | -0.05 | 0.47 | .160 |
| | Olz | 224 | 36.74 | 0.45 | 0.01 | 0.48 | (.173) |
| SYSBP_SU | Placebo | 134 | 120.07 | 13.00 | 0.86 | 12.47 | .173 |
| | Olz | 224 | 121.37 | 14.54 | -0.51 | 12.79 | (.317) |
| DIABP_SU | Placebo | 134 | 75.95 | 9.22 | 0.76 | 9.20 | .315 |
| | Olz | 224 | 75.83 | 10.04 | 0.40 | 9.88 | (.170) |
| SYSBP_ST | Placebo | 134 | 120.86 | 14.07 | 0.16 | 11.29 | .260 |
| | Olz | 224 | 121.34 | 15.71 | -0.04 | 12.81 | (.088) |
| DIABP_ST | Placebo | 134 | 77.98 | 10.47 | 1.45 | 9.62 | .175 |
| | Olz | 224 | 78.23 | 11.04 | 0.01 | 10.61 | (.455) |
| PULSE_SU | Placebo | 134 | 75.78 | 10.68 | -0.86 | 11.36 | .834 |
| | Olz | 224 | 76.93 | 10.56 | -0.84 | 11.10 | (.632) |
| PULSE_ST | Placebo | 134 | 81.59 | 11.63 | -1.22 | 11.35 | .932 |
| | Olz | 224 | 82.94 | 11.97 | -0.06 | 12.65 | (.609) |
| SYSBP_OR | Placebo | 134 | -0.79 | 7.09 | 0.71 | 9.98 | .737 |
| | Olz | 224 | 0.02 | 8.50 | -0.47 | 11.11 | (.284) |
| PULSE_OR | Placebo | 134 | 5.82 | 8.77 | -0.07 | 9.68 | .842 |
| | Olz | 224 | 5.97 | 7.69 | 0.82 | 9.52 | (.101) |

Note: The following investigators were pooled
004 007 010 011 013 007 010 011 013 014
015 018 021 030 034 036 041 042 050

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Table ISS.6.16. **Vital Signs and Weight**
**Potentially Clinically Significant Changes**
**HGHL, Double-Blind Treatment**
**Placebo-Controlled Maintenance Database**

| Vital | Direction | No. | Therapy | N | n | (%) | - p-Values - Overall |
|---|---|---|---|---|---|---|---|
| Orthostatic Hypotension | Footnote A | 1) | Placebo | 97 | 2 | 2.1% | .057 |
| | | 2) | Olz | 165 | 13 | 7.9% | |
| Orthostatic Sys BP | Decrease | 1) | Placebo | 134 | 1 | 0.7% | .416 |
| | | 2) | Olz | 223 | 5 | 2.2% | |
| Standing Diastolic BP | High | 1) | Placebo | 133 | 1 | 0.8% | .260 |
| | | 2) | Olz | 218 | 6 | 2.8% | |
| | Low | 1) | Placebo | 133 | 2 | 1.5% | .558 |
| | | 2) | Olz | 223 | 1 | 0.4% | |
| Standing Pulse | High | 1) | Placebo | 134 | 2 | 1.5% | .634 |
| | | 2) | Olz | 222 | 2 | 0.9% | |
| | Low | 1) | Placebo | 134 | 0 | 0.0% | 1.000 |
| | | 2) | Olz | 224 | 1 | 0.4% | |
| Standing Systolic BP | High | 1) | Placebo | 134 | 0 | 0.0% | 1.000 |
| | | 2) | Olz | 224 | 1 | 0.4% | |
| | Low | 1) | Placebo | 132 | 3 | 2.3% | .546 |

Footnote A: Orthostatic Hypotension is defined as a 20 mmHg decrease in systolic BP concurrent with a 10 bpm increase in pulse comparing standing versus supine vitals signs assessments.

Table ISS.6.16. Vital Signs and Weight
Potentially Clinically Significant Changes
HGHL, Double-Blind Treatment
Placebo-Controlled Maintenance Database (continued)

| Vital | Direction | No. | Therapy | N | n | (%) | - p-Values - Overall |
|---|---|---|---|---|---|---|---|
| Standing Systolic BP | Low | 2) | Olz | 219 | 8 | 3.7% | |
| Supine Diastolic BP | High | 1) | Placebo | 134 | 1 | 0.7% | 1.00 |
| | | 2) | Olz | 219 | 3 | 1.4% | |
| | Low | 1) | Placebo | 134 | 2 | 1.5% | .633 |
| | | 2) | Olz | 223 | 2 | 0.9% | |
| Supine Pulse | High | 1) | Placebo | 134 | 0 | 0.0% | |
| | | 2) | Olz | 224 | 0 | 0.0% | |
| | Low | 1) | Placebo | 134 | 1 | 0.7% | 1.00 |
| | | 2) | Olz | 223 | 2 | 0.9% | |
| Supine Systolic BP | High | 1) | Placebo | 134 | 0 | 0.0% | |
| | | 2) | Olz | 222 | 0 | 0.0% | |
| | Low | 1) | Placebo | 133 | 7 | 5.3% | .401 |
| | | 2) | Olz | 221 | 7 | 3.2% | |
| Temperature (C) | High | 1) | Placebo | 133 | 0 | 0.0% | 1.00 |
| | | 2) | Olz | 224 | 1 | 0.4% | |

Footnote A: Orthostatic Hypotension is defined as a 20 mmHg decrease
in systolic BP concurrent with a 10 bpm increase in pulse
comparing standing versus supine vitals signs assessments.
PCS Event defined by a vital result outside defined limits at anytime post-baseline
Frequencies analyzed using two-tailed Fisher's Exact Test

Table ISS.6.16. Vital Signs and Weight
Potentially Clinically Significant Changes
HGHL, Double-Blind Treatment
Placebo-Controlled Maintenance Database (concluded)

| Vital | Direction | No. | Therapy | N | n | (%) | - p-Values - Overall |
|---|---|---|---|---|---|---|---|
| Weight (kg) | Gain | 1) | Placebo | 133 | 3 | 2.3% | <.001 |
| | | 2) | Olz | 224 | 36 | 16.1% | |
| | Loss | 1) | Placebo | 133 | 17 | 12.8% | .089 |
| | | 2) | Olz | 224 | 16 | 7.1% | |

Footnote A: Orthostatic Hypotension is defined as a 20 mmHg decrease
in systolic BP concurrent with a 10 bpm increase in pulse
comparing standing versus supine vitals signs assessments.
PCS Event defined by a vital result outside defined limits at anytime post-baseline
Frequencies analyzed using two-tailed Fisher's Exact Test

Table ISS.11.13. **Incidence of Weight Gain of at Least 7% Summary Across Databases**

| Database | Therapy | Weight Gain of at Least 7% N | n | % | P |
|---|---|---|---|---|---|
| HGHL | olanzapine | 224 | 36 | 16.1% | <.001 |
| | placebo | 133 | 3 | 2.3% | |
| HGHT | olanzapine | 215 | 64 | 29.8% | <.001 |
| | lithium | 214 | 21 | 9.8% | |
| HGHQ | olanzapine | 123 | 47 | 38.2% | .040 |
| | divalproex | 123 | 31 | 25.2% | |
| HGFU | olanzapine+MS | 71 | 23 | 32.4% | .001 |
| | placebo+MS | 64 | 6 | 9.4% | |
| OID | olanzapine | 1502 | 599 | 39.9% | Na |

Abbreviations: N = number of patients with a normal baseline and at least one postbaseline assessment; n = number of patients meeting the criterion postbaseline; p = p-value determined using a two-tailed Fisher's exact test; MS = mood stabilizer (lithium or divalproex).

Sources: Table ISS.6.16 (HGHL), Table ISS.7.16 (HGHT), Table ISS.7.35 (HGHQ), Table ISS.8.16

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Table ISS.11.10. **Treatment-Emergent Adverse Events Related to Glucose in the Overall Integrated Database**

| Category of Event | Event | Incidence (%) |
|---|---|---|
| Treatment-emergent (all) | diabetes mellitus NOS | 9 (0.6%) |
| | blood glucose increased | 4 (0.3%) |
| | hyperglycemia NOS | 2 (0.1%) |
| | blood glucose abnormal | 1 (0.1%) |
| | diabetes mellitus non-insulin-dependent | 1 (0.1%) |
| | glucose tolerance impaired | 1 (0.1%) |
| | ketosis | 1 (0.1%) |
| Serious | diabetes mellitus NOS | 1 (0.1%) |
| Leading to discontinuation | blood glucose increased | 1 (0.1%) |

**Table HGHL.11.33. Time-to-Relapse Subgroup Analyses**
**Double-Blind Treatment**

| Interaction Subgroup | Stratum | Therapy | N | 25th Pct | 50th Pct | Within Strata P-Value | Hazard Ratio | P-Value |
|---|---|---|---|---|---|---|---|---|
| Age | <40 | Placebo | 69 | 13 | 22 | <.001 | 3.02 | .397 |
| | | Olz | 104 | 29 | 206 | | | |
| | >=40 | Placebo | 67 | 9 | 21 | <.001 | 2.38 | |
| | | Olz | 121 | 30 | 165 | | | |
| Gender | Male | Placebo | 53 | 13 | 28 | <.001 | 2.51 | .718 |
| | | Olz | 87 | 29 | 296 | | | |
| | Female | Placebo | 83 | 10 | 21 | <.001 | 2.78 | |
| | | Olz | 138 | 29 | 174 | | | |
| Origin | Caucasian | Placebo | 120 | 13 | 22 | <.001 | 2.57 | .496 |
| | | Olz | 195 | 29 | 149 | | | |
| | Other | Placebo | 16 | 8 | 26 | .004 | 3.45 | |
| | | Olz | 30 | 35 | NA | | | |
| Psychotic Features | No | Placebo | 108 | 10 | 22 | <.001 | 2.62 | .743 |
| | | Olz | 187 | 29 | 149 | | | |
| | Yes | Placebo | 28 | 14 | 27 | <.001 | 2.94 | |
| | | Olz | 38 | 43 | 252 | | | |
| Mania Type | Manic | Placebo | 88 | 13 | 43 | <.001 | 2.83 | .985 |
| | | Olz | 144 | 40 | NA | | | |
| | Mixed | Placebo | 45 | 9 | 15 | <.001 | 2.81 | |
| | | Olz | 76 | 22 | 46 | | | |
| Rapid Cycler | No | Placebo | 76 | 14 | 43 | <.001 | 2.45 | .331 |
| | | Olz | 106 | 31 | 206 | | | |
| | Yes | Placebo | 60 | 9 | 15 | <.001 | 3.21 | |
| | | Olz | 119 | 24 | 105 | | | |

Table HGHL.11.34. Relapse Incidence Subgroup Analyses
Double-Blind Treatment

| Subgroup | Strata | Therapy | N | n | (%) | Fisher's Exact p-value | Breslow Day p-value |
|---|---|---|---|---|---|---|---|
| Age | < 40 | Placebo | 69 | 57 | (82.6%) | <.001 | 0.403 |
| | | Olz | 104 | 47 | (45.2%) | | |
| | >= 40 | Placebo | 67 | 52 | (77.6%) | <.001 | |
| | | Olz | 121 | 58 | (47.9%) | | |
| Gender | Female | Placebo | 83 | 70 | (84.3%) | <.001 | 0.367 |
| | | Olz | 138 | 67 | (48.6%) | | |
| | Male | Placebo | 53 | 39 | (73.6%) | <.001 | |
| | | Olz | 87 | 38 | (43.7%) | | |
| Mania Type | Mixed | Placebo | 45 | 41 | (91.1%) | <.001 | 0.441 |
| | | Olz | 76 | 45 | (59.2%) | | |
| | Pure | Placebo | 88 | 65 | (73.9%) | <.001 | |
| | | Olz | 144 | 57 | (39.6%) | | |
| Origin | Caucasian | Placebo | 120 | 97 | (80.8%) | <.001 | 0.370 |
| | | Olz | 195 | 93 | (47.7%) | | |
| | Other | Placebo | 16 | 12 | (75.0%) | 0.032 | |
| | | Olz | 30 | 12 | (40.0%) | | |
| Psychotic Features | No | Placebo | 108 | 87 | (80.6%) | <.001 | 0.964 |
| | | Olz | 187 | 88 | (47.1%) | | |
| | Yes | Placebo | 28 | 22 | (78.6%) | 0.011 | |
| | | Olz | 38 | 17 | (44.7%) | | |
| Rapid Cycling | No | Placebo | 76 | 57 | (75.0%) | <.001 | 0.263 |
| | | Olz | 106 | 47 | (44.3%) | | |
| | Yes | Placebo | 60 | 52 | (86.7%) | <.001 | |
| | | Olz | 119 | 58 | (48.7%) | | |

N - Number of patients randomized.
n - Number of patients who met symptomatic relapse criteria.
Bipolar relapse is defined as meeting criteria for either manic or depressive relapse.
Report HLOF234B

# NARRATIVES OF DEATHS:

## HGHL 204-8803

This 60 year-old Caucasian male entered the study in a pure manic state without psychotic features on 20-Dec-2000 with a total Y-MRS score of 24 and a total HAMD-21 score of 4. The patient began treatment with 10.0mg/day olanzapine at visit 2 on 27-Dec-2001. The dose was increased to 15.0mg/day on 08-Jan-2001 and decreased again to 10.0mg/day on 22-Jan-2001. On 26-Feb-2001, visit 11, the patient was randomized to 10.0mg/day olanzapine with a total Y-MRS score of 9 and a total HAMD-21 score of 0. On 24-Jul-2001, the patient was discontinued from the double-blind randomization phase, with a total Y-MRS score of 2 and a total HAMD-21 score of 22, due to the adverse event of bipolar disorder. On that same day, the patient entered the open-label rescue therapy period at a dose of 10.0mg/day olanzapine. The dose was decreased to 5.0mg/day on 28-Aug-2001.

Patient:022-1053

Summary Paragraph (cont'd)

022-1053

This 51 year-old Caucasian male entered the study in a pure manic state without psychotic features on 01-May-2000 with a total Y-MRS score of 22 and a total HAMD-21 score of 6. The patient began treatment with 5.0mg/day olanzapine at visit 2 on 08-May-2000. The dose was increased to 10.0mg/day on 17-May-2000, increased again to 15.0mg/day on 24-May-2000, and decreased to 10.0mg/day on 31-May-2000. On 21-Jun-2000, visit 8, the patient was randomized to 10.0mg/day olanzapine with a total Y-MRS score of 4 and a total HAMD-21 score of 8. The dose was increased to 15.0mg/day on 02-Aug-2000. On 28-Aug-2000, the patient was discontinued from the double-blind randomization phase, with a total Y-MRS score of 9 and a total HAMD-21 score of 16, due to lack of efficacy in the perception of the patient and the investigator. On that same day, the patient entered into the open-label rescue therapy period at a dose of 10.0mg/day olanzapine. The last dose of study drug was taken on 13-Sep-2000 and the patient discontinued from the study on [redacted] due to personal conflict or other patient decision. At the time of discontinuation from the study, the patient had a total Y-MRS score of 9 and a total HAMD-21 score of 16. b(6)

The patient entered the study with a historical diagnosis of suicide attempt in 1967. On [redacted], approximately four weeks after last dose of study drug and three weeks after discontinuation from study, the patient committed suicide by a gunshot wound to the head. The patient had returned to his primary treating physician on 26-Sep-2000. In the opinion of the investigator, the serious adverse event of suicide attempt was not related to study drug or protocol procedures. b(6)

## Narratives of Deaths: HGEH

Summary Paragraph

This 33 year old Caucasian male was randomized to placebo treatment at Visit 2 on 02 MAY 97. Patient began open-label olanzapine treatment on the evening of Visit 5 on 23 MAY 97. Patient completed study at Visit 315 on 01 MAY 98, following 343 days of olanzapine treatment. Patient began using commercial olanzapine on this day. The [redacted] patient was found dead by his sister. ECG results from Visit 315 showed a normal sinus rhythm, with poor precordial R wave progression consistent with faulty lead placement. This abnormality was deemed to be not clinically significant when compared with the baseline ECG from Visit 1 on 28 APR 97. Baseline (Visit 2) weight was 136.30 kg, and his weight at Visit 315 was 128.82 kg. Patient was a cigarette smoker of 2 packs per day at the time of study end. Hypertension and hyperlipidemia reported as adverse events present since prior to study entry. Patient also was diagnosed with Type II diabetes mellitus, which was stable since prior to study entry from use of Amaryl. Patient was also taking Lopid, Atenolol, and Lotensin at the time of study end for his secondary medical conditions. Results of the autopsy indicated the cause of death was arteriosclerotic cardiovascular disease with myocardial fibrosis and diabetes mellitus as contributing factors.

b(6)

## HGHQ DEATH

Summary Paragraph

This 30 year-old Caucasian male began olanzapine therapy on the evening of Visit 2 on 28-Apr-1999. The patient continued on olanzapine therapy until [redacted] days after the first dose, when he was involved in a motorcycle accident and hospitalized in the intensive care unit. He suffered severe head trauma and several broken bones. The patient died on [redacted] as a result of the head trauma. It is unknown if an autopsy was performed.

b(6)

In the opinion of the investigator the event was not related to study drug or protocol procedures.

# HGGY DEATHS:

Summary Paragraph

This 44 year-old, Hispanic female was randomized to olanzapine on 28-Feb-2001 during the acute double-blind phase. At visit 9, on 10-Apr-2001, the patient continued into the open-label extension phase at a dose of 5.0mg/day olanzapine. At this visit, the patient had a total Y-MRS score of 0 and a total MADRS score of 25. The dose was increased to 10.0mg/day on 22-Apr-2001. The last dose of study drug was taken on 01-May-2001.

On [redacted] the serious adverse event of suicide attempt was reported after the patient died by hanging. Throughout the study, the patient presented with psychomotor retardation, anergy, anhedonia, pathological sadness, difficulty concentrating and thinking, insomnia, and depression that included guilt, hopelessness, worthlessness, and wishes of dying. The patient had no history of suicide attempts or psychiatric conditions. Concomitant medications included lorazepam 1.0mg for insomnia. At visit 301 on 27-Apr-2001, the last observation of the rating scales, the patient had a total Y-MRS score of 2 and a total MADRS score of 39. The investigator stated that suicide is a symptom of the disease and in the opinion of the investigator, the event was not related to study drugs or protocol procedures.

b(6)

Summary Paragraph

This 54 year-old, Caucasian male was randomized to olanzapine on 01-Aug-2001 during the acute double-blind phase. At visit 8, on 25-Sep-2001, the patient continued into the open-label extension phase at a dose of 10.0mg/day olanzapine. At this visit, the patient had a total Y-MRS score of 4 and a total MADRS score of 40. The investigator commented that he considered the elevated MADRS score to be related to an incident that resulted in psychological trauma, but no medical injury, to the patient.

Summary Paragraph (cont'd)

On [redacted] days following beginning of open-label extension phase, the serious adverse event of suicide attempt was reported after the patient's family reported his death by hanging. An autopsy was done and the cause of death was confirmed as mechanic asphyxia by suicide/hanging. The investigator commented that the patient did not previously present with suicidal tendencies in 27 years of illness. In the opinion of the investigator, the serious adverse event was not related to either the study drug or to the protocol procedures.

b(6)

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/s/
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Teresa Podruchny
9/4/03 07:28:03 AM
MEDICAL OFFICER

Paul Andreason
9/8/03 10:40:10 AM
MEDICAL OFFICER
I recommend that the Division issue an Approvable Action (AE). See my memo to the file dated September 8, 2003.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-592/S-019**

# CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

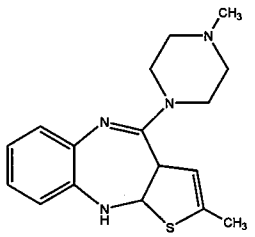
| | |
|---|---|
| 1. **ORGANIZATION:** | HFD-120 |
| 2. **NDA** | **20-592** |
| 3. **SUPPLEMENT NUMBER AND DATES:** | **SE1-019** |
| LETTER DATE: | 11-20-02 |
| STAMP DATE: | 11-26-02 |
| 4. **AMENDMENT/REPORTS/DATES:** | |
| LETTER DATE: | 12-12-02 |
| 5. **RECEIVED BY CHEMIST:** | 12-17-02 |

6. **APPLICANT NAME & ADDRESS:** Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

7. **NAME OF DRUG:** Zyprexa® Tablets

8. **NONPROPRIETARY NAME:** Olanzapine

9. **CHEMICAL NAME and STRUCTURE:** 2-methyl-4-(4-methyl-1-piperazinly)-10H-thieno[2,3-b][1,5]benzodiazepine




10. **DOSAGE FORMS:** Tablets

11. **POTENCY:** 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg

12. **PHARMACOLOGICAL CATEGORY:** antipsychotic

13. **HOW DISPENSED:** __X__(Rx) _____(OTC)

14. **RECORD and REPORTS CURRENT:** __X__Yes _____No

15. **RELATED IND/NDA/DMF:** n/a

16. **SUPPLEMENT PROVIDES FOR:** This supplement provides for the use of Zyprexa Tablets for the long-term treatment of bipolar I disorder.

17. **ADDITIONAL COMMENTS:** The applicant indicates that all relevant CMC information is provided in NDA 20-592. All Chemistry manufacturing and control information pertaining to the drug substance and the drug product remain unchanged.

18. **CONCLUSIONS & RECOMMENDATIONS:**
The applicant has provided adequate information to support this change. From a CMC perspective, it is recommended that this supplement be **APPROVED**.

cc: NDA 20-592 Division file
TOliver
SMclamore
DBates

1 Page(s) Withheld

Chemistry Review

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Sherita McLamore
1/10/03 11:46:35 AM
CHEMIST

Thomas Oliver
1/13/03 06:39:34 AM
CHEMIST

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-592/S-019**

# STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

# STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

| | |
|---|---|
| NDA /Serial Number: | NDA 20-592 S-019 |
| Name of Drug: | Zyprexa (olanzapine) |
| Applicant: | Eli Lilly and Company |
| Indication: | Bipolar I Disorder, Maintenance |
| Dates: | Nov. 20, 2002 |
| | |
| Biometrics Division: | Division of Biometrics I (HFD-710) |
| Statistical Reviewer: | Roswitha Kelly, M.S. |
| Concurring Reviewers: | Kun Jin, Ph.D., Team Leader |
| | George Chi, Ph.D., Director |
| | |
| Medical Division: | Neuropharmacological Drug Products (HFD-120) |
| Clinical Team: | Teresa Podruchny, M.D. (HFD-120) |
| Medical Team Leader: | Paul Andreason, Ph.D. (HFD-120) |
| Project Manager: | Doris Bates, Ph.D. (HFD-120) |

Keywords: olanzapine, relapse, maintenance, Kaplan-Meier estimates, log-rank test, Fisher's Exact test

# Table of Contents

## Table of Tables



b(4)

## Table of Figures

# 1 Executive Summary of Statistical Findings

## 1.1 Recommendations and Conclusions

Study HGHL is considered the pivotal study, which can satisfy the regulatory requirement for a maintenance claim. It assesses the efficacy of olanzapine compared to placebo in bipolar I patients who had responded to acute open-label olanzapine treatment and were in symptomatic remission of an index manic or mixed episode. The primary endpoint was relapse to a manic, depressive, or mixed episode. Study HGHL demonstrated a statistically significantly longer time to relapse and a smaller proportion of patients relapsing on olanzapine 5-20 mg/day than on placebo during the double blind maintenance period. However, patient attrition was substantial with only 4 olanzapine patients and only one placebo patient being treated for a whole year. Subgroup analyses for country, age, gender, origin, and concomitant benzodiazepine use maintained the superiority of olanzapine, usually to a statistically significant degree. There were some discrepancies between this reviewer's and the sponsor's findings, but the resolution of these differences is not expected to affect the conclusions.

## 1.2 Brief Overview of Clinical Studies

This application consists of nine separate study reports. Study HGHL is the pivotal study, which can satisfy the regulatory requirement for a maintenance claim and is being reviewed here in depth. None of the remaining studies are being reviewed statistically, as their potential efficacy has no bearing on the maintenance claim sought by the sponsor.

## 1.3 Statistical Issues and Findings

**Statistical Issues:**

There are no statistical issues in the primary efficacy analyses of time to relapse or proportion of patients relapsing. For most analyses, and in particular, for the primary analyses, findings for patients on olanzapine were statistically significantly better than for patients on placebo. However, for some subgroup analyses, there was only numeric superiority for olanzapine patients.

There are at least two concerns with implied meanings by the sponsor with which this reviewer does not agree. One is that this study may show 'prevention of relapse'. Study HGHL shows a significant superiority of Zyprexa over placebo in time to relapse and in proportion of patients relapsing, which is, however, not synonymous with prevention. Another concern lies with the statement that there is

a substantial number of patients 'completing the study interval', which can be interpreted as a substantial number of patients having been on treatment for a full year. However only 4 (1) olanzapine (placebo) patients completed one year of treatment.

There were some discrepancies in the number of patients in certain subgroups. The differences between the sponsor's reports and the data from the submitted data files could not be reconciled. However, resolution of these differences is not expected to affect the conclusions.

There was concern with the data of [ ] investigators, namely [ ] 034. This reviewer gives all analyses with or without their data. b(4)

**Findings:**

Only one trial is being considered. Study HGHL appears to meet the requirement for a maintenance claim by having shown statistically significant superiority of olanzapine over placebo in time to relapse and in proportion of patients relapsing. Patients were on study for up to one year. However, attrition was substantial and only 4 patients on olanzapine (1.8%) and only one patient on placebo (0.7%) remained in the study for one year. Robustness analyses and most subgroup analyses maintained the statistically significant superiority of olanzapine over placebo among bipolar I patients who have remitted on open label olanzapine.

# 2 Introduction

## 2.1 Overview

### 2.1.1 Background

Olanzapine is currently approved for the treatment for schizophrenia and for acute mania in patients with bipolar I disease. This submission provides information on olanzapine during acute, maintenance, and extension treatment phases of bipolar I disorder. The pivotal study for the maintenance claim, HGHL, is reviewed below. There were additional eight study reports which are not statistically reviewed as they have little bearing on the efficacy part of the sponsor's maintenance claim. Briefly, the other studies are: Study HGHT is an active-controlled trial comparing olanzapine with lithium with no concurrent placebo arm. The acute and maintenance periods of Study HGFU are treated as two studies. In the acute phase of HGFU, the responses to olanzapine plus one of two mood stabilizers (lithium or valproate) are compared. For the maintenance period, responders are re-randomized to olanzapine or placebo, while maintaining the mood stabilizer. Study HGHQ compares patients on olanzapine with patients on divalproex in the

treatment of acute mania, again with no concurrent placebo arm. Study HGHD is also treated as two studies. The first one is the comparison of olanzapine versus haloperidol in the treatment of acute mania. The second study addresses the open label extension phase. Finally, Study HGEH investigates the treatment of olanzapine versus placebo in the treatment of mania associated with bipolar I disorder. The ninth study report addresses special issues found in Study HGEH.

### 2.1.2 Major Statistical Issues

In this report only the pivotal study HGHL is being reviewing and no statistical issues were discerned for the primary endpoint analyses.

However, the attrition of the number of patients is of concern. A total of 731 patients received open-label olanzapine. Of these, over 50% did not sufficiently respond to olanzapine. Conversely, 361 (49.4%) were considered remitters and were randomized at a 2:1 ratio to olanzapine (n=225) and placebo (n=136). Treatment was planned for up to one year but only 4 (1.8%) patients on olanzapine and only 1 patient (0.7%) on placebo actually remained on study for a full year.

At times the sponsor refers to 'preventing relapse' as the purpose of the study. In this reviewer's opinion, a conventional understanding of prevention of relapse infers a greater benefit than improved times to relapse, particularly in light of almost all patients relapsing before one year.

Another concern lies with the sponsor mentioning 66 patients (53 olanzapine, 13 placebo, Table HGHL.10.3 and Table HGHL.14.3) completing the 'interval'. This can be interpreted as being on study for one year, which is not the case. This reviewer found 68 patients (54 olanzapine, 14 placebo) having a study visit 116, which was the end of the trial. This group included the four olanzapine patients and the one placebo patient who had a full year. The remaining patients had less than one year of treatment, some as little as 15 days. The discrepancy of two patients (66 versus 68) between the sponsor and this reviewer could not be reconciled.

Finally, there were concerns with the data from [ ] investigators: [ ] 034. b(4)
Therefore, this reviewer presented the primary analyses with and without the data from these investigators.

### 2.2 Data Sources

Data used for review are from the electronic submission received on 11/20/02. The network path is \\Cdsesub1\n20592\S_019\2002-11-20\CRT. This reviewer relied mostly on the data in the sponsor's relapse.xpt file.

## 3 Statistical Evaluation

### 3.1 Evaluation of Efficacy

Study HGHL is considered the pivotal study, which can satisfy the regulatory requirement for a maintenance claim. This reviewer did not address the additional studies/reports submitted by the sponsor as they have little bearing on the efficacy part of the maintenance claim.

#### 3.1.1 Study HGHL

##### 3.1.1.1 Introduction

Study HGHL is the pivotal study to assess the efficacy of olanzapine compared to placebo among bipolar I patients who had responded to acute open-label olanzapine treatment and were in symptomatic remission of an index manic or mixed episode. It had been agreed upon by the FDA (Feb. 20, May 2002) that this study could meet the regulatory requirement for a maintenance claim. After a 2-7 day screening period (Study Period I), qualifying in- or outpatients received open label olanzapine (5-20 mg/day) for 6-12 weeks (Study Period II). Patients who met criteria for symptomatic remission of an index manic or mixed episode were randomized (2:1) to either olanzapine or placebo for a double-blind period lasting up to one year (Study Period III). Time to relapse was the primary efficacy measure. Patients who did not respond to open-label olanzapine and did not meet the symptomatic remission criteria by the end of Study Period II were discontinued. Patients who relapsed during Study Period III entered an open-label olanzapine rescue treatment period (Study Period IV), which did not exceed 6 months.

##### 3.1.1.2 Statistical Issues

The sponsor powered the study on the primary efficacy variable of time to relapse. Time to relapse was estimated via Kaplan Meier curves and the distributions were compared via the log-rank test. Relapse rates were compared by Fisher's Exact test. Subgroup differences were tested by Mantel-Haenszel common odds ratio and the Breslow-Day test for homogeneity across strata.

Continuous variables were analyzed via ANOVA with or without interactions terms as appropriate. The sponsor states that no adjustments for covariates were performed. However, in the logistic regression model, baseline apparently was used as a covariate. This reviewer confirmed the primary analyses and several subgroup analyses but did not confirm the secondary analyses based on the continuous variables (HAMD-21, etc.). However the sponsor's statistical approach appears appropriate for all measures.

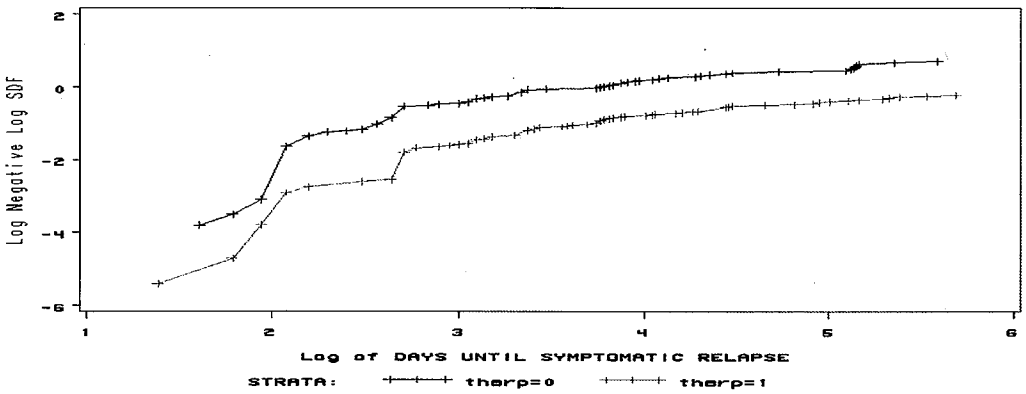
For the primary analyses this reviewer produced the same number of patients and p-values as reported by the sponsor. For some subgroup analyses this reviewer obtained different sample sizes from the data files than were cited in the sponsor's report. However the conclusions remained consistent.

There were concerns with the data from [ ] investigators: [ ] 034. Therefore, this reviewer presented the primary analyses with and without the data from these investigators. b(4)

At times the sponsor presents a [ ] b(4)
[ ] This reviewer considers the study design adequate for a maintenance claim only, particularly in light of the large attrition during the study and the small number of patients (4 onlanzapine, 1 placebo) completing one year.

If either log (survival) or log(-log) survival curves result in linear plots, the data may be assumed to come from an exponential or Weibull distribution respectively. In none of this reviewer's analyses (overall or subgroups) did these plots appear linear. However, most log(-log) survival plots would indicate that the proportional hazard assumption is met (Figure 1) and therefore the p-values cited for the log-rank test are valid even though the underlying distribution could not be identified.

**Figure 1: Log(-log) Relpase Distribution in Study HGHL**




### 3.1.1.3 Study Objectives

Study HGHL, a placebo-controlled trial, had been agreed upon by the FDA that it can meet the regulatory requirement for a maintenance claim. It was designed to establish superiority of olanzapine over placebo in time to symptomatic relapse into a manic, mixed, or depressive episode among bipolar I patients who have responded to open label acute olanzapine treatment and were in symptomatic remission of an index manic or mixed episode. [ ] b(4)

### 3.1.1.4 Efficacy Endpoints

The primary efficacy endpoint was symptomatic relapse (including hospitalization) into either a manic, mixed, or depressive episode by patients in symptomatic remission of an index manic or mixed episode. The time interval for this double-blind period lasted from time of randomization to the time of relapse or hospitalization or the end of the study, i.e. until drop out. The double blind period lasted up to 12 months. Proportions of patients relapsing were also compared between the treatment groups.

Secondary objectives assessed the efficacy of olanzapine in improving symptomatology or sydrome at the end of the 6-12 week open label therapy (i.e. reduction of scores from baseline); the efficacy of olanzapine in further improving clinical symptomatology after 12 months of therapy among patients who had responded during the acute open-label phase; and at US sites only the functional

status and QL associated with acute open label olanzapine, as well as with long-term olanzapine compared to placebo.

### 3.1.1.5 Sample Size Considerations

Sample size was calculated based on the 'time to relapse' endpoint. A sample size of approximately 315 remitting patients was needed to give an 85% power to detect a difference in the Kaplan-Meier 'survival' curves (i.e. in time to relapse), using the log-rank test, assuming a 12-month relapse rate of 50% for placebo and 30% for olanzapine and a 50% censoring rate for either treatment. This study showed much greater relapse rates for both treatment groups than estimated. However, since the treatment effect was greater than estimated, the sample size was sufficient to show highly statistically significant results.

### 3.1.1.6 Stratification

The sponsor pooled sites with small numbers of patients (n<2 per treatment). In addition, geographic areas (US and Romania), as well as gender, age, racial origin, type of bipolar I disorder (mixed versus pure manic), presence of psychotic features, and presence of rapid-cycling were considered in subgroup analyses. This reviewer verified subgroup analyzes for geocode, gender, age, racial origin, and type of relapse.

The quality of the data from [ ]sites (# [ ] 34) was of concern. Therefore, this reviewer also performed all main analyses with these [ ]sites excluded. b(4)

On the request of the reviewing medical officer, this reviewer also assessed the treatment effect for patients with/out concomitant benzodiazepine use.

### 3.1.1.7 Interim Analysis

One interim analysis was planned using Armitage, McPherson, and Rowe adjustments to alpha. However, no interim analysis was actually performed and no adjustments were made to the significance levels of the treatment comparisons. This approach is acceptable.

### 3.1.1.8 Efficacy Analysis Methods

The sponsor's primary analysis is a comparison of survival (relapse) curves (Kaplan-Meier estimates) between the ITT olanzapine treated and placebo treated groups using the log-rank test. In addition, incidences of relapse per treatment group were compared via Fisher's Exact test. The effect of country on relapse was examined using Cochran-Mantel-Haenszel analyses. Continuous data are

analyzed via ANOVA using Type III sums of squares. Changes from baseline to endpoint within a period (open label or double-blind) used LOCF. Treatment comparisons are made with alpha=0.05, two-sided. Treatment by investigator, treatment by country, and treatment by subgroup interactions, and heterogeneity across sites were tested at alpha=0.10. For the analysis of Period III data, the double blind period, baseline measurements were the final observation in Period II, the open label period.

This reviewer did not analyze changes from baseline, but the methods proposed by the sponsor for these as well as the primary efficacy measures appeared acceptable.

### 3.1.1.9 Sponsor's Results and Statistical Reviewer's Findings/ Comments

#### 3.1.1.9.1 Baseline Characteristics

The sponsor's Table ISE.6.2 (not reproduced) shows good balance in patient characteristics for Study HGHL. The distributions of sex, origin (race), age, type of current episode and course of disease (rapid cycling vs. not rapid cycling) are compared between the two treatment groups via Fisher's Exact test. None of the p-values approached statistical significance. This reviewer accepts these findings without further analyses.

#### 3.1.1.9.2 Primary Efficacy Analyses

Many of this reviewer's analysis results were numerically identical to the sponsor's and this reviewer agrees with the sponsor that patients on olanzapine experienced a significantly longer time to relapse than patients on placebo ($p<0.0001$). Furthermore, the proportion of patients relapsing on olanzapine was statistically significantly smaller than the proportion of patients relapsing on placebo ($p<0.001$). These findings are summarized in Table 1 and Figure 2. However, it is noted that only 4 olanzapine patients and only 1 placebo patient received treatment for a full year.

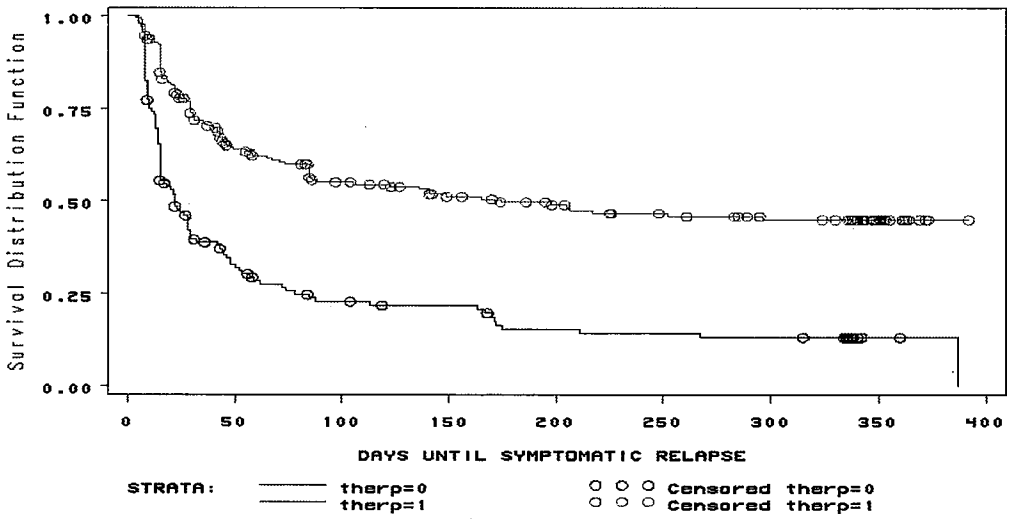
There are some concerns regarding the quality of the data from investigators # [ ] 034. They contributed [ ] and 3 patients respectively. Excluding the data from these [ ] investigators had a minor effect on the mean time to relapse but no effect on the significance level of these findings and the conclusions. b(4)

**Table 1: Overall Statistical Findings for Double-Blind Period of Study HGHL**

| ITT Population | Sample Size | Mean Survival Time (Days) | Percent Relapsing | Percent Censored | p-Value Survival Times | p-Value Proportions |
|---|---|---|---|---|---|---|
| Olanz | 225 | 166.7 | 46.7 | 53.3 | <0.0001 | <0.0001 |
| Placebo | 136 | 86.5 | 80.1 | 19.9 | | |
| | | | | | | |
| Olanz* | 195 | 171.1 | 46.2 | 53.9 | <0.0001 | <0.0001 |
| Placebo | 121 | 73.5 | 79.3 | 20.7 | | |

* Excluding data from investigators # [ ]34. b(4)

**Figure 2: Relapse Distributions for Study HGHL***




*** 0=placebo, 1=olanzapine**

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### 3.1.1.9.3 Secondary Efficacy Analyses

Overall and for the groupings formed by this reviewer (geocode and gender) substantially fewer patients are censored from the placebo group than from the olanzapine treated group. In order to assess a possible bias due to uneven censoring, this reviewer compared the days on study between the two treatment groups, i.e. treating censoring times as relapse times. The mean time on study for olanzapine treated patients was 129.4 days. For placebo treated patients it was 64.14 days. The difference between the two distributions was statistically significant at $p<0.0001$ (by log-rank, Wilcoxon and likelihood ratio tests). Figure 3 below gives the time-on-study distributions of the two treatment groups treating censoring times as times to relapse. As a worst case scenario, this reviewer assumed all censored times of olanzapine patients as times to relapse, but maintained the censoring for the placebo patients. The log-rank test comparing these two distributions had a p-value of 0.0012, again indicating that olanzapine treated patients remained on study longer (mean time = 129.4 days) than placebo treated patients (mean time = 86.5 days). The distributions of this worst case scenario are given in Figure 4. It can therefore be concluded, that the differential amount of censoring does not negate the drug effect.

**Figure 3: Considering All Patients as Relapsed**

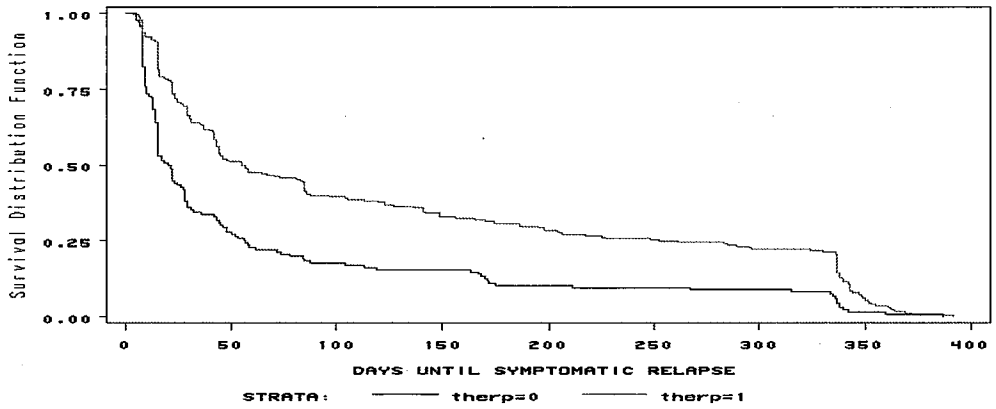


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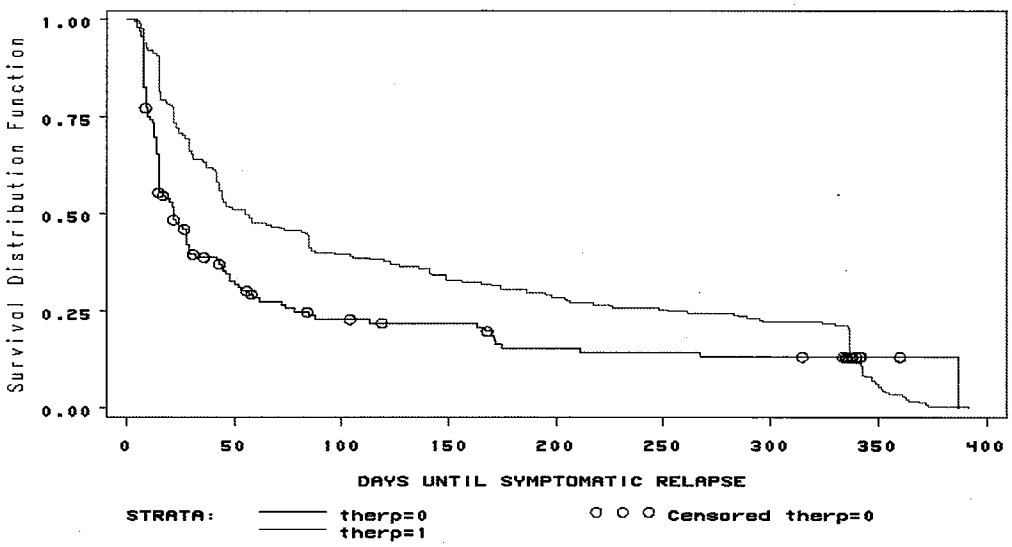
**Figure 4: Considering All Olanzapine Patients as Relapsed but Placebo Patients Were Censored**




The sponsor reports 53 (23.6%) olanzapine patients and 13 (9.6%) placebo patients as having the 'interval completed'. These patients were in the study when it was terminated at Study Visit 116, but these numbers should not be interpreted that 66 patients completed a full year of study. On the contrary, only 4 olanzapine and 1 placebo patient completed a full year of treatment. For the remainder of these patients, time on study ranged from 15 to 364 days. As noted above, this reviewer actually counted 68 patients having a Visit 116 (Table 2).

**Table 2: Days on Study for Patients with Visit 116**

| Days/Number of Patients | Olanzapine | Placebo |
|---|---|---|
| 15-60 | 1 | 3 |
| 61-120 | 2 | 0 |
| 121-180 | 1 | 0 |
| 181-240 | 1 | 0 |
| 241-300 | 0 | 0 |
| 301-330 | 1 | 1 |
| 331-340 | 22 | 7 |
| 341-350 | 14 | 1 |
| 351-360 | 4 | 1 |
| 361-364 | 4 | 0 |
| 365-392 | 4 | 1 |

When exploring the drug effect on time to relapse or proportion of relapses to either manic, depressive, or mixed episode, the numbers of patients differ between the sponsor and this reviewer (Table 3). The sponsor defined a relapse into depression (mania) as a HAMD-21 (YMRS) total score of 15 or greater or hospitalization due to depression (mania) at any time during the double-blind period. This reviewer took the variables 'Type of Symptomatic Relapse' and 'Reason for Hospitalization' as indicators of depressive, manic, or mixed relapses from the relapse data file. The tallies should be identical, but were not. This reviewer was not able to reconcile the differences. It is noted that Type of Symptomatic Relapse was not necessary coded the same as Reason for Hospitalization. This may explain why the number of patients in the three types of relapse may be larger than the total sample sizes.

Time to relapse and proportion relapsing into mania was significantly superior for olanzapine over placebo treated patients ($p<0.001$) by both the sponsor's and this reviewer's analysis. Similarly, time to relapse into depression was assessed equivalently by the sponsor and this reviewer ($p<0.001$). The level of significance for proportion of patients relapsing into depression was different between the sponsor and this reviewer, with this reviewer showing only a borderline significant result in favor of olanzapine ($p=0.0562$). The sponsor had not reported results for relapses labeled as 'mixed'. When insisting that both variables (Type of Symptomatic Relapse and Reason for Hospitalization) were labeled as 'mixed', olanzapine showed nominal statistical superiority ($p<0.05$). When requiring that Type of Symptomatic Relapse be labeled as 'mixed' but allowing Reason for Hospitalization to be different, statistical superiority of olanzapine is at a level of $p<0.005$. In summary, only proportion of relapse into a depressive episode did not reach statistical significance at 0.05, but approached it. All other tests clearly reached statistical significance in favor of olanzapine. Excluding the data from investigators [redacted] 034 did not affect the levels of significance or the conclusions. b(4)

The sponsor combined data from investigators who had less than two patients. As this approach might combine data from the two geographic regions (US and Romania), this reviewer first attempted a logistic regression model with relapse = treatment, investigators and treatment-by-investigator. Due to the many investigators with very few patients, this model was unstable. The second approach modeled geographic region rather than grouped and ungrouped investigators. A model using relapse = treatment geocode treatment*geocode was considered and found to be stable. The interaction term was very non-significant ($p>0.89$), but both geocode (US and Romania) and treatment were significant. It was found that there is a statistically significant difference ($p<0.01$) in relapse rates between Romania and the US. In Romania, the relapse rates for both

**Table 3: Symptomatic Relapse* into Manic, Depressive, or Mixed Episode**

| Relapse | Olanzapine (n=225) | Placebo (n=136) | Log rank p-value | Fisher's Exact p-value |
|---|---|---|---|---|
| | Total Relapses=105 | Total Relapses=109 | | |
| ***Sponsor*** | | | | |
| *Depressive* | *78 (34.7%)* | *65 (47.8%)* | *<0.001* | *0.015* |
| *Manic* | *37 (16.4%)* | *56 (41.2%)* | *<0.001* | *<0.001* |
| **Reviewer@** | | | | |
| Depressive | 68 (30.2%) | 53 (39.0%) | <0.0001 | 0.0562 |
| Manic | 27 (12.0%) | 45 (33.1%) | <0.0001 | <0.0001 |
| Mixed** | 10 (4.4%) | 13 (9.6%) | 0.0028 | 0.0459 |
| Mixed*** | 12 (5.3%) | 19 (14.0%) | <0.0001 | 0.0046 |
| **Excluding Sites ✓, 34** | | | | |
| Depressive** * | 58/195 (29.4%) | 50/121 (41.3%) | <0.0001 | 0.0238 |
| Manic** | 24/195 (12.3%) | 36/121 (29.8%) | 0.0001 | 0.0001 |
| Mixed** | 8/195 (4.1%) | 12/121 (9.9%) | 0.0016 | 0.0356 |
| Mixed*** | 9/195 (4.6%) | 18/121 (14.9%) | <0.0001 | 0.0017 |

b(4)

@ Analyzing one type of relapse at a time while treating the other types as censored
* includes hospitalization
** 'Depressive ', 'Manic', and 'Mixed' defined by both Type of Relapse and Reason for Hospitalization
*** 'Mixed' defined by Type of Relapse or any Reason for Hospitalization

olanzapine treated and placebo treated patients were lower than these rates in the US, but olanzapine relapse rates were lower than placebo relapse rates in both countries. In Romania, the relapse rate for olanzapine was statistically significantly lower than placebo ($p<0.03$) with point estimates of 27.6 and 62.5 percent relapse for olanzapine and placebo, respectively. The total sample size for Romania was 45. In the US, the relapse rate of olanzapine was statistically significantly lower than placebo ($p<0.0001$) with point estimates of 49.5 and 82.5 percent relapse for olanzapine and placebo, respectively. As the estimated treatment effect was of the same magnitude in either country (34.9% in Romania and 33.0% in the US) the difference in relapse rates between the countries are most likely due to geographic differences in scoring the assessment tools (YMRS, HAMD-21, etc.). The Sponsor reported the same relapse rates and basically identical p-values using somewhat different methodology, namely Breslow-Day and Cochran-Mantel-Haenszel tests. Both investigators [ ] 034 were from the US, so no adjustment needs to be made to findings from Romania. The adjustment to the US data are found below in Section 4, Table 4.

b(4)

In addition, the sponsor reported that statistical significance was maintained in secondary measures, namely rate-of- and time-to-syndromic relapse, as well as in changes from baseline in the assessment tools such HAMD-21, etc. This reviewer did not verify the accuracy of these secondary measures.

### 3.1.1.10 Sponsor's Conclusions and Reviewer's Conclusions/Comments

The sponsor concluded, and this reviewer agrees, that study HGHL was a randomized placebo-controlled double-blind trial in which patients who had remitted on open label olanzapine and had been randomized to olanzapine showed significantly longer time to relapse than patients who had been randomized to placebo. Concerns with uneven censoring led to a worst-case analysis, where all censored patients on olanzapine were assumed to have relapsed but placebo patients retained their censored status. Again, olanzapine treated patients remained statistically significantly longer on study than did placebo patients. In addition, during the maintenance period the proportion of relapse among olanzapine treated patients was significantly smaller than the proportion of relapse among placebo treated patients.

It is noted that there was substantial attrition during this trial. Of the 731 patients on open label olanzapine only 361 (49.4%) responded and were considered remitters. After six months of treatment, 156 (61.2%) of the 225 patients randomized to olanzapine had either relapsed or were censored. Of the 136 patients randomized to placebo, 122 (89.7%) had relapsed or were censored by six months. Only 4 olanzapine patients and only 1 placebo patient completed a full year of treatment.

In addition, the sponsor states that 66 patients 'completed the study interval'. This can lead to the misinterpretation that 66 patients received treatment for a full year, which is not the case. These patients were in the study when the study was terminated (Visit 116). This reviewer actually counted 68 patients with Study Visit 116, a figure that included the 5 patients who had a full year of treatment. For the remaining patients, their time on study ranged from 15 - 364 days.

It appears that this trial meets the sponsor's maintenance claim, that olanzapine is superior over placebo in time to symptomatic relapse into a manic, mixed, or depressive episode among bipolar I patients who have responded to open label acute olanzapine treatment and are in symptomatic remission of an index manic or mixed episode.

### 3.2 Evaluation of Safety

For the safety evaluation of any of the studies the reader is referred to the medical officer's review.

## 4 Findings in Special/Subgroup Populations

The same types of statistical analyses performed on all the data, namely log-rank test for time to relapse and Fisher's Exact test for proportion relapsing, were also performed for each subgroup separately. In addition, homogeneity across subgroups was tested.

### 4.1 Gender

Table 4 shows the results for time to relapse and proportion relapsing for all males (Figure 5) and all females (Figure 6), as well as for each gender within the geographic regions. Using all the data, the results show clear superiority of olanzapine over placebo for all males and for the females in the US. For the males in Romania, mean days till relapse is actually somewhat shorter for the olanzapine patients than for the placebo patients, but time to relapse and proportion relapsing reached statistical significance in favor of olanzapine at the nominal p-values. Similarly, for all females and for the females in the US there is no dispute of the superiority of olanzapine over placebo. For the females in Romania, olanzapine patients had numeric superiority over placebo patients, but the difference did not reach statistical significance. The reduced levels of statistical significance can in part be attributed to the smaller sample sized in these subgroups.

In Table 5 the results were analyzed with the data from investigators [ ]034 excluded. As these investigators were from the US, the data from Romania stay as reported in Table 4. The adjusted data for the US were essentially identical to the all data with no effect on the results or conclusions

b(4)

**Table 4: Statistical Findings by Gender and Geocode**

| | Therapy | Sample Size | Mean Survival Time (Days) | Percent Relapsing | Percent Censored | p-Value, Survival Times | p-Value, Proportions |
|---|---|---|---|---|---|---|---|
| All **Males** | Olanz | 87 | 173.6 | 43.7 | 56.3 | <0.0001 | <0.0005 |
| | Placebo | 53 | 74.7 | 73.6 | 26.4 | | |
| Males US | Olanz | 78 | 161.6 | 47.4 | 52.6 | <0.0001 | 0.0019 |
| | Placebo | 45 | 54.0 | 75.6 | 24.4 | | |
| Males Romania | Olanz | 9 | 149.0 | 11.1 | 88.9 | 0.0511 | 0.0430 |
| | Placebo | 8 | 153.6 | 62.5 | 37.5 | | |
| | | | | | | | |
| All **Females** | Olanz | 138 | 143.8 | 48.6 | 51.4 | <0.0001 | <0.0001 |
| | Placebo | 83 | 77.5 | 84.3 | 15.7 | | |
| Females US | Olanz | 118 | 116.9 | 50.8 | 49.2 | <0.0001 | <0.0001 |
| | Placebo | 75 | 61.0 | 86.7 | 13.3 | | |
| Females Romania | Olanz | 20 | 211.3 | 35.0 | 65.0 | 0.1996 | 0.1826 |
| | Placebo | 8 | 173.8 | 62.5 | 37.5 | | |

**Table 5: Statistical Findings by Gender and Geocode Excluding Investigators**

b(4) [ ]034*

| | Therapy | Sample Size | Mean Survival Time (Days) | Percent Relapsing | Percent Censored | p-Value, Survival Times | p-Value, Proportions |
|---|---|---|---|---|---|---|---|
| All **Males** | Olanz | 80 | 179.0 | 42.5 | 57.5 | <0.0001 | 0.0002 |
| | Placebo | 49 | 75.4 | 75.5 | 24.5 | | |
| Males US | Olanz | 71 | 166.6 | 46.5 | 53.5 | <0.0001 | 0.0009 |
| | Placebo | 41 | 54.1 | 78.1 | 21.9 | | |
| | | | | | | | |
| All **Females** | Olanz | 115 | 146.9 | 48.7 | 51.3 | <0.0001 | <0.0001 |
| | Placebo | 72 | 66.4 | 81.9 | 18.1 | | |
| Females US | Olanz | 95 | 117.9 | 51.6 | 48.4 | <0.0001 | <0.0001 |
| | Placebo | 64 | 42.5 | 84.4 | 15.6 | | |

* Excluded investigators were US only

**Figure 5: Relapse Distributions for Males Only**

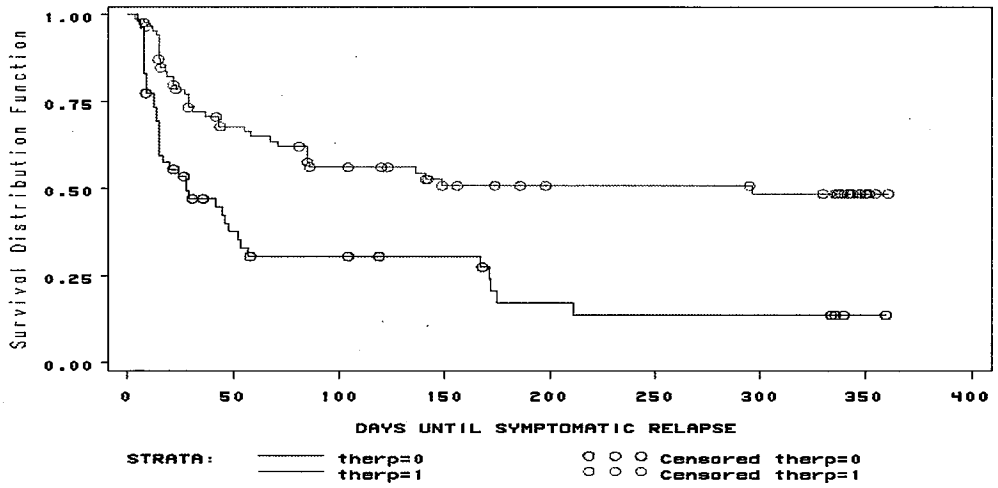
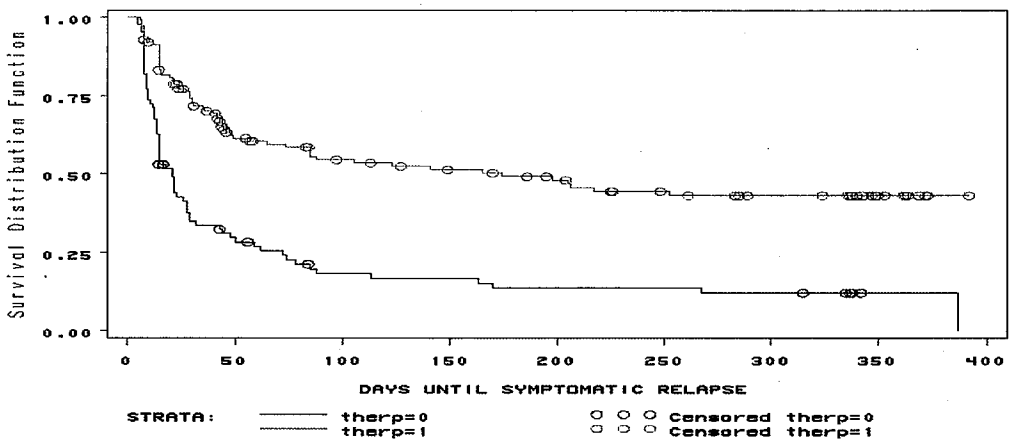



**Figure 6: Relapse Distributions for Females Only**




## 4.2 Race

The sponsor tested the proportion of relapse between treatments for Caucasian origin and for 'other' origin. In both cases, olanzapine patients relapsed significantly less than placebo patients ($p<0.004$). The test for homogeneity of findings across race groups was non-significant ($p=0.496$). This reviewer produced similar results. As can be seen from Table 6 and Figure 7 below, this reviewer analyzed results for subgroups of Caucasian, African American, and

Other origins. By far the largest group was Caucasian (87.3%). For this subgroup the overall findings of statistically significantly longer time to relapse and smaller proportion of patients relapsing were reproduced ($p<0.0001$). For the 27 African American, patients on olanzapine showed longer mean time to relapse and a smaller portion of relapsing. However, the findings did not reach statistical significance ($p>0.06$). For the 19 patients of other racial origin, the results also went in favor of olanzapine with borderline statistical significance ($p<0.04$ for log rank test and $p<0.08$ for Fisher's Exact). The lack of statistical significance for the non-Caucasian subgroups can at least in part be attributed to the small sample sizes. A test for homogeneity of treatment effect across racial subgroups was not significant ($p=0.7617$). Excluding the data from investigators [ ] 034 had no effect on the results for the Caucasian group. For the African American and Other groups, olanzapine maintained only numeric superiority over placebo. b(4)

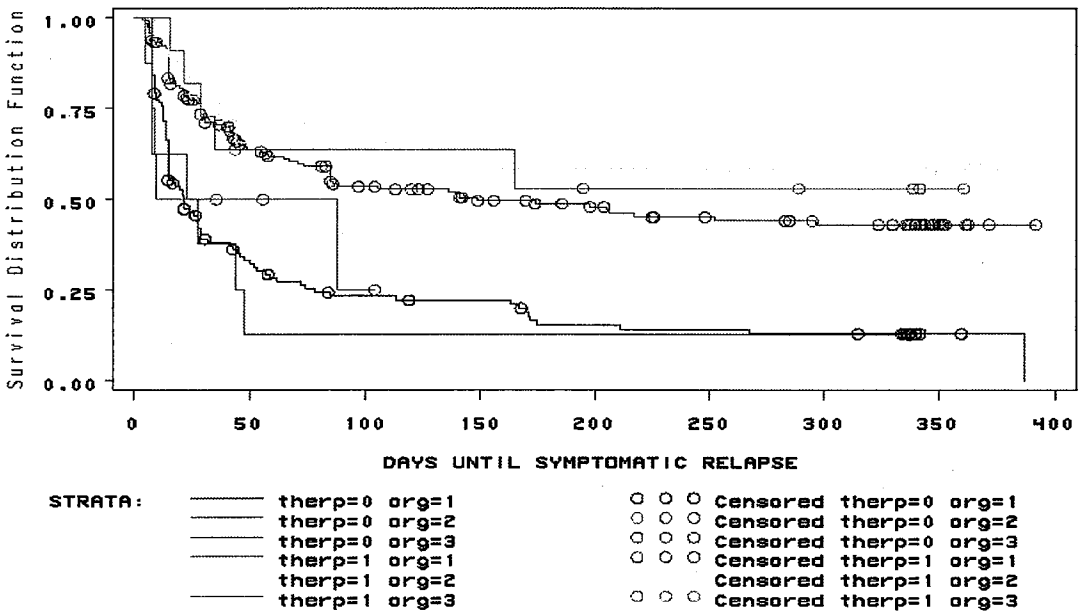
**Table 6: Statistical Findings of Study HGHL by Origin**

| | Therapy | Sample Size | Mean Survival Time (Days) | Percent Relapsing | Percent Censored | p-Value, Survival Times | p-Value, Proportions* |
|---|---|---|---|---|---|---|---|
| Caucasian | Olanz | 195 | 163.3 | 47.7 | 52.3 | <0.001 | <0.0001 |
| | Placebo | 120 | 86.2 | 80.8 | 19.2 | | |
| | | | | | | | |
| Caucasian** | Olanz | 167 | 169.8 | 46.7 | 53.3 | <0.0001 | <0.0001 |
| | Placebo | 106 | 73.3 | 80.2 | 19.8 | | |
| | | | | | | | |
| African American | Olanz | 19 | 89.5 | 36.8 | 63.2 | 0.0613 | 0.2116 |
| | Placebo | 8 | 48.0 | 62.5 | 37.5 | | |
| | | | | | | | |
| African American** | Olanz | 18 | 87.5 | 38.9 | 61.1 | 0.1865 | 0.3515 |
| | Placebo | 7 | 54.1 | 57.1 | 42.9 | | |
| | | | | | | | |
| Other | Olanz | 11 | 114.3 | 45.5 | 54.5 | 0.0397 | 0.0799 |
| | Placebo | 8 | 26.9 | 87.5 | 12.5 | | |
| | | | | | | | |
| Other** | Olanz | 10 | 109.2 | 50.0 | 50.0 | 0.0687 | 0.1199 |
| | Placebo | 8 | 26.9 | 87.5 | 12.5 | | |

* Breslow-Day for homogeneity of treatment effect across origin groups:p=0.7617.

** Results with investigators [ ] 034 excluded; the Breslow-Day for homogeneity of treatment effect across origin groups has a p-value of 0.6518. b(4)

**Figure 7: Time to Relapse by Origin and Treatment Group***




*** Therp=0 is Placebo, Therp=1 is Olanzapine; Org=1 is Caucasion, Org=2 is African American, Org=3 is 'Other'.**

## 4.3 Age

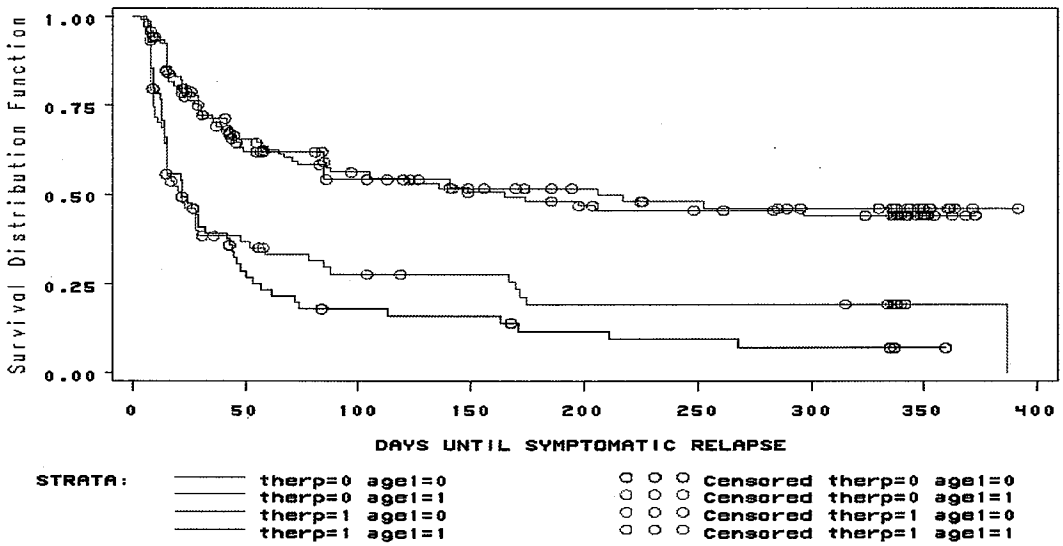
The relapse distribution and proportions of relapse were similar for patients under 40 as for patients 40 and over. The log rank test for time to relapse and the Fisher's Exact test for proportions favored olanzapine in all cases with p-values of <0.0001 (Table 7, Figure 8). The Breslow-Day p-value for testing homogeneity of treatment differences was 0.4027 for both the sponsor and this reviewer, indicating that the treatment difference was similar in either age group. Excluding the data from investigators [redacted] 034 had minimal effect on the findings, still maintaining the highly statistically significant superiority of olanzapine over placebo. b(4)

**Table 7: Study HGHL: Proportion of Relapse per Age Group**

| | Olanzapine | Placebo | Log-Rank p-Value | Fisher's Exact p-Value |
|---|---|---|---|---|
| Under 40 (n=104 olanz, 69 placebo) | 47 (45.2%) | 57 (82.6%) | <0.0001 | <0.0001 |
| 40 and Over (n=121 olanz, 67 placebo) | 58 (47.9%) | 52 (77.6%) | <0.0001 | <0.0001 |
| | | | | |
| Under 40* (n=89 olanz, 59 placebo) | 40 (44.9%) | 49 (83.1%) | <0.0001 | <0.0001 |
| 40 and Over* (n=106 olanz, 62 placebo) | 50 (47.2%) | 47 (75.8%) | <0.0001 | 0.0002 |

*Excluding investigators [ ] 034. b(4)

**Figure 8: Time to Relapse by Age and Treatment Group ***




- * Therp=0 is Placebo, Therp=1 is Olanzapine; Age1=0 is Under 40, Age1=1 is 40 and Over.

**Other Special/Subgroup Populations**

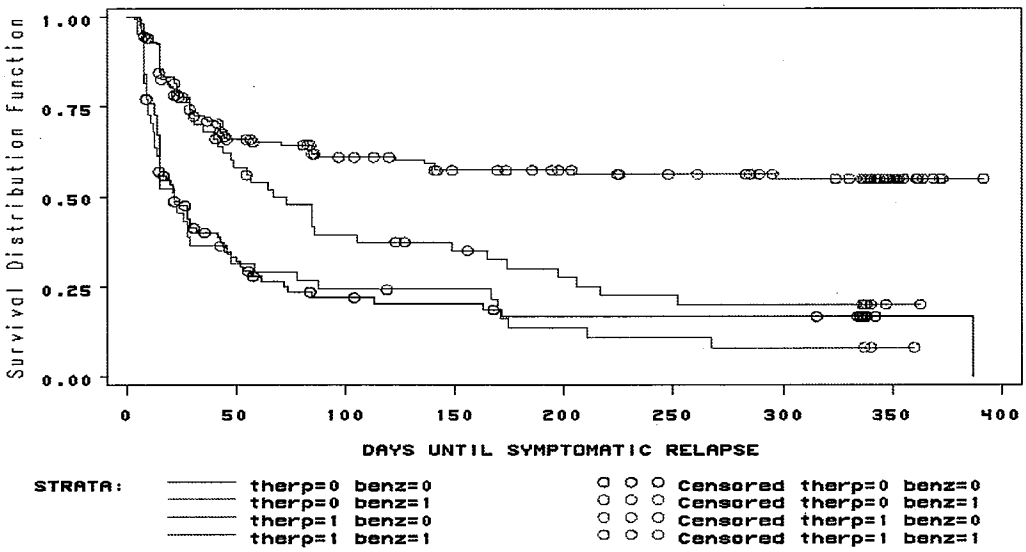
The reviewing medical officer requested an investigation of the treatment effect with respect to use of concomitant benzodiazepine during the double blind maintenance period. The sponsor reported 60 (26.7%) olanzapine patients and 49 (36.0%) placebo patients using concomitant benzodiazepine. Based on the variable 'Used Benzodiazpines during double blind therapy phase' in the relapse data file or from the concomitant therapy data file, this reviewer found 55 olanzapine patients and 44 placebo patients with 'yes' for concomitant benzodiazepine use. Overall, patients with concomitant benzodiazepine use fared worse than patients who did not need concomitant benzodiazepine. Specifically, for patients with no concomitant benzodiazepine use, the mean time to relapse was 185.1 days for olanzapine treated patients and 91.5 days for placebo treated patients (Table 8). This difference resulted in a log-rank test with a p-value of <0.0001. For the patients with concomitant benzodiazepine use, the mean time to relapse was 110.8 days for olanzapine treated patients and 69.6 days for placebo treated patients. The log-rank test reached statistical significance at p<0.01. Figure 9 shows, that the survival curve for patients on olanzapine and having had concomitant benzodiazepine use is worse than the curve for olanzapine patients with no concomitant benzodiazepine use. However, the former curve is still better than either relapse curve of placebo patients. This can also be observed in the proportions of relapses. A large proportion of patients on olanzapine having concomitant benzodiazepine use relapsed (70.9%). However, this proportion was still significantly less (p=0.0271) than the corresponding proportion of placebo patients. The smaller treatment effect and lower level of significance may at least in part be due to the smaller sample size. The Breslow-Day test for homogeneity of the treatment effect supports the notion of a consistent treatment effect across the benzodiazepine use groups by a non-significant p-value of 0.4754. Excluding the data from investigators [ ] 034 did not affect the findings or conclusions. b(4)

**Table 8: Proportion of Relapse among Patients with or without Concomitant Benzodiazepine Use**

| | Olanzapine | Placebo | Log-Rank p-Value | Fisher's Exact p-Value |
|---|---|---|---|---|
| No Benzodiazepine Use (n=170 olanz, 92 placebo) | 66 (38.8%) | 70 (76.1%) | <0.0001 | <0.0001 |
| Benzodiazepine Use (n=55 olanz, 44 placebo) | 39 (70.9%) | 39 (88.6%) | 0.0062 | 0.0271 |
| | | | | |
| No Benzodiazepine Use* (n=143 olanz, 77 placebo) | 53 (37.1%) | 57 (74.0%) | <0.0001 | <0.0001 |
| Benzodiazepine Use * (n=52 olanz, 44 placebo) | 37 (71.2%) | 39 (88.6%) | 0.0044 | 0.0306 |

* Excluding US investigators [ ] 034 b(4)

**Figure 9: Relapse Distributions for Concomitant Benzodiazepine Use**




# 5 Summary and Conclusions

## 5.1 Statistical Issues and Collective Evidence

There were several inconsistencies in the study report and between the study report and the data extracted from the data files. For example, it appears that in some places in the submission depression is still an optional index episode, whereas the study was conducted in patients with manic or mixed index episodes only. Other inconsistencies include number of patients in subgroup analyses, which did not match between the sponsor's report and the numbers obtained by this reviewer from the data files. In addition, there were several tables submitted by the sponsor, which this reviewer could not reproduce. However, this reviewer expects the resolution of these differences not to affect the overall efficacy results. This reviewer spot-checked the relapse data file for accuracy and found no errors.

There were concerns about the data quality of investigators [ ] 034. With few exceptions in some subgroups, the exclusion of the data from these [ ] investigators did not affect the findings nor change any of the conclusions. b(4)

At various places of the submission, the sponsor refers to [redacted] b(4)
[redacted] In this reviewer's opinion, the literal sense of relapse prevention infers a greater benefit than one can measure with time to relapse or proportion relapsed in a time period that lasted at most one year. In particular, attrition was substantial and after six months already 61.2% of olanzapine patients and 89.7% of placebo patients were lost to relapse or to censoring. Only 4 patients on olanzapine (1.8%) and only one patient on placebo (0.7%) remained on treatment for a full year. However, the broader concept of maintenance is supported by the findings.

There were only few instances where the data from the olanzapine group did not reach statistical superiority over the placebo group. Two such occurrences with for the subgroups of African American and Other origin. In particular, when the data from investigators [redacted] 034 were excluded, olanzapine showed only b(4)
numeric superiority. There was one incidence where placebo showed a numeric superiority, which was for mean time to relapse for Romanian males. In all these cases, it appears that small sample size may have contributed to the lack of statistical significance. In addition, any test for homogeneity of treatment effect performed across subgroups was found non-significant supporting the consistency of the drug effect across subgroup. This is also borne out in the figures of the Kaplan Meier curves for relapse and censoring times.

This submission contained eight other study reports, which were not reviewed by the statistical reviewer, as the pivotal study appears to meet the regulatory requirement for the maintenance claim from the statistical point of view.

### 5.2 Conclusions and Recommendations

Study HGHL was the pivotal study for a maintenance claim for olanzapine in bipolar I patients. This reviewer agrees in principle with the sponsor's design, analysis, and conclusion for this trial. Olanzapine has been shown to provide statistically significantly longer times to relapse and smaller proportions of patients relapsing than placebo among bipolar I patients who had remitted on open label olanzapine. Robustness analyses as well as subgroup analyses almost always showed numeric and statistically significant superiority of olanzapine over placebo. From a statistical point of view, this study appears to meet the regulatory requirement for a maintenance claim. However, it needs to be kept in mind that there was substantial attrition from the number of patients entered into the study to the number of remitters, and finally to only five patients remaining on study for a full year.

Roswitha E. Kelly, M.S.
Primary Statistical Reviewer
Date:

Concur: Dr. Kun Jin
Team Leader

Dr. George Chi
Division Director, DBI

Cc:
HFD-120/ Dr. Bates
HFD-120/ Dr. Podruchny
HFD-120/ Dr. Andreason
HFD-710/ Ms. Kelly
HFD-710/ Dr. Jin
HFD-710/ Dr. Chi
HFD-700/ Dr. Anello
HFD-700/ Dr. Dubey

This review consists of 27 pages of text, tables, and figures. Sept. 03, 2003.
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Roswitha Kelly
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Kun Jin
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BIOMETRICS

George Chi
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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-592/S-019**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Clinical Pharmacology/Biopharmaceutics Review

| | |
|---|---|
| PRODUCT (Generic Name): | Olanzapine |
| PRODUCT (Brand Name): | ZYPREXA |
| DOSAGE FORM: | Tablets |
| DOSAGE STRENGTHS: | 2.5, 5, 7.5, 10, 15 and 20 mg |
| NDA: | 20-592 (SE1-018 and 019) |
| NDA TYPE: | 6S |
| INDICATION: | SE1-018: Zyprexa in combination with lithium and valproate for the treatment of manic episodes associated with Bipolar I disorder<br>SE1-019: Long-term treatment of bipolar I disorder |
| SUBMISSION DATE: | 9/16/02, 11/20/02 |
| SPONSOR: | Eli Lilly and Company |
| REVIEWER: | Veneeta Tandon, Ph.D. |
| TEAM LEADER: | Ramana Uppoor, Ph.D. |
| OCPB DIVISION: | DPE I, HFD 860 |
| OND DIVISION: | HFD 120 |

## TABLE OF CONTENTS

## EXECUTIVE SUMMARY

The objective of NDA 20-592 (SE1- 018) is to gain approval for the use of Zyprexa in combination with lithium or valproate for the treatment of acute manic episodes associated with bipolar disorder. NDA 20-592 (SE1- 019) is submitted to gain approval for the use of Zyprexa for the long term treatment of bipolar I disorder.

The efficacy of ZYPREXA in combination with lithium or valproate was established in two randomized, double-blind placebo-controlled studies in patients with acute manic or mixed episode with or without psychotic features (Protocol F1D-MC-HGFU: Olanzapine Added to Mood Stabilizers in the Treatment of Bipolar Disorder). Olanzapine doses studied were 5, 10, 15 and 20 mg/day given once a day for 6 weeks.

A drug interaction study was also conducted to assess the effect of olanzapine on steady state valproate levels (Protocol F1F-LC-HGGB: Olanzapine- Divalproex sodium interaction trial).

The results showed that in vivo administration of olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. The effect of valproate on olanzapine pharmacokinetics could not be determined robustly from this study.

The information on Lithium interaction with olanzapine has been taken from Study E001; submitted September 21,1995 with NDA 20-592. The results indicated that there was no interaction between olanzapine and lithium.

## RECOMMENDATION

NDA 20-592 (018 and 019) are acceptable from the viewpoint of Office of Clinical Pharmacology and Biopharmaceutics. The sponsor's labeling changes in the Drug Interaction section under PRECAUTIONS are acceptable and should apply to both SE1-018 and SE1- 019.

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D._____

**LABELING RECOMMENDATION**

The following Labeling changes made by the sponsor in the Drug interaction Section under PRECAUTIONS are acceptable and should apply to both supplements 018 as well as 019. The original valproate section has been deleted and a new section has been added. Lithium has been given its own sub heading and has been removed from a list of general drugs that did not show interaction.

~~Valproate — Studies in vitro using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. Thus, a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.~~

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium.

Valproate — Studies in vitro using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. In vivo administration of olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam and its active metabolite N-desmethyldiazepam, ~~lithium,~~ ethanol, or biperiden. However, the co-administration of either diazepam or ethanol with olanzapine potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

***Study F1D-LC-HGGB:*** ***Olanzapine-Divalproex sodium/valproic acid interaction trial***

The objectives of the study were:

Part A: To determine any pharmacokinetic or pharmacodynamic drug interaction, safety, to assess effects of single and multiple doses of olanzapine on steady-state valproic acid concentrations; and to evaluate neuroendocrine effects during coadministration of divalproex sodium (hereafter designated as divalproex) and olanzapine.

Part B: To determine any pharmacokinetic drug interaction during coadministration of divalproex/valproic acid and olanzapine, to determine effects of multiple-dose divalproex on olanzapine concentration profiles, and to assess the effects of multiple doses of olanzapine on steady-state valproic acid concentrations.

The study design is as follows:

| | |
|---|---|
| Study Design | Part A was designed as a parallel comparison of olanzapine versus placebo coadministered with divalproex.<br>Part B was designed for competitive enrollment with Part A and was a parallel comparison of olanzapine versus placebo coadministered with divalproex from patients with bipolar illness obtained from Study F1D-MC-HGFU (only 1 patient enrolled in this part) |
| Study Population | N=42 patients with bipolar or schizoaffective disorder stabilized on divalproex (blood levels of valproic acid: 50-125 µg/mL) for 2 months and possibly on stable dose of lithium (minimum blood levels of 0.6 mEq/L).<br>Patients could also be entered into the trial if they were stabilized for at least 2 months on one of the following: bupropion (up to a 300-mg daily dose) or an SSRI antidepressant (other than fluvoxamine).<br><br>27 out of 42 subjects completed the trial.<br><br>Gender: 20M & 22F,<br>Ages: 18-65 yrs<br>Weight: 54.1-151 kg<br>Race: 2 Black, 1 Hispanic, 1 Other, 38 Caucasian |
| Treatment Group | A: Olanzapine/daily divalproex (Stabilized on divalproex)<br>B: Placebo/ daily divalproex (Stabilized on divalproex) |
| Dosage and Administration | A: Olanzapine: 10 mg as a single dose and then as a multiple dose regimen of 10 mg once daily for approximately 2 weeks<br>A 6 days washout between single and multiple dose regimen<br>10 mg tablets (CT04017, CT10117, CT11817)<br><br>B: Placebo (CT08802, CT08960, CT10215)<br><br>Divalproex: An individualized dosage (500 to 2250 mg per day) which maintained valproic acid plasma concentrations within the |

| | |
|---|---|
| | therapeutic range (50-125 µg/mL). Supplied as 125-mg, 250-mg, 500-mg, 750-mg, 1000-mg, or 1500-mg delayed-release tablets from various manufacturer's lot numbers. Administered once or twice daily.<br><br>Daily regimen maintained throughout the study.<br><br>Diet: On the day indicated for pharmacokinetic studies, patients ate a regular diet in the evening and could take olanzapine (or placebo) plus divalproex with a snack approximately 2.5 hours before bedtime. On these occasions, patients were asked to remain upright for approximately 2 hours after dosing. |
| Sampling: Blood | For Olanzapine/metabolites:<br>For single dose part:<br>At Day 1: At 0,1,2,4,6,8,10,12,24,36,48,72,96, and 120 hours postdose.<br>For multiple dose part:<br>At the end of Week 1(Day 13): At 0, 2,4,8,12, and 24 hours<br>At the end of Week 2 (Day 20): At 0, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, and 120 hours postdose<br><br>For Valproic acid:<br>At Days (-14), (-1), 1, 13, and 20: 12 hours before and 12 hours after the evening drug administration. Samples were obtained before the morning drug doses if the patient was on a twice-daily dosing schedule.<br>At Days (-1), 13 and at discharge: for therapeutic concentrations |
| Urine | For Valproic acid/metabolites: 12 hour urine on Days (-14), (-1), 13, and 20 for valproic acid and metabolite ratios. |
| Feces | none |
| Analysis | HPLC for olanzapine in plasma<br>GC for valproic acid in plasma and urine<br><br>Lower Limits of Quantitation<br>Olanzapine: Plasma 0.25 ng/mL<br>Valproic Acid: Plasma 10 mcg/mL; Urine 40 mcg/mL<br><br>Assay validation complete and acceptable (see Page 20) |
| PK Assessment | Plasma concentrations of valproic acid and olanzapine were used to assess the potential effects of each drug upon the other. Excretion of valproic acid in urine was assessed.<br>Cmax, t1/2, CL and Vd of olanzapine and metabolites |
| PD Assessment | CGI-BP and alertness assessments were evaluated during olanzapine-divalproex coadministration and compared with assessments during placebo-divalproex. |
| Safety | Comparisons between treatment groups for the QTc and prolactin values were performed during the olanzapine-divalproex treatment group versus the placebo-divalproex group. Liver tests were evaluated for evidence of clinically significant liver injury. |

Patient Disposition

27 out of 42 patients completed the study according to the protocol. A total of 12 patients excluded from the trial were attributed to unstable therapeutic levels of valproic acid during the 14 day evaluation period to assess the stability of therapeutic valproic acid concentrations. Other reasons were exclusionary laboratory results at entry or failure to meet other entry criteria. These patients signed the informed consent but did not receive any study drug.

The following Table shows the disposition of subjects in the study.

Table: Accounting of Patients in Pharmacodynamic and Local Laboratory Valproic Acid Plasma Concentration Data Statistical Analyses

| Treatment | Patient ID | Total |
|---|---|---|
| Placebo Group | 1001, 2414, 2594, 3014, 3031 3191, 3353, 5003, 5010, 5011 5012, 5018, 5019,6002, 6003 | 15 |
| Olanzapine Group | 2419, 2493, 2535, 2586[a], 2595 2634, 5001, 5008, 5013, 5016 6001[a], 6006 | 12 |
| Sub Total | | 27 |
| Part B Placebo Group | 3053[b] | 1 |
| Not Assigned to Treatment [c] | 2632, 2637, 5002, 5004, 5005, 5006, 5007, 5009, 5014, 5015, 6004, 6005 | 12 |
| Dropouts with Partial Data Not Included in Statistical Assessment | Placebo Group 2001[d] | 1 |
| | Olanzapine Group 5017[d] | 1 |
| Grand Total | | 42 |

[a] Dropouts with partial data included in the analysis under ITT.
[b] Local lab valproic acid concentrations used in statistical assessment.
[c] Discharged before study drug administered. No analysis performed.
[d] Not included in statistical assessment based because of minimal data (< 3 doses of study drug).

Patients included in the final pharmacokinetic analysis are given in the following Table:

Table: Patients included in the final pharmacokinetic analysis

| Patient Number | Treatment Group Assignment | | | PK of Plasma Olanzapine by Dose | | | PK of Plasma Valproic Acid by Treatment | | | PK of Urine Valproic Acid by Treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | N/A | 1st | 8th | 15th | A | B | N/A | A | B | N/A |
| 1001 | | X | | | | | | X | | | X | |
| 2001 | | X | | | | | | X | | | P | |
| 2414 | | X | | | | | | X | | | X | |
| 2419 | X | | | X | X | X | X | | | X | | |
| 2493 | X | | | X | X | X | X | | | X | | |
| 2535 | X | | | X | X | X | X | | | X | | |
| 2586 | X | | | P | P | | | | | P | | |
| 2594 | | X | | | | | | X | | | X | |
| 2595 | X | | | X | X | X | X | | | X | | |
| 2632 | | | X | | | | | | N | | | P |
| 2634 | X | | | X | X | X | | | | X | | |
| 2637 | | | X | | | | | | N | | | N |
| 3014 | | X | | | | | | X | | | X | |
| 3031 | | X | | | | | | X | | | X[a] | |
| 3191 | | X | | | | | | X | | | X | |
| 3353 | | X | | | | | | X | | | X | |
| 5001 | X | | | X | X | X | X | | | X | | |
| 5002 | | | X | | | | | | P | | | P |
| 5003 | | X | | | | | | X | | | X | |
| 5004 | | | X | | | | | | P | | | P |
| 5005 | | | X | | | | | | P | | | P |
| 5008 | X | | | X | X | X | X | | | X | | |
| 5010 | | X | | | | | | X | | | X[a] | |
| 5011 | | X | | | | | | X | | | BD | |
| 5012 | | X | | | | | | X | | | X | |
| 5013 | X | | | X | X | X | X | | | X | | |
| 5016 | X | | | X | X | X | X | | | X | | |
| 5017 | X | | | P | | | X | | | P | | |
| 5018 | | X | | | | | | X | | | X | |
| 5019 | | X | | | | | | X | | | X | |
| 6001 | X | | | P | | | P | | | P | | |
| 6002 | | X | | | | | | | | | X | |
| 6003 | | X | | | | | | | | | X | |
| 6004 | | | X | | | | | | | | | N |
| 6006 | X | | | X | X | X | | | | X[a] | | |
| 3053 | | X | | | | | | | | | N | |
| 2001A | | X | | | | | | X | | | P | |
| 5001A | X | | | | | | P | | | P | | |
| Total | 14 | 18 | 6 | 13 | 11 | 10 | 9 | 15 | | 10 | 14 | |
| Overall | | 38 | | | 10 | | | 24 | | | 24 | |

Abbreviations: X = data analyzed, P = partial data (not included in group), N = no data, BD = below detection.

[a] Urine data for these patients not included in percentage of dose excreted in urine calculation.

Pharmacokinetic Results:

***Olanzapine and Olanzapine metabolites***:

Plasma samples obtained during this study were analyzed for olanzapine and olanzapine after [ ] of the sample. The difference in these two measurements provides the plasma concentration of olanzapine glucuronide. b(4)

Mean±SD pharmacokinetic parameters for the olanzapine and its metabolite is given in the following Tables. For measurement of olanzapine glucuronide metabolite, the plasma samples were subjected to [ ] Measurement of [ ] sample reflects the summation of the concentrations of olanzapine plus its glucuronide conjugates. After subtraction of the olanzapine plasma concentration values from the measured concentration after [ ] the resulting difference is considered to be a calculated result reflecting the concentration of olanzapine glucuronide. b(4)

Table: Mean Olanzapine Pharmacokinetic Characteristics

| Olanzapine Pharmacokinetics for olanzapine dose given with divalproex N = 10 Patients [a] | Mean (Range) Cmax (ng/mL) | Mean (Range) Half-Life (hr) | Mean (Range) Clearance (L/hr) | Mean (Range) Volume of Distribution (L/kg) |
|---|---|---|---|---|
| Single Dose | 9.28±3.29 (4.5 to 16.8) | 37.8±7.94 (24.7 to 52.4) | 26.7±12 (17.3 to 56.9) | 14.3±3.8 (8.8 to 22.4) |
| 8th Multiple Dose | 21.9±7.48 (10.8 to 38.1) | n.a. | 27.8±10.3 (16.0 to 50.3) | n.a. |
| 14th or 15th Multiple Dose | 25.3±8.54 (11.4 to 41.4) | 38.7±11.6 [b] (24.9 to 63.5) | 24.9±9.23 (14.9 to 42.7) | 13.2±2.92 [b] (10.3 to 18.1) |

[a] N = Number of patients who completed the trial and had a full profile of olanzapine pharmacokinetics.
n.a. not available (could not be estimated).
[b] N = 9

Table: Mean Olanzapine [ ] Pharmacokinetic Characteristics b(4)

b(4)

| Olanzapine [ ] Pharmacokinetics for olanzapine dose given with divalproex N = 10 Patients [a] | Mean (Range) Cmax (ng/mL) | Mean (Range) Half-Life (hr) | Mean (Range) Clearance (L/hr) | Mean (Range) Volume of Distribution (L/kg) |
|---|---|---|---|---|
| Single Dose | 14.6±4.30 (8.75 to 22.9) | 37.7±9.11 (22.9 to 54.6) | 18.7±7.39 (11.6 to 37.6) | 10.0±2.46 (5.2 to 14.6) |
| 8th Multiple Dose | 30.9±8.37 (18.5 to 44.8) | n.a. | 19.8±7.37 (11.3 to 35.8) | n.a. |

| | | | | |
|---|---|---|---|---|
| 14th or 15th Multiple Dose | 34.2±10.9 (14.5 to 56.2) | 39.5±9.69 b (26.4 to 55.6) | 19.2±8.09 (11.2 to 38.6) | 10.4±3.36 b (5.4 to 17.6) |

[a] N = Number of patients who completed the trial and had a full profile of olanzapine pharmacokinetics.
n.a. not available (could not be estimated).
[b] N = 9

Table: Mean Olanzapine Glucuronide Pharmacokinetic Characteristics

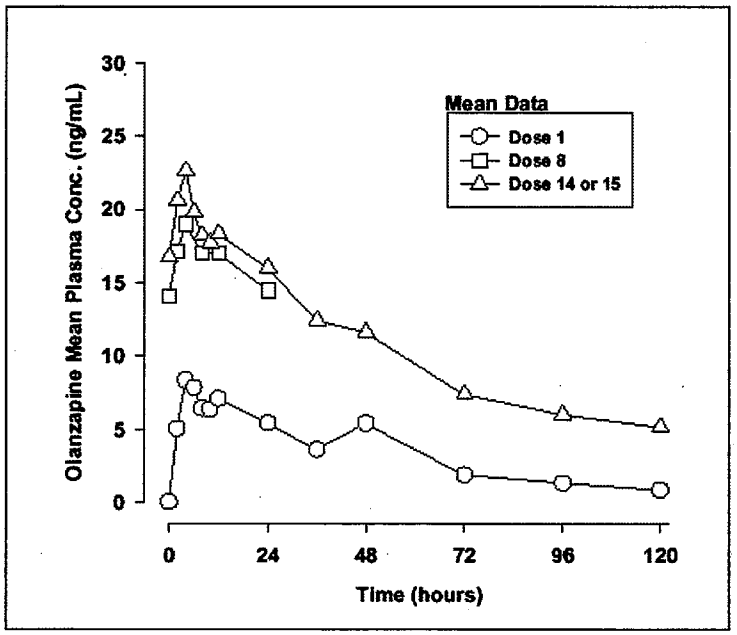
| Olanzapine Glucuronide Pharmacokinetics for olanzapine dose given with divalproex N = 10 Patients [a] | Mean (Range) Cmax (ng/mL) | Mean (Range) Half-Life (hr) | Mean (Range) Clearance (L/hr) | Mean (Range) Volume of Distribution (L/kg) |
|---|---|---|---|---|
| Single Dose | 6.20±2.89 (2.3 to 12.7) | 46.7±32.2 (13.8 to 107) | 69.7±41.1 (24.8 to 162) | 39.9±20.4 (13.0 to 66.7) |
| 8th Multiple Dose | 11.2±6 (5.3 to 22.1) | n.a. | 75.6±36.3 (24.0 to 125) | n.a. |
| 14th or 15th Multiple Dose | 10.6±6.05 (4.5 to 21.2) | 52.0±23 b (23.3 to 88.5) | 113±92.9 b (25.3 to 299) | 88.9±115 b (11.2 to 387) |

[a] N = Number of patients who completed the trial and had a full profile of olanzapine pharmacokinetics.
n.a. not available (could not be estimated).

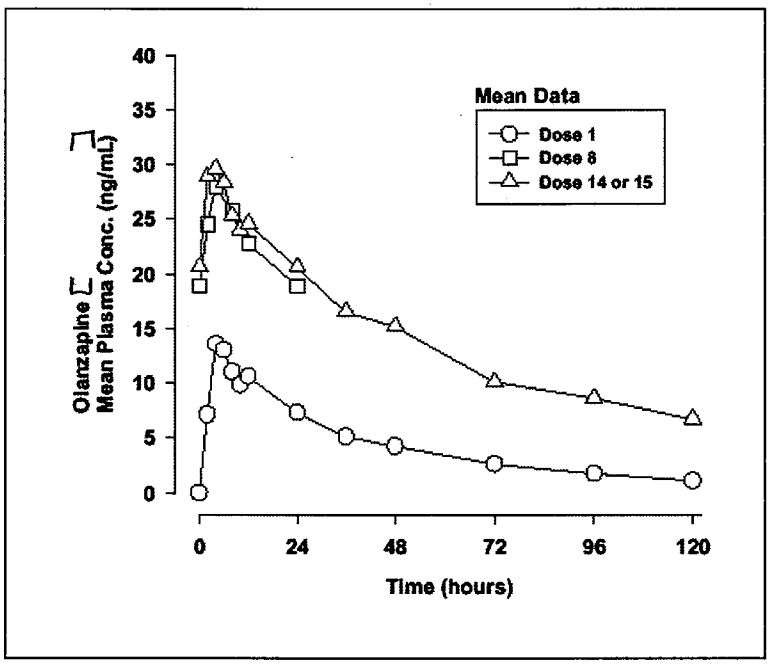
Observations:

- Upon multiple dose administration, concentrations of olanzapine and its metabolites had accumulated approximately two or three-fold higher than the single dose concentrations.

Mean Olanzapine plasma concentration profile after single and multiple doses is shown in the following figure:

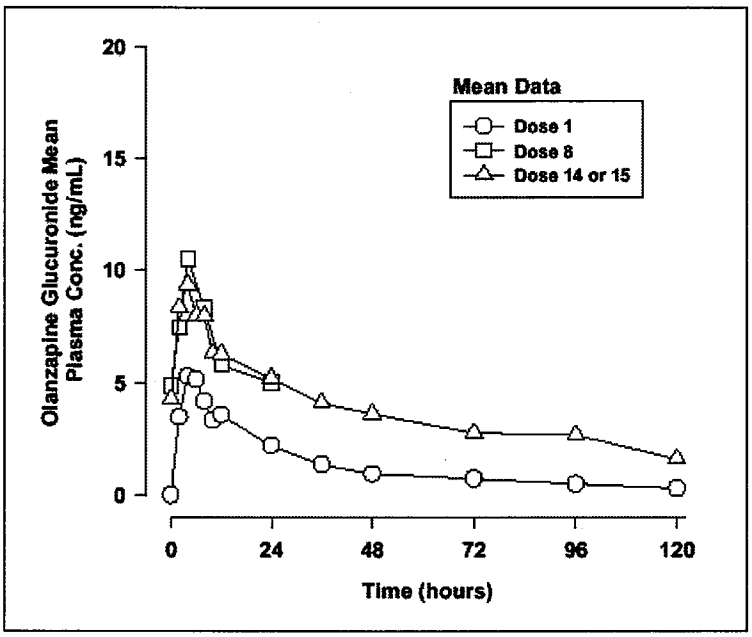


Mean Olanzapine [ ] plasma concentration profile after single and multiple doses is shown in the following figure: b(4)




b(4) )

Mean Olanzapine glucuronide plasma concentration profile after single and multiple doses is shown in the following figure:



This study did not permit a rigorous and controlled evaluation of the impact of valproate on the pharmacokinetics of olanzapine, a comparison to historical pharmacokinetic characteristics for olanzapine and its metabolites was done by the sponsor.

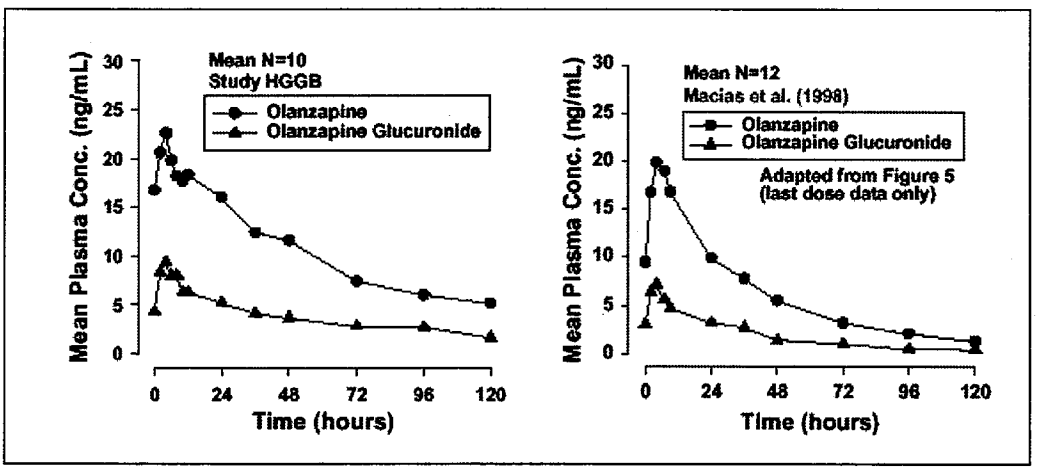
A steady state study (10 mg daily) conducted by Macias et. al. showed olanzapine and its glucuronide pharmacokinetic parameters to be similar to that obtained from this study. Comparative results are shown in the following Table:

Table: Mean (±SD) Olanzapine and its Glucuronide Pharmacokinetic Characteristics

| Pharmacokinetic Characteristic | Macias et. al (1998) N=12 | Study HGGB N = 10 |
|---|---|---|
| **OLANZAPINE** | | |
| $C_{max}$ (ng/mL) | 20.5 ± 4.9 | 25.3 ± 8.5 |
| $T_{max}$ (hrs) | 5.5 ± 1.6 | 3.9 ± 3.2 |
| $AUC_{0-24}$ (ng×hr/mL) | 368 ± 95.8 | 442 ± 129 |
| Half-Life (hrs) | 36.0 ± 5.1 | 38.7 ± 11.6 |
| CLp/F (L/hr) | 29.4 ± 9.4 | 24.9 ± 9.2 |
| $V\lambda z^F$ (L/kg) | 19.2 ± 6.2 | 13.2 ± 2.9 |
| **OLANZAPINE GLUCURONIDE** | | |
| $C_{max}$ (ng/mL) | 8.2 ± 3.1 | 10.6 ± 6.1 |
| $T_{max}$ (hrs) | 5.1 ± 2.7 | 5.7 ± 3.6 |
| $AUC_{0-24}$ (ng×hr/mL) | 118 ± 55.7 | 153 ± 112 |
| Half-Life (hrs) | 39.6 ± 10.4 | 52.0 ± 23.0 |

This comparison showed a 20-30% increase in Cmax and AUC between studies. CL of olanzapine was 15% lower. Significance of these differences is unknown due to cross study comparisons.

Comparative profiles from the two studies is shown in the following figures:



From studies done by Callaghan et.al. (1999), the mean half-life was 33 hours ranging from 21 to 54 hours, mean apparent clearance was 26 L/hr ranging from 12 L/hr to 47 L/hr (also in the approved package insert).

These pharmacokinetic characteristics for olanzapine are consistent with the pharmacokinetic values observed for olanzapine in this study. Olanzapine half-life ranged from 24.9-63.5 hours (mean (38.7 hours) and CL ranged from 14.9 to 42.7 L/hr (mean 24.9 L/hr) in this study.

***Valproic Acid:***

Valproic acid concentrations were measured for therapeutic drug monitoring. The concentration was measured 12 hours before and after dosing. The data did not suggest any impact of olanzapine on the valproic acid concentrations. Statistical comparison of the local-laboratory valproic acid concentrations between the placebo and olanzapine groups confirmed that the two treatment regimens maintained similar therapeutic concentrations. The therapeutic concentration range for valproic acid extends from 50 µg/mL to 125 µg/mL.

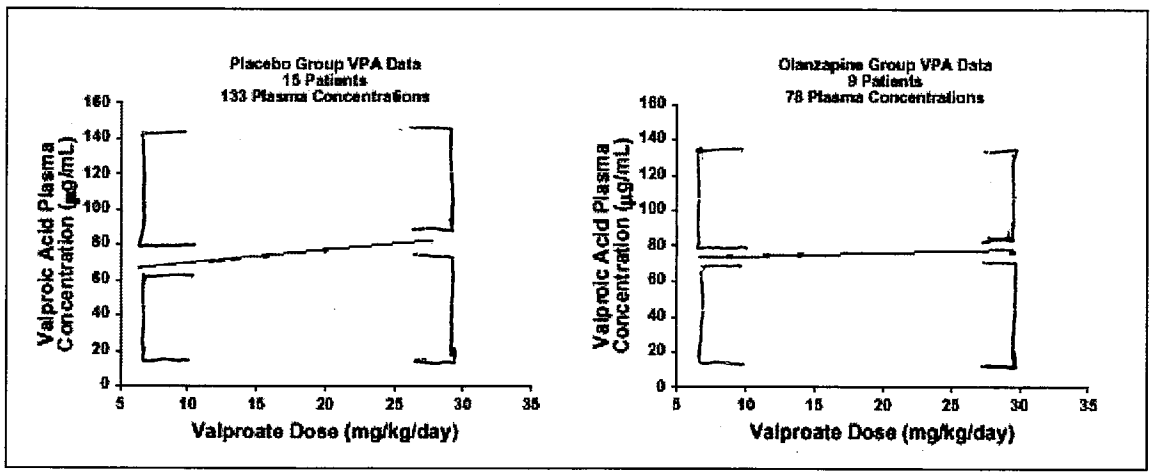
- At the local laboratory, the placebo group registered a least-square mean concentration of 74.6 µg/mL while the olanzapine group yielded a least-square mean concentration of 71.1 µg/mL. These differences were not statistically different (p=0.663).

- At the central laboratory, the placebo group registered a least-square mean concentration of 73.0 µg/mL while the olanzapine group yielded a least-square mean concentration of 70.4 µg/mL. These differences were not statistically different (p>0.5).

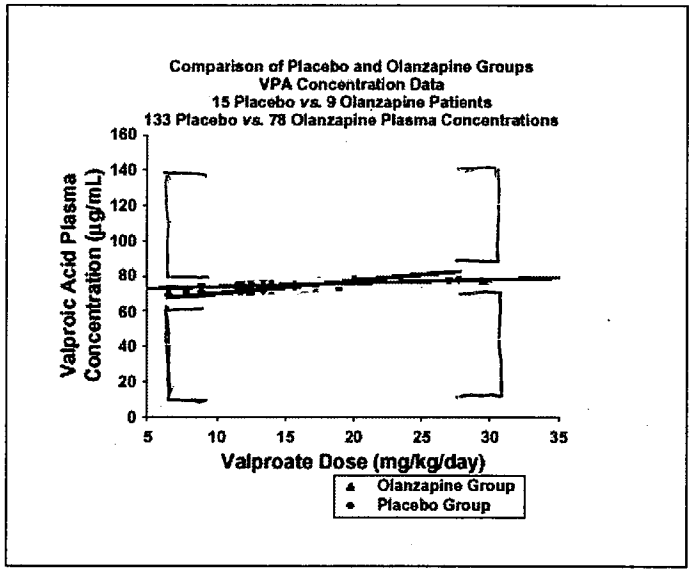
Although the protocol permitted dose adjustments of divalproex to maintain therapeutic concentrations, the divalproex dosage was not changed except in one individual where the dosage was increased. Thus, an interpretation of the mean valproic acid concentrations reflects the impact of olanzapine on the exposure to fixed doses (although the divalproex dosage was variable between individual patients ranging from 500 to 2250 mg/day).

The impact of various doses of divalproex upon the observed plasma concentrations was also assessed. Individual patients were given divalproex doses of 500 mg to 2250 mg per day to maintain concentrations of valproic acid in the therapeutic concentration range (50 to 125 µg/mL).

The following figures show the relationship between the valproic acid dose and the achieved valproic acid plasma concentrations. The regression relationships are similar (not significantly different) between the placebo and olanzapine patient groups.




b(6)




b(6)

Table: Statistical Evaluation of the Regression between Valproic Acid Plasma Concentrations and Valproate Dose

| Statistical Regression Line Testing | p-Value | Placebo Estimate | Olanzapine Estimate |
|---|---|---|---|
| Regression on Dose | 0.055 | | |
| Inter-Treatment Comparison of Regression Intercepts | 0.812 | 53.7 | 57.8 |
| Inter-Treatment Comparison of Regression Slopes | 0.642 | 0.017 | 0.010 |

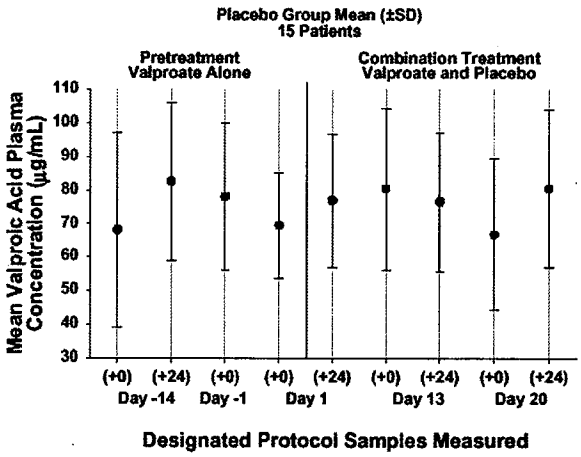
The statistical analysis did not reveal any statistically significant differences in the plasma concentrations of valproic acid between the placebo group and the olanzapine group, or between the pretreatment versus co-administration within each treatment group.

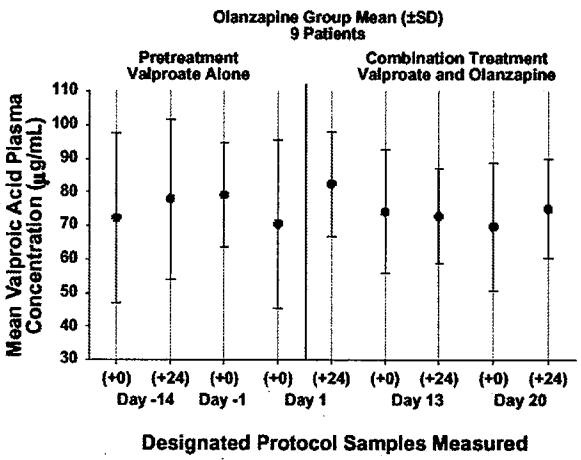
Table: Statistical Evaluation of the Valproic Acid Plasma Concentrations between Treatment Groups and Within Each Treatment Group Pre-treatment and Combined Treatment[a]

| Treatment | Phase | LS Mean | Difference | p-Value [b] |
|---|---|---|---|---|
| Placebo | Pretreatment | 73.0 | 2.2 | 0.592 |
| | Co-administered | 75.3 | | |
| Olanzapine | Pretreatment | 70.4 | 0.6 | 0.911 |
| | Co-administered | 70.9 | | |
| Olanzapine difference minus Placebo difference [c] | | | -1.7 | 0.800 |

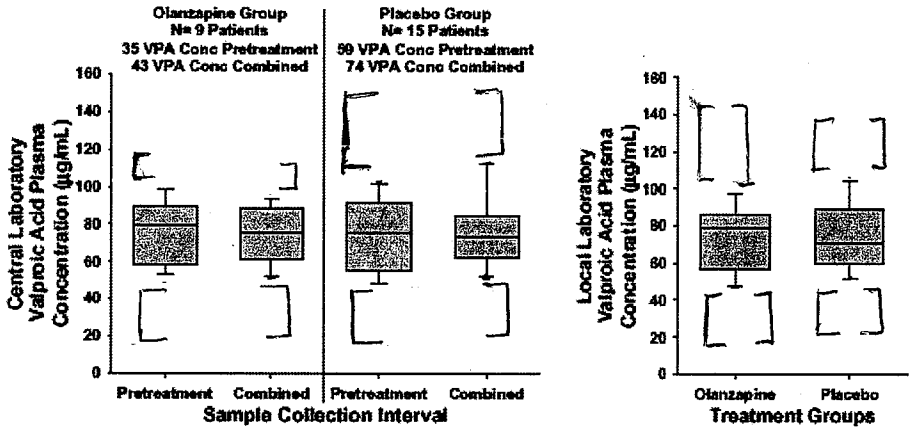
[a] Values reported are rounded from the values given in the statistical printouts
[b] Adjusted for multiple comparisons
[c] Olanzapine (Co-administered – Pre-Treatment) minus Placebo (Co-administered – Pre-Treatment)

Further comparisons are shown in the following figures:



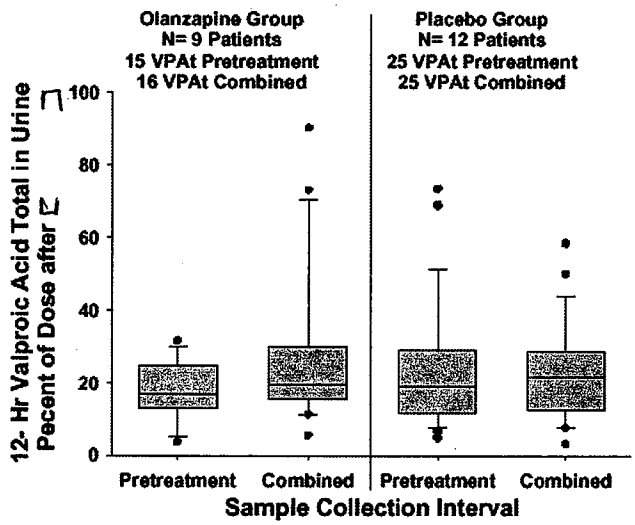
The following box plots show the central and local laboratories valproic acid plasma concentrations in the olanzapine and placebo groups.




b(6)

The box plot showing the percentage of the dose excreted in the urine after [ ] [ ] of the urine sample is shown in the following figure.

b(4)




b(4)

Valproic acid metabolite concentrations were not measured.

**Conclusions based on Pharmacokinetics:**

It is difficult to assess the effect of valproate on olanzapine pharmacokinetics based on this study. Patients on stable doses of divalproex were enrolled in this study, therefore without the olanzapine control arm the study design did not permit a direct assessment of changes in olanzapine pharmacokinetics, such as would be possible in a classical crossover design. The sponsor has shown some historical comparisons of the data, which is not really a robust comparison. However, the pharmacokinetic data for olanzapine are similar to those in other studies and show a lack of any substantial difference from previous results. The package insert for olanzapine gives a wide range of half-life and clearance values and the data obtained from this study does fall within the range reported in the label.

The effect of olanzapine on valproate pharmacokinetics has been assessed by measuring valproic acid concentrations at 12 hours before and 12 hours after dosing. No significant difference in the plasma concentrations between the olanzapine and placebo group was observed.

Olanzapine is predominantly oxidized by cytochrome P450 (CYP) 1A2 and 2D6 (minor) while approximately 40% of a valproic acid dose undergoes mitochondrial beta-oxidation. CYP 2C9 and 2A6 oxidize about 15% of the valproic acid dose (*Sadeque AJM, Fisher MB, Korzekwa KR, Gonzalez FJ, Rettie AE. 1997; Human CYP2C9 and CYP2A6 mediate formation of the hepatotoxin a4-ene-valproic acid. J Pharmacol Exp Ther 283(2):698-703*). In addition, both drugs are glucuronidated (40-50%), olanzapine undergoes N-glucuronidation. Valproic acid undergoes conjugation via UGT1A6, 1A8, and possibly 2B7 to form an ester glucuronide (*Levy RH, Mather GG, Anderson GD. 2000. Anticonvulsants. In Levy RH, Thummel KE, Trager WF, Hansten PD, and Eichelbaum M, editors. Metabolic Drug Interactions. Philadelphia: Lippincott Williams and Wilkins. p. 557-562*).

Any interaction based on CYP 450 metabolism in not likely because of the different pathways of metabolism. However, both drugs undergo glucuronidation. Hence, inhibition of the glucuronidation is possible to some extent. The study design was not robust to pick any small change that could occur due to possible inhibition of glucuronidation. The data from this study did not give any evidence towards a major pharmacokinetic drug interaction, any changes if possible are likely to be only small.

Two controlled clinical studies have also been performed to assess efficacy and safety of olanzapine in combination with divalproex and lithium in the treatment of bipolar mania.

**Conclusions from Pharmacodynamic Evaluation:**

The sponsor's conclusion regarding pharmacodynamic evaluation from this study is summarized here:
Statistical evaluation of CGI scores for mania, depression, and bipolar disorder disclosed no significant differences between the olanzapine + valproate and placebo + valproate groups. Because most enrolled patients were scored as not ill, it would be difficult to assess statistical improvement with these groups of patients. However, it is possible to

say that clinical deterioration was not observed for either group during the course of the study.

Alertness was evaluated by questionnaire. Statistical analyses for each question revealed a significant treatment difference for selected questions. In general, a decrease in alertness was noted. The differences occurred subsequent to the 10-mg single-dose administration of olanzapine, as observed in earlier studies in healthy subjects. These earlier studies tended to show adaptation of the responses with continued dosing. In this study as well, this observation was confirmed.

Two clinical studies have been conducted to evaluate efficacy and safety in combination with divalproex and lithium. The analyses of pivotal clinical studies as summarized by the sponsor suggested that olanzapine in a dose of 5, 10, 15, or 20 mg/day is an effective agent for the treatment of acute manic or mixed bipolar episodes, with or without psychotic features, when combined with lithium or valproate. For the combined primary efficacy analysis, the Y-MRS (Young-Mania Rating Scale) total score improvement in the olanzapine added to current mood stabilizer therapy group (-13.11) was statistically significantly greater than in the placebo added to current mood stabilizer therapy group (-9.10) (p=.003).

**Conclusions from Safety Evaluation:**

Ten patients experienced events after olanzapine treatment. The adverse events on olanzapine were generally those observed in prior studies and included asthenia, somnolence, dry mouth, and headache. One patient experienced akathisia, dyskinesia, hypertonia, myalgia, nervousness, anxiety, diarrhea, rhinitis, and abnormal thinking. The symptom complex may have been related to use of olanzapine.

In prior clinical pharmacology studies in healthy subjects, olanzapine did not show increases in the corrected QT interval. In this study, comparisons between treatment groups for the QTc (Bazett correction) showed no statistically significant differences. However, 1 patient given olanzapine had a post-treatment QTc interval >450 msec; the corrected QT interval was prolonged >30 msec more than her averaged control value. Because this change was observed only after single-dose olanzapine and not multiple-dose olanzapine, the clinical relevance of this is unknown and may not be related to olanzapine treatment.

Prolactin values also were increased during the olanzapine-divalproex treatment in comparison to the placebo-divalproex treatment.

No laboratory values (hematology, liver enzymes) were significantly different between the olanzapine and placebo groups that could be related to any clinical significance.

**OVERALL CONCLUSIONS**

The data for valproic acid plasma concentrations show that over the dosage range of

divalproex (500 to 2250 mg per day), the range of therapeutic concentrations for valproic acid (50-125 µg/mL) were not influenced substantially by coadministration of olanzapine (10 mg daily for 2 weeks). These results, therefore, support the conclusion that olanzapine does not affect the pharmacokinetics of divalproex.

Since patients on stable doses of divalproex were enrolled in this study, the study design did not permit a direct assessment of changes in olanzapine pharmacokinetics, such as would be possible in a classical crossover design. Nevertheless, the pharmacokinetic data for olanzapine are similar to those in other studies and the lack of a substantial difference from previous results suggests that valproic acid does not substantially affect the pharmacokinetics of olanzapine.

## ASSAY VALIDATION

*Olanzapine in human plasma:*

Method type: HPLC with [ ] b(4)
Limit of Quantitation: 0.25 ng/mL
Validation range: 0.250 ng/mL to 50.0 ng/mL,
0.250 ng/mL to 100 ng/mL (SAP 820-0192).
Validation accuracy: The inter-day range of accuracy during validation was 5.1% to 11.7% RE for olanzapine.

Validation precision: The inter-day range of precision during validation was 1.7% to 2.4% RSD for olanzapine.

Stability: Matrix: 48 hours at room temperature for olanzapine
Extract: 48 hours at room temperature for olanzapine
F/T: 5 cycles at approximately -80°C for olanzapine
Long term in matrix: 7 months at approximately -80°C for olanzapine and metabolites; 16 months at approximately -20°C for olanzapine; at least 10 months for olanzapine at approximately -60°C.

*Valproic Acid in Human Plasma:*

Method type: GC with [ ] b(4)
Limit of Quantitation: 10 µg/mL
Validation range: 10.0 µg/mL to 250 µg/mL.
Validation accuracy: 1.5% to 2.8%
Validation precision: 1.6% to 5.9%
Stability: Valproic Acid is stable in Human Plasma for 24 hours at ambient temperature. Processed Human Plasma samples are stable for 48 hours at ambient temperature.

*Valproic Acid in Human Urine:*

Method type: GC with [ ] b(4)
Limit of Quantitation: 40 µg/mL
Validation range: The validated calibration curve range is 40.0 to 1000 µg/mL. Samples above the limit of quantitation were diluted and reanalyzed to yield results within the calibrated range.
Validation accuracy: -0.4% to 0.4%
Validation precision: 1.5% to 1.8%
Stability: Valproic Acid in Human Urine is stable for 24 hours at ambient temperature. The processed samples are stable for 4 days at ambient temperature.

# FILING AND REVIEW FORM

## Office of Clinical Pharmacology and Biopharmaceutics

*New Drug Application Filing and Review Form*

General Information About the Submission

| | Information | | Information |
|---|---|---|---|
| **NDA Number** | **N20-592 (SE1-018)** | **Brand Name** | **ZYPREXA** |
| **OCPB Division (I, II, III)** | **I** | **Generic Name** | **Olanzapine** |
| **Medical Division** | **120** | **Drug Class** | **selective monoaminergic antagonist** |
| **OCPB Reviewer** | **Veneeta Tandon** | **Indication(s)** | **The combination of ZYPREXA with lithium or valproate is indicated for the treatment of acute manic episodes.** |
| **OCPB Team Leader** | **Ramana Uppoor** | **Dosage Form** | **Fast Disintegrating Tablets** |
| | | **Dosing Regimen** | **Begin with 10 mg QD. No information on doses greater than 20 mg QD. To be dosed with a particular dose range of lithium or valproate** |
| **Date of Submission** | **9/16/02** | **Route of Administration** | **Oral** |
| **Estimated Due Date of OCPB Review** | **4/25/02** | **Sponsor** | **Eli Lilly and Co.** |
| **PDUFA Due Date** | **7/16/02** | **Priority Classification** | **6S** |
| **Division Due Date** | **5/1/02** | | |

Background:

Olanzapine has been approved for the treatment of schizophrenia and bipolar mania as monotherapy. This efficacy supplement is for the treatment of bipolar mania as a combination therapy with mood stabilizers, lithium and valproate. An efficacy study has also been conducted in combination with the mood stabilizers for the treatment of bipolar I disorders. Clinical study evaluated doses in the range of 5-20 mg per day for 6 weeks.

Clin. Pharm. and Biopharm. Information

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | X | | | |
| **Tabular Listing of All Human Studies** | X | | | |
| **HPK Summary** | | | | |
| **Labeling** | X | | | |
| **Reference Bioanalytical and Analytical Methods** | X | | | Validation provided |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| Healthy Volunteers- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |

| | | | | |
|---|---|---|---|---|
| In-vivo effects of primary drug: | X | 1 | | Drug interaction study with valproate (divalproex sodium) Cross reference to NDA 20-592 for drug interaction study with lithium (Study E001) |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| AIDS patients | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | 1 | | | |
| **Total Number of Studies** | | 1 | | |
| | | | | |

**Filability and QBR comments**

| | "X" if yes | Comments |
|---|---|---|
| **Application filable ?** | X | Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one? |
| **Comments sent to firm ?** | | **None** |
| **QBR questions (key issues to be considered)** | • **Is there a drug interaction between olanzapine and valproic acid?**<br>• **Are appropriate doses evaluated in this drug-drug interaction study?** | |

| | |
|---|---|
| **Other comments or information not included above** | **PK datasets have not been submitted, but will be submitted within 45 days of the submission date. Safety datasets from this study have been provided electronically.** |
| **Primary reviewer Signature and Date** | **Veneeta Tandon, Ph.D** |
| **Secondary reviewer Signature and Date** | **Ramana Uppoor, Ph.D** |

CC: NDA 20-592, HFD-850(Electronic Entry or Lee), HFD-120(CSO), HFD-860(Uppoor, Sahajwalla, Meh

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

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/s/

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Veneeta Tandon
3/17/03 11:14:29 AM
BIOPHARMACEUTICS

Ramana S. Uppoor
3/17/03 11:34:24 AM
BIOPHARMACEUTICS

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-592/S-019**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

**EXCLUSIVITY SUMMARY for NDA # 20-592 SUPPL # 019**
**Trade Name Zyprexa Generic Name olanzapine**

**Applicant Name Eli Lilly & Co., Inc. HFD- 120**
**Approval Date See Signature Page**

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

___THREE_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # NDA 21-086, Zyprexa Zydis Orally Disintegrating Tablets

NDA # NDA 21-520, SYMBYAX (olanzapine / fluoxetine HCl) Capsules (approved December 24, 2003)

NDA #

2. Combination product. NOT APPLICABLE - SINGLE ACTIVE INGREDIENT

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications

(i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X_/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # F1D-MC-HGHL

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

| | | |
|---|---|---|
| Investigation #1 | YES /___/ | NO /_X_/ |
| Investigation #2 | YES /___/ | NO /___/ |
| Investigation #3 | YES /___/ | NO /___/ |

If you have answered "yes" for one or more investigations, identify each such investigation and the

NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

| | | |
|---|---|---|
| Investigation #1 | YES /___/ | NO /_X_/ |
| Investigation #2 | YES /___/ | NO /___/ |
| Investigation #3 | YES /___/ | NO /___/ |

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # F1D-MC-HGHL
Investigation #__, Study #
Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

| | |
|---|---|
| Investigation #1 | |
| IND # 28,705 YES /X/ | NO /___/ Explain: |
| Investigation #2 | |
| IND # _____ YES /___/ | NO /___/ Explain: |

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? **NOT APPLICABLE**

| | |
|---|---|
| Investigation #1 | |
| YES /___/ Explain _____ | NO /___/ Explain _____ |
| _____ | _____ |
| _____ | _____ |
| Investigation #2 | |
| YES /___/ Explain _____ | NO /___/ Explain _____ |
| _____ | _____ |
| _____ | _____ |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

See Electronic Signature page for signature and Date
Signature of Preparer Date
(Doris J. Bates, Ph.D.)

Title: Regulatory Project Manager

See Electronic Signature Page for Signature and Date
Signature of Office or Division Director Date
(Russell Katz, M.D.)

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Doris Bates
1/13/04 03:11:53 PM

Russell Katz
1/14/04 12:51:14 PM

# PEDIATRIC PAGE

**(Complete for all APPROVED original applications and efficacy supplements)**

*Although the Pediatric Rule is no longer in effect a Pediatric Page should be filled out as if it were still in effect to document what the Division would have done under the Rule. Therefore, if the Division would have deferred and/or waived specific age ranges for the application under review, this information should be captured on this Pediatric Page. Furthermore, if any pediatric studies were completed for this application, then that information should be captured as well.*

**NDA/BLA # :** 20-592

**Supplement Type (e.g. SE5):** SE1 019

**Stamp Date:** Nov. 21, 2002 **Action Date:** See electronic signature page

**HFD** 120 **Trade and generic names/dosage form:** Zyprexa (olanzapine)

**Applicant:** Eli Lilly & Co., Inc. **Therapeutic Class:** antimanic

**Indication(s) previously approved:** schizophrenia, acute mixed or manic episodes associated with Bipolar I Disorder

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

**Number of indications for this application(s):** 1

**Indication #1:** maintenance treatment of Bipolar Disorder

**Is there a full waiver for this indication (check one)?**

☑ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
**NOTE: More than one may apply**
**Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

## Section A: Fully Waived Studies

**Reason(s) for full waiver:**

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☑ **Other: acute pediatric studies in this class and indication are being conducted with other products**

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

**Age/weight range being partially waived:**

**Min**____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____
**Max**____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____

**Reason(s) for partial waiver:**

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**

☐**Too few children with disease to study**
☐**There are safety concerns**
☐**Adult studies ready for approval**
☐**Formulation needed**
☐**Other:**_____

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred: Pediatric patients age 10-17 years.**

**Min**_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
**Max**_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

**Reason(s) for deferral:**

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**___

**Date studies are due (mm/dd/yy):** _____

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section D: Completed Studies

**Age/weight range of completed studies:**

**Min**_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
**Max**_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

**Comments:**

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**This page was completed by:**
*{See appended electronic signature page}*

_____

**Doris J. Bates, Ph.D.**
**Regulatory Project Manager**
**cc: NDA**
**HFD-960/ Grace Carmouze**
**(revised 10-14-03)**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

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

/s/

Doris Bates
1/13/04 03:14:24 PM
Action due date is January 14, 2004. Action letter will be signed on January 14, 2004.

# REQUEST FOR WAIVER OF PEDIATRIC STUDIES

As a Phase 4 commitment for the bipolar mania monotherapy indication, Lilly is conducting a 3-week placebo-controlled study of olanzapine monotherapy in adolescent patients (ages 13 to 17 years) diagnosed with manic or mixed episode associated with bipolar I disorder (with or without psychotic features). However, Lilly does not intend to conduct studies in the pediatric population (ages birth to 17 years) to evaluate olanzapine for the long-term treatment of bipolar I disorder since a pediatric waiver was granted during the May 30, 2002 pre-NDA meeting (see FDA meeting minutes issued July 2, 2002).

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| Application Information | | |
|---|---|---|
| NDA 20-592 | Efficacy Supplement Type SE- 1 | Supplement Number 019 |
| Drug: ZYPREXA (OLANZAPINE) | Applicant: LILLY | |
| RPM: BATES | HFD- 120 | Phone # 6-2850 |
| Application Type: (X) 505(b)(1) ( ) 505(b)(2) | Reference Listed Drug (NDA #, Drug name): N/A | |

| | |
|---|---|
| ❖ Application Classifications: | |
| • Review priority | (X) Standard ( ) Priority |
| • Chem class (NDAs only) | |
| • Other (e.g., orphan, OTC) | |
| ❖ User Fee Goal Dates | 1/14/2004 |
| ❖ Special programs (indicate all that apply) | (X) None<br>Subpart H<br>( ) 21 CFR 314.510 (accelerated approval)<br>( ) 21 CFR 314.520 (restricted distribution)<br>( ) Fast Track<br>( ) Rolling Review |
| ❖ User Fee Information | |
| • User Fee | (X) Paid |
| • User Fee waiver | ( ) Small business<br>( ) Public health<br>( ) Barrier-to-Innovation<br>( ) Other |
| • User Fee exception | ( ) Orphan designation<br>( ) No-fee 505(b)(2)<br>( ) Other |
| ❖ Application Integrity Policy (AIP) | N/A |
| • Applicant is on the AIP | ( ) Yes ( ) No |
| • This application is on the AIP | ( ) Yes ( ) No |
| • Exception for review (Center Director's memo) | |
| • OC clearance for approval | |
| ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent. | (X) Verified |
| ❖ Patent | |
| • Information: Verify that patent information was submitted | (X) Verified |
| • Patent certification [505(b)(2) applications]: Verify type of certifications submitted | 21 CFR 314.50(i)(1)(*i*)(A)<br>( ) I ( ) II ( ) III ( ) IV<br><br>21 CFR 314.50(i)(1)<br>( ) (ii) ( ) (iii) |
| • For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). | ( ) Verified |
| ❖ Exclusivity Summary (approvals only) | ✓ |
| ❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)* | |

| | |
|---|---|
| ❖ Actions | |
| • Proposed action | (✓) AP ( ) TA ( ) AE ( ) NA |
| • Previous actions (specify type and date for each action taken) | AE, 9/22/2003 |
| • Status of advertising (approvals only) | (✓) Materials requested in AP letter<br>( ) Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | (✓) Yes ( ) Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | ( ) None<br>(✓) Press Release<br>( ) Talk Paper<br>( ) Dear Health Care Professional Letter |
| ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | ✓ |
| • Most recent applicant-proposed labeling | N/A |
| • Original applicant-proposed labeling | N/A |
| • Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)* | ✓ |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | N/A |
| Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | N/A |
| • Applicant proposed | N/A |
| • Reviews | N/A |
| ❖ Post-marketing commitments NONE | |
| • Agency request for post-marketing commitments | |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | ✓ TAB 10 |
| ❖ Memoranda and Telecons | ✓ TAB 10 |
| ❖ Minutes of Meetings AE PACKAGE | |
| • EOP2 meeting (indicate date) | |
| • Pre-NDA meeting (indicate date) | |
| • Pre-Approval Safety Conference (indicate date; approvals only) | |
| • Other | |
| ❖ Advisory Committee Meeting N/A | |
| • Date of Meeting | |
| • 48-hour alert | |
| ❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable) N/A | |

| | |
|---|---|
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)* | ✓ TAB 7 & 8 |
| ❖ Clinical review(s) *(indicate date for each review)* | ✓ TAB 9 |
| ❖ Microbiology (efficacy) review(s) *(indicate date for each review)* | N/A |
| ❖ Safety Update review(s) *(indicate date or location if incorporated in another review)* | N/A |
| ❖ Pediatric Page(separate page for each indication addressing status of all age groups) | ✓ TAB 6 |
| ❖ Statistical review(s) *(indicate date for each review)* | AE PKG |
| ❖ Biopharmaceutical review(s) *(indicate date for each review)* | N/A |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)* | N/A |
| ❖ Clinical Inspection Review Summary (DSI) AE PKG. | |
| • Clinical studies | |
| • Bioequivalence studies | |
| **CMC Information** | |
| ❖ CMC review(s) *(indicate date for each review)* AE PKG | |
| ❖ Environmental Assessment AE PKG | |
| • Categorical Exclusion *(indicate review date)* | ✓ |
| • Review & FONSI *(indicate date of review)* | |
| • Review & Environmental Impact Statement *(indicate date of each review)* | |
| ❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)* | N/A |
| ❖ Facilities inspection (provide EER report) N/A | Date completed:<br>( ) Acceptable<br>( ) Withhold recommendation |
| ❖ Methods validation N/A | ( ) Completed<br>( ) Requested<br>( ) Not yet requested |
| **Nonclinical Pharm/Tox Information** | |
| ❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | N/A |
| ❖ Nonclinical inspection review summary | N/A |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | N/A |
| ❖ CAC/ECAC report | N/A |

20592_019responsetoapprovable

NDA-20592_s019

Sponsor: Eli Lilly and Company

Drug Name: Zyprexa® (olanzapine)

Proposed Indication: Long-term treatment of Bipolar I Disorder

Date Submitted: November 20, 2002

User Fee Date: September 21, 2003

Approvable Letter Issued: September 22, 2003

Complete Response to Approvable Letter: November 13, 2003

Review of Response Completed: January 12, 2004

Action Date on Response: January, 14, 2004

Reviewer: Teresa A. Podruchny, M.D.

Background:

The NDA supplemental application for the use of olanzapine (Zyprexa®) in the maintenance treatment of bipolar I disorder was submitted to the Division of Neuropharmacological Drug Products (DNDP) in November of 2003. Subsequent to review, an approvable letter was issued with proposed labeling and requests for further clinical information . The requests were refined and clarified over several phone calls and resulted in the complete response to the approvable letter submission of which is the basis for this review.

The major points of the approvable letter were: establishing duration of effect; addressing class labeling for diabetes; addressing time-to-event excluding sites [ ] 34; exploring suicidality as per the method used with fluoxetine; recoding patient disposition tables; defining or clarifying terms such as "reporting interval completed" and "days in remission"; expanding on the presentation of time in remission to time- to- event and time- to- relapse data; expanding and/or re-examining certain laboratory data such as cholesterol; and providing further information about certain safety findings such as a convulsive event in the open-label and certain PCS events. b(4)

The sponsor' response is outlined below and will be addressed as per this outline. Additionally, the labeling section includes an explanation of the reviewer's proposed changes for the label and a re-examination of the data of trial HGHL.

Question 1: Labeling (see pages 3-7)
Question 2: Diabetes class label accepted by Lilly and submitted as CBE on 09-18-03?
Question 3:

a) Perform analysis of time-to-event without sites [ ]34. b(4)
b) Perform analysis of treatment emergent suicidality using HAM-D items 1 and 3 as per the fluoxetine algorithm.
c) Recode the disposition tables and explain discrepancies of patients 201, 233, 560, 563, 564, and 603.
d) Discuss patient 212 who is coded as discontinued at visit 110 however relapsed at 101
e) Define the term " Reporting Interval Completed" in the disposition table for the double-blind period in study HGHL.
f) Discuss "Days in Remission" Table HGHL.14.11 and clarify when patients were randomized as it appeared randomization criteria were not always met, for example, patient 455.
g) Symptomatic relapse, Table HGHL.14.12 stratifies relapse by time intervals. Please do this for the intervals days 21-28 and =35. Please show time in remission to time-to-relapse and time in remission to time-to-event
h) Re-analyze the cholesterol data using 250mg/dL after normal baseline or change of 50 from baseline.
i) Eosinophils, uric acid, urine ketones, and cholesterol from the beginning of open-label to the last visit of double-blind for HGHL and all other studies with double-blind extensions. This was revised to be study HGHL and HGGY with visit 8 data, present labs for EOS, uric acid, and cholesterol 250 mg/dL after baseline of 200mg/dL or change of 50mg/dL. HGHL comparative data for olanzapine versus placebo from the beginning of open-label to the end of double-blind. Use the first visit of open-label as baseline.

j) Provide a detailed description of any tests or consultations of the convulsive event seen in the open-label period of HGHL.
k) Discuss clinically significant EKG or syncopal events to include vital signs taken at the time of events.
l) Although not essential to approval, explain patients whose time in the study was greater than 365 days.

## 1) LABELING:

The sponsor submitted track-change label text changes in the following areas of the label:

a) DESCRIPTION: CMC change to one word as per CBE submitted August 05, 2003.
b) Clinical Efficacy Data: Bipolar Disorder Monotherapy: [

b(4)

**Sponsor's proposed label:**

**Bipolar Disorder**

[ ]

~~Monotherapy~~ [ ] — The efficacy of olanzapine in the treatment of acute manic or mixed episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

b(4)

b(4)

[redacted] — The efficacy of olanzapine with concomitant lithium or valproate in the treatment of acute manic episodes was established in two controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course. The results of the trials follow:

(1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

b(4)

**Reviewer's Response:** HGHL does not provide data to support a long-term claim. I think the most appropriate place for this trial description is as a third trial under the Monotherapy [redacted] heading.

b(4)

**Reviewer's suggested labeling:** (Under the [redacted] section)

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar disorder [redacted] who responded during an initial open-label treatment phase for about two weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n = 225) or to placebo (n = 136), for observation of [redacted] relapse. Approximately 50% of the patients discontinued from the olanzapine group by day 59 and 50% of the placebo group [redacted] by day 23 of double-blind treatment. Response during the open label phase was defined by having a decrease of the YMRS total score to / 12 and HAM-D 21 to / 8. Relapse during the double-blind phase was defined as an increase of the YMRS or HAM-D 21 total score to / 15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

b(4)

c) INDICATIONS AND USAGE, Bipolar Disorder: A heading for Monotherapy with subheadings of Acute [redacted] and Maintenance [redacted] was added. [redacted]

b(4)

**The sponsor's proposed label:**

**Bipolar Disorder**

**Monotherapy**

Acute Monotherapy [redacted] — ZYPREXA is indicated for the treatment of acute mixed or manic episodes associated with Bipolar I Disorder.

The efficacy of ZYPREXA was established in two placebo-controlled trials (one 3-week and one 4-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

Maintenance Monotherapy [redacted]

b(4)

276 [
277
278
279
280 [ ] the physician who elects to use ZYPREXA for extended
281 periods should periodically re-evaluate the long-term usefulness of the drug for the individual
282 patient (see DOSAGE AND ADMINISTRATION).
283 [
284 ~~Combination Therapy~~ [ ] — The combination of ZYPREXA with lithium or
285 valproate is indicated for the short-term treatment of acute manic episodes associated with
286 Bipolar I Disorder.
287 The efficacy of ZYPREXA in combination with lithium or valproate was established in
288 two placebo-controlled (6-week) trials with patients meeting DSM-IV criteria for Bipolar I
289 Disorder who currently displayed an acute manic or mixed episode with or without psychotic
290 features (see CLINICAL PHARMACOLOGY).

b(4)

**Reviewer's response**: I do not believe there should be language regarding maintenance and recommend deleting this entire section of the label beginning with the word Maintenance and ending with the word ADMINISTRATION.

d) DOSAGE AND ADMINISTRATION, Bipolar Disorder: [ ]

b(4)

**The sponsor's proposed label:**

969 **Bipolar Disorder**
970 ~~Monotherapy~~
971 ~~Usual Monotherapy Dose~~ [ ] – Olanzapine should be administered on a
972 once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage
973 adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting
974 the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose
975 increments/decrements of 5 mg QD are recommended.
976 Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to
977 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in
978 clinical trials.
979 [ ] ~~Maintenance Monotherapy~~ [ ]
980 [
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987 ]
988 [ ]
989 ~~Bipolar Mania: Usual Dosage Combination with Lithium or Valproate~~ [ ] –
990 When administered in combination with lithium or valproate, olanzapine dosing should generally
991 begin with 10 mg once-a-day without regard to meals.
992 Short-term (6 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to
993 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in
994 clinical trials.

b(4)

**Reviewer's response:** I recommend removal of language regarding maintenance treatment. Usage of two weeks is included within the acute treatment label and offers no further clinical information.

**Explanation of reviewer's label suggestions/re-examination of HGHL:**

With further consideration of the pivotal trial HGHL, it is my opinion that data from HGHL cannot answer the question of long-term treatment as it is not designed to do so. Traditionally the Division viewed this type of design as reasonable to answer questions of long term utility. However, as the development of the treatment of bipolar illness evolves and multiple treatment options are sought, data indicate that this design may not allow one to answer maintenance type

questions.[1] In fact, the rapid attrition of the treatment group in HGHL as well as the rapid relapse of the placebo group highlighted this to a level that requires intense deliberation about how to interpret the data of HGHL.

As a means of review of the trial, over 700 patients entered an open-label period. The purpose of the open-label period was to taper concomitant medications and stabilize index manic or mixed patients. These patients were considered "in remission"[2] by meeting predefined scale criteria at two consecutive visits[2]. In order to be randomized, patients had to meet this criteria and be in the open label period for six weeks. 361 patients finished open-label and were randomized (225 treatment; 136 placebo). Within about 20 days, half of the placebo group was out of the study primarily due to relapse (63/68). Within 60 days, half of the treatment group was out of the study (77 relapsed, 36 censored=a loss of 113/225). In the later months of the double blind period, about 23% of the treatment group remains and about 8-9% of the placebo group remains. P values for differences in time to relapse between the groups are strong and significant. So, what does this mean?

Although there are many factors to consider in trying to interpret this data, the major concepts that I will address in some detail are the time in "remission", attrition and lack of retention, the fact that these ideas are interwoven, and the primary efficacy measure of time- to- relapse. Additionally, I offer what I think the data mean or do not mean.

The placebo group relapsing quickly maybe could be attributed to an expected effect of stopping the drug. However, one can also postulate that this effect was amplified, or maybe precipitated, by short times in "remission" which created a group of patients that were not "remitted" long enough to establish that they were clinically stable before they were withdrawn from medication. Clinically, psychiatrists would not take a patient so acutely remitting (the bulk of the patients were "in remission"[2] 7-20 days) off drug. Therefore, to do so does not translate to clinical practice and to do so and then try to describe what happens to the group left on drug, seems to have little clinical utility.

The rate and amount of attrition in the treatment group is more bothersome. At randomization, these people were not taken off medication yet they still leave fairly quickly, although not nearly as quickly as the placebo group and for more varied reasons. One can postulate that after randomization, this group of patients continues to "remit" on drug. However, within 8-9 weeks, for various reasons, 50% of this group is not retained. Patients who are not on drug cannot be maintained. Further, an extrapolation, that is somewhat flawed however may be reasonable, is that from the viewpoint of the Division's current thinking with regard to the open label period, even this group of olanzapine patients probably would not be "remitted" long enough to consider conducting the type of trial the Division now sees as necessary to establish maintenance.

Does the 23% of the olanzapine patients left at later months reflect some utility in the group who responded? To conclude that, one would need to assume this group had at least a close approximation of enough time in remission to look at maintenance. If so, as the placebo group did not have this time in remission, the longer term data essentially is uncontrolled. What does it means that 50% of the randomized olanzapine patients continued to remit for on average two

months while the placebo group relapsed in 20 days? Maybe this indicates what the Division already has concluded; that olanzapine has acute efficacy for some time period in this disorder.

The median times-to-relapse are significantly different between the two groups. However, this effect must be viewed within the context of an apparent inability to retain most patients for more than two months after "remission". Therefore, the clinical ramifications of the median time to relapse (174 days) are greatly reduced by the median time to discontinuation for any reason (55 days per raw data). Additionally, the large difference in the median times to relapse between the two groups is not unexpected if the placebo group is not clinically stable and the withdrawal of medications allows or precipitates deterioration while the treatment group continues to achieve the maximum remission they will achieve on this drug.

In summary, interpretation of this data is complicated and there are many issues to consider. The overwhelming information of study HGHL is that you have low retention and fast attrition in both groups in the face of statistically significant findings in a population of patients who largely were not "remitted" long enough to translate to a clinical practice situation. I do not think this trial design allows one to make maintenance decisions and recommend that perhaps the sponsor consider performing a trial to ascertain this data. The data from HGHL suggest to me that this may be difficult as attrition will be high.

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[1][The larger issues of optimal trial design(s) to answer clinical questions such as how long a treatment will keep a patient "well" or is the patient better off on drug x at six months than off drug x, are at the core of the issues with any proposed drug for use as either [ ] b(4) or "maintenance". Resolution of these issues is outside of the scope of this review and requires input from multiple disciplines.]

[2] Days in remission were calculated for most patients, "from the first of any consecutive visits at which a patient had qualifying YRMS and HAMD-21 scores and was randomized while still meeting score criteria, with the first day of meeting score criteria counting as day 1". To be randomized patients had to receive open-label treatment for a minimum of 6 weeks and be in symptomatic remission. Therefore the earliest randomization could occur was at about week 6 (visit 8).

**2)** Class labeling was accepted.

**3a)** Time-to-event analysis excluding sites [ ] 34: Kaplan-Meier was submitted. The b(4) sponsor also submitted a time-to-relapse survival curve excluding these sites. This data do not contribute to the overall process of determining efficacy, did not show significant changes in the results, and do not reveal concepts not addressed in principle in the original review.

**3b)** Suicidality as assessed by HAM-D items 1 and 3 was requested. The sponsor presented discussions of suicidality and depression which included discussion of treatment emergent adverse events (TEAEs) related to suicide and depression. Attrition rates reduce the populations available for long term data.

**TEAES related to suicide:** To assess this, the sponsor looked for multiple suicide- related MEDRA terms. During the open –label period 14 patients (1.9%) experienced TEAEs related to suicidality which included 3 attempts, two of which led to discontinuation.

During the double-blind period, 3 patients in the placebo group and 1 in the olanzapine group experienced a TEAE.

**HAM-D item 3 analysis:** defined as increase on item 3 to 3-4 (suicidal idea/gestures-attempt) in a patient who had a 0 or 1 (absent or feels life is not worth living) at baseline. An analysis of worsening or improvement based on the endpoint score being worse or better than the baseline score was performed. Open-label used visit 2 as baseline and looked across visits. Three percent (3%) of patients with scores of 0 or 1, increased to 3 or 4. Most of the patients had a score of 0 at entry. 23.2% demonstrated a worsening of at least 1 point at endpoint. 76% of 171 patients who had a baseline score greater than 0, had an improvement of at least 1 point at the end of open-label treatment. During the double-blind period, using as baseline the score at randomization, 3.6% of olanzapine treated patients and 4.5% of placebo treated patients with scores of 0 or 1 at randomization increased to a 3 or 4 during double-blind treatment. Most patients in both groups had a score of 0 at randomization. Worsening by at least one point occurred in 29% of the olanzapine patients and 38.8% of the placebo patients (p=.063). Open label rescue period data were supplied but this data likely are confounded with other medications.

**TEAEs related to depression:** During the open-label period, 29 patients (4.0%) experienced TEAEs related to depression. During the double-blind period, 11.6% of the olanzapine patients and 8.1% o the placebo patients had TEAEs related to depression. 145 patients discontinued either due to an AE of depression or relapse to depression with more in the placebo group. Patients discontinuing for lack of efficacy it appears would not be captured in this number.

**HAM-D item 1 analysis:** During open-label treatment, 13.9% of patients with a score of 0 or 1 at baseline had increases to 3 or 4. During the analysis of worsening, 40.6% demonstrated a worsening of at least one point by endpoint of this phase. Generally patients entered manic/mixed, this one point difference may not be meaningful. 1.5% of patients discontinued this phase due to depression-related AEs. The mean within-group change indicates improvement in HAMD-21 total scores (-5.7±8.6). During the double-blind period, 25.4% of the olanzapine patients and 30.2% of the placebo patients experienced a change from 0 or 1 to 3 or 4. The groups were about equal with respect to worsening by one point (66.5%olanzapine, 65.7%placebo). HAMD-21 total score mean changes were 6.0 ± 7.7 for the olanzapine group and 9.7 ± 9.2. HAMD-21 item 1 mean score changes were 0.8 ± 1.3 for the olanzapine group and 1.1 ± 1.3 for the placebo group. About the same amount of patients showed improvement in each group. Approximately 18% of the olanzapine group and 10% of the placebo group who experience TE depression improved to a 2 or better by endpoint of double-blind.

**Table 3b.4. Scoring Patterns for Patients with Treatment-Emergent Depression Based on HAMD-21 Item 1 (Depressed Mood) Study HGHL**

| | Study Phase | | | | |
|---|---|---|---|---|---|
| | Lead-In | Double-Blind | | | Rescue |
| Number of Patients | Olanzapine | Olanzapine | Placebo | p-Value[a] | Olanzapine |
| Item 1 Characteristics | | | | | |
| 3 or 4 any time post-BL | 59 | 55 | 39 | | 10 |
| Maximum score of 3 | 53 (89.8%) | 47 (85.5%) | 35 (89.7%) | .755 | 8 (80%) |
| Score ≤2 by endpoint | 30 (50.8%) | 10 (18.2%) | 4 (10.3%) | .383 | 4 (40%) |
| Score ≤1 by endpoint | 25 (42.4.%) | 6 (10.9%) | 2 ( 5.1%) | .462 | 2 (20%) |
| HAMD-21 Total Score | | | | | |
| Endpoint ≤ baseline | 26 (44.1%) | 0 ( 0.0%) | 1 ( 2.6%) | .415 | 2 (20%) |

Abbreviations: BL = baseline; na = not applicable.
[a] P-value calculated using Fisher's exact test.
Sources: Reports USBF12HL, USBF19HL, USBQ12HL, USBQ19HL

**Conclusions:** Interpreting the data is somewhat problematic as the open-label data is uncontrolled and the double-blind data is based on groups that had high attritions with the placebo group attrition very early. Person-time data might be helpful but also would be confounded some by the open-label treatment perhaps carrying over into the double-blind period.

More events of treatment-emergent depression occurred in the olanzapine group during the double blind period while a greater percentage of placebo patients "relapsed". The groups were about equal with respect for any worsening or improvement in HAMD-21 item 1. Additionally, data from HGHL show that of the "relapsers", the olanzapine group more frequently "relapsed" to depression than either mania or mixed (~65% vs ~ 35%) while the placebo group overall "relapsed" a little more into mixed/or manic than into depression (~ 51% mixed/manic versus ~ 49% depression). Taken together this may suggest olanzapine is not protecting against depression in this population and perhaps in future studies, the issue of whether it may facilitate depression should be investigated again.

**3cde):** Disposition Tables:

We asked for an explanation of the term "Reporting Interval Completed" (RIC). One reason the disposition tables were difficult to understand is that "relapse" was not defined as a reason for discontinuation (within the CRFs and therefore the table). When patients discontinued from the double-blind phase, PIs had to identify the primary reason using the choices of "protocol completed", "adverse event", "death", "satisfactory response (patient perception, physician perception, or both), lack of efficacy (varies by perception), lost to follow-up, patient moved, patient decision, physician decision, protocol violation, or sponsor decision. Patients who were listed as RIC were those with "protocol completed" as the reason for discontinuation.

The sponsor re-calculated patient disposition counting relapse as a separate reason for discontinuation. Otherwise, the disposition table should reflect the primary reason for discontinuation using the categories as above.

**Table 3cde.1. Patient Disposition (Number and Percent) When Relapse Is Considered a Reason for Discontinuation Study HGHL**

| Patient Disposition | Olz (N=225) | Pla (N=136) | Fisher's Exact Test p-value |
|---|---|---|---|
| Completed 12 mo. of treatment | 48 (21.3%) | 9 ( 6.6%) | <.001 |
| Discontinued due to: | | | |
| Relapse | 105 (46.7%) | 109 (80.1%) | <.001 |
| Adverse event | 17 ( 7.6%) | 0 ( 0.0%) | <.001 |
| Patient decision | 22 ( 9.8%) | 6 ( 4.4%) | .070 |
| Loss to follow-up | 19 ( 8.4%) | 5 ( 3.7%) | .085 |
| Protocol violation | 6 ( 2.7%) | 1 ( 0.7%) | .262 |
| Lack of efficacy | 4 ( 1.8%) | 2 ( 1.5%) | 1.00 |
| Sponsor decision | 1 ( 0.4%) | 0 ( 0.0%) | 1.00 |
| Physician decision | 3 ( 1.3%) | 4 ( 2.9%) | .433 |
| Satisfactory response | 0 ( 0.0%) | 0 ( 0.0%) | - |
| Other | 0 ( 0.0%) | 0 ( 0.0%) | - |

Abbreviations: mo. = months; N = sample size; Olz = olanzapine; Pla = placebo.
Source: Report S03F01HL

Specific patients of interest:

Patient 212- As the sponsor noted earlier in this response that relapse was not a reason for disposition in the original disposition table, the coding is somewhat less confusing. Additionally, for purposes of primary efficacy analysis, this patient was coded correctly for relapse although there was a protocol violation in allowing the patient to continue in the double-blind study period.

Patient 012-563- Originally coded as discontinuation secondary to "patient decision" , the sumytext.jmp indicates the person was experiencing depressive symptoms. This patient did not meet reach criteria for relapse although the HAM-D did increase. The sponsor notes that in the open-label rescue, the patient's HAM-D scores improved. From the [ ] database, it looks like this person was placed on fluoxetine during the open-label rescue period. b(4)

**Conclusion:** The sponsor addresses other specific patients and as stated in my original review, these appear to have been appropriately coded for relapse. However, the configuration of the original disposition tables created confusion for this reviewer, increased the review time, and made it more difficult to have confidence in the data without a large amount of cross checking. The new disposition table reflecting relapse as a separate category, on face, seems easier to interpret although some categories are still open and in looking at certain patient dispositions, perhaps several different reasons could be chosen.

The sponsor notes that the PIs made valid decisions based on CRF available choices for discontinuation. Some cases are noted in which lack of efficacy would have seemed perhaps a more appropriate code (pt 6051, with notes of "return of pre-study symptoms" and coded as physician decision), such as cases of relapse.

Also, I understand at times there were perhaps multiple factors happening simultaneously that contributed to discontinuation. There are cases in which assignment may not be so clear and mistakes relative to coding will occur in large trials. However, in general, it seems that there is a need to re-evaluate the categories of disposition available to the PI and standardize as much as possible, where responses should be captured in future studies. A major purpose of the disposition table is to provide a summary of how patients left the study as accurately as possible in terms of the efficacy and safety of the drug studied. Therefore, to categorize as "physician decision" a patient who is worsening but not meeting criteria does not as clearly represent the information as perhaps a category of lack of efficacy, patient and/or physician perception would. For purposes of review, this type of choice provides more information. These issues likely are not specific to either this indication or this sponsor.

## 3f and 3g):

The sponsor was asked to clarify when patients were randomized, define "Days in Remission" as seen in Table HGHL.14.11, provide the percentage of patients relapsing, as per Table HGHL.14.11 for 21-28 days and $\geq$ 35 days, and provide an analysis of time in "remission" compared to time to "relapse" and an analysis of time in "remission" compared to time-to-event.

**When Patients were randomized**: patients were randomized when they were considered to be in "symptomatic remission" in open label at least 6 weeks and with two consecutive YMRS and HAM-D scores of a certain level.

**Time in Remission:** Table HGHL.14.11: days in remission were calculated from the first of any consecutive visits at which a patient had qualifying YMRS and HAM-D scores and was randomized while still meeting score criteria, with the first day meeting score criteria counting as 1 day.

4 patients with protocol violations were randomized in violation of the protocol (all had either too high YMRS or HAM-D scores or both). For these four patients, the days in remission were counted as 0. The sponsor revised Table HGHL.14.11 and presented both tables. Visual inspection does not indicate significant changes.

The sponsor discussed instances of protocol violation with respect to randomization and errors (caught while preparing this response) in time to remission created by inappropriate randomization. This does not appear to be significant when viewed within the major data of the trial.

The sponsor presented the following corrected table of percent of patients by time intervals in remission. Overall, it is not significantly different from the table in the original submission but is included below as these intervals were used in labeling decisions.

**Table 3fg.3. Number (Percent) of Patients in Categories Based on Time in Remission Before Randomization HGHL, Double-Blind Maintenance Period**

| | As Shown in Table HGHL.14.11 | | Revised | | ANOVA |
|---|---|---|---|---|---|
| Time (Days) in Remission[a] | Olz (%) (N=225) | Pla (%) (N=135) | Olz (%) (N=225) | Pla (%) (N=136) | comparing means[b] |
| 0-6 | 19 ( 8.4) | 10 ( 7.4) | 20 ( 8.9) | 13 ( 9.6) | |
| 7-13 | 101 (44.9) | 55 (40.7) | 100 (44.4) | 54 (39.7) | |
| 14-20 | 40 (17.8) | 28 (20.7) | 40 (17.8) | 27 (19.9) | |
| 21-27 | 23 (10.2) | 12 ( 8.9) | 23 (10.2) | 12 ( 8.8) | |
| 28-34 | 22 ( 9.8) | 14 (10.4) | 22 ( 9.8) | 14 (10.3) | |
| ≥35 | 20 ( 8.9) | 16 (11.9) | 20 ( 8.9) | 16 (11.8) | |
| | Days | Days | Days | Days | |
| Mean | 16 | 17 | 15.9 | 16.7 | .456 |
| Median | 10 | 14 | 10 | 14 | |

Abbreviations: ANOVA = analysis of variance; Olz = olanzapine; Pla = placebo.

[a] Days in remission were calculated from the first of any consecutive visits at which a patient had qualifying YMRS and HAMD-21 scores and was randomized still meeting score criteria, unless the patient was randomized at the first visit with qualifying scores, in which case the days in remission was calculated from that visit.

[b] The ANOVA model contained terms for therapy, investigator, and the therapy-by-investigator interaction.

Source: Table HGHL.14.11 and Report USFQ01HL

**Time in Remission to % of relapse:** The sponsor provided the following table, which I have included as a point of completeness. With further consideration, I do not believe the data from this has useful interpretation as it does not speak to when people relapsed and the longest time interval is not a time when most clinicians would withdraw medication.

**Table 3fg.4. Estimated Percentage of Patients with Symptomatic Relapse by Time in Remission Before Randomization HGHL, Double-Blind Maintenance Period**

| | As Shown in Table HGHL.14.12 | | | | Revised | | | |
|---|---|---|---|---|---|---|---|---|
| Time (Days) | Olz (%) (N=225) | Pla (%) (N=135) | p-Value | Therapy Interaction p-Value | Olz (%) (N=225) | Pla (%) (N=136) | p-Value | Therapy Interaction p-Value |
| 7 | 52.1 | 83.8 | <.001 | 0.925 | 52.1 | 84.0 | <.001 | 0.961 |
| 14 | 47.7 | 81.5 | <.001 | | 47.7 | 81.6 | <.001 | |
| 21 | 43.5 | 78.9 | <.001 | | 43.4 | 78.9 | <.001 | |
| 28 | 39.3 | 76.1 | <.001 | | 39.1 | 76.0 | <.001 | |

Abbreviations: Olz = olanzapine; Pla = placebo.

Estimated relapse rates and p-values are from a logistic regression model using therapy as a main effect, days in remission as a covariate, and included the therapy-by-days in remission interaction.

Source: Table HGHL.14.12 and Report USFQ01HL

**Table 3fg.6. Rate of Bipolar Relapse Stratified by Length of Time in Remission HGHL, Double-Blind Maintenance Period**

| Length of Time in Remission (Days) | Therapy | N | n (%) | Within Strata p-Value | Therapy-by-Subgroup Interaction p-Value | Log-Rank p-Value[a] |
|---|---|---|---|---|---|---|
| 0-6 | Olanzapine | 20 | 10 (50.0%) | .310 | .001 | .450 |
| | Placebo | 13 | 9 (69.2%) | | | |
| 7-13 | Olanzapine | 100 | 57 (57.0%) | <.001 | | <.001 |
| | Placebo | 54 | 50 (92.6%) | | | |
| 14-20 | Olanzapine | 40 | 13 (32.5%) | <.001 | | <.001 |
| | Placebo | 27 | 24 (88.9%) | | | |
| 21-27 | Olanzapine | 23 | 12 (52.2%) | .725 | | .833 |
| | Placebo | 12 | 5 (41.7%) | | | |
| 28-34 | Olanzapine | 22 | 3 (13.6%) | <.001 | | <.001 |
| | Placebo | 14 | 11 (78.6%) | | | |
| ≥35 | Olanzapine | 20 | 10 (50.0%) | .515 | | .362 |
| | Placebo | 16 | 10 (62.5%) | | | |

Abbreviations: N = total number of patients; n = number who relapsed.
[a] Comparing Kaplan-Meier Curves for time to relapse.
Source: Report USFQ01HL

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**Time in Remission to % of Discontinuation (for any reason):**

**Table 3fg.7. Estimated Percentage of Patients Who Discontinued For Any Reason or Relapsed by Time in Remission Before Randomization HGHL, Double-Blind Maintenance Period**

| Time (Days) | Olz (%) (N=225) | Pla (%) (N=136) | p-Value | Therapy Interaction p-Value |
|---|---|---|---|---|
| 7 | 81.2 | 93.4 | .013 | .575 |
| 14 | 79.4 | 93.4 | <.001 | |
| 21 | 77.4 | 93.4 | <.001 | |
| 28 | 75.4 | 93.4 | .002 | |

Abbreviations: Olz = olanzapine; Pla = placebo.
Estimated rates of discontinuations including relapse and p-values are from a logistic regression model using therapy as a main effect, days in remission as a covariate, and included the therapy-by-days in remission interaction.
Source: USFQ02HL

**Conclusion:**
Time-in-Remission to time-to-event: The sponsor provided this information, as requested, for the time intervals. I have included these in the appendix of the document but am not sure these can be meaningful interpreted given that the interval of remission for most patients in the study does not seem long enough to translate to clinical practice and the placebo group relapses quickly.

While the sponsor indicates the results of these analyses support that the treatment effect was not significantly influenced by the time in remission, one might also note that after treating patients to "remission" for 35 days or more, the rates of discontinuation are not statistically different and the curves for patients "remitted" both 0-6 days and ≥ 35 days are similar for the placebo and olanzapine treated groups.

## 3h and 3i:)

The sponsor was asked to re-examine cholesterol, eosinophil, and uric acid data. Essentially, the sponsor was asked to look for people with a change of 50mg/dL or a value of 250mg/DL when the baseline was <200. The randomized period included few placebo patients past three weeks, therefore, long term data are not provided in this study. Additionally, this information was requested primarily secondary to the high PCS value used in the original supplement for cholesterol.

LOCF data from HGHL and HGGY were presented in the response. Data from HGHL considered the double-blind period compared to pre-exposure to olanzapine (baseline visit 2) and HGGY considered from the beginning of double-blind to the end of double-blind.

EOS: The EOS data indicates that 2.3% of olanzapine patients experienced TE high EOS versus 0% of the placebo patients in HGHL. HGGY, which covered an 8 week acute treatment phase shows the placebo group had an incidence of 2.2% with respect to TE EOS. Overall, this data as presented, does not suggest concern with regard to eosinophils.

URIC ACID: The sponsor notes that olanzapine treated patients had statistically significant within-group mean increases from baseline to endpoint in both HGHL and HGHY. The sponsor did not view these as clinically significant. The placebo groups experienced little change from baseline. The incidence of TE high uric acid in the olanzapine-treated patients in both HGHL and HGGY was less than 3% with the incidence of PCS high uric acid less than 1% in both databases.

**CHOLESTEROL:** Cholesterol data indicate that olanzapine treated patients had within-group mean increases from baseline to endpoint. Placebo patients in HGHL sustained increases in cholesterol primarily in the open-label treatment period.

HGHL baseline cholesterols were 198mg/dL and 190.9 mg/dL in olanzapine and placebo treated patients respectively and 205.4mg/dL (olanzapine) and 206.6 mg/dL (placebo) in HGGY.

- Using the definition of ≥ 250mg/dL or increase of ≥ 50, the incidence of PCS high cholesterol in olanzapine-treated patients was 5.7% in HGGY and 22.6% in HGHL.
- 0% of the patients in HGGY and 7.8% of the patients in HGHL went from below 200 mg/dL to above 250 mg/dL.
- Using an increase of ≥ 50 mg/dL yet not reaching 250 mg/dL yielded 5.7% of the olanzapine-treated patients in HGGY and 13.9% in HGHL.

**Table 3hi.9. Cholesterol (mg/dL)**
**Mean Change from Baseline to Endpoint**
**Summary Across Requested Periods/Studies**

| | | | Baseline[a] | | Change to Endpoint[a] | | Within-Treatment | Between-Treatment |
|---|---|---|---|---|---|---|---|---|
| Database | Therapy | N | Mean | SD | Mean | SD | p-Value[b] | p-Value[b] |
| HGHL | olanzapine | 216 | 198.0 | 46.5 | 10.9 | 34.8 | <.001 | .079 |
| | placebo | 128 | 190.9 | 36.3 | 4.1 | 26.4 | .082 | |
| HGGY | olanzapine | 181 | 205.4 | 44.9 | 9.7 | 32.1 | <.001 | <.001 |
| | placebo | 144 | 206.6 | 52.3 | -6.5 | 27.7 | .006 | |

Abbreviations: N = number of patients in each group having the variable in both baseline and postbaseline visits; na = not applicable; SD = standard deviation.

[a] To convert conventional units (mg/dL; shown here) to SI units (mmol/L), multiply by 0.02586.

[b] Within group p-values calculated with Student's t-test; treatment group differences calculated with ANOVA.

The sponsor performed analysis looking at mean change in cholesterol since screening for the open-label period. This sponsor notes that analysis indicated a fairly rapid increase during the first 3 weeks of open-label treatment and somewhat of a plateau in the remaining time before randomization. Placebo treated patients "showed an immediate mean decrease in cholesterol between randomization and Week 4," The sponsor notes that olanzapine-treated patients cholesterol stabilized out (cholesterol values were "relatively stable" over double-blind treatment phase) and indicated that a possible contributor might be weight gain. The sponsor notes that many patients who met PCS criteria at some point during the study later had values that no longer met this and notes that 56.3% of the 32 patients who met $\geq$ 50 mg/dL increase criterion without going over the 250mg/dL had cholesterol values that returned below 200 mg/dL by the time they left the study. I am uncertain whether this means these decreases occurred while still on olanzapine during the double-blind period. Sponsor provided graphs are included in the appendix.

**Conclusion:** The cholesterol data indicates that overall, initially, olanzapine increases cholesterol. Whether it is dependent on weight gain is not clear nor is whether it returns to normal over time with continued treatment.

**3j)** There is no additional information regarding the convulsive event in patient 762 of trial HGHL

**3k)** We asked for information such as EKGs, vital signs, for the PCS EKGs or syncope, SAEs related to EKG findings or syncope, or discontinuations secondary to either EKG findings or syncope within the active and placebo-controlled databases. With regard to syncope, it appears no EKGs were taken at the time of the event in these 9 patients. Most syncope is not due to arrhythmia, so this is not necessarily unexpected. As per the sponsor, EKGs on the patients while in the study did not reveal treatment emergent QTc changes. It appears orthostatic vital signs were not gathered at the time of each event of syncope. In the two who apparently had such measures, these showed "vital sign changes at the time of the event". Regarding three convulsive events, one was a known epileptic who underwent withdrawal of valproic acid and one was felt due to alcohol abuse. There was little information on the 3rd patient.

No obvious new safety concerns were seen in the data the sponsor sent with this section.

**3l)** Although not essential to approval, we asked for the sponsor to explain patients in the study greater than 365 days. The information the sponsor submitted indicates some visits were out of the window periods, early or late, for various reasons or no reason was given (6 patients and 25 visits, minimum 1 day out of window, maximum 33 days). One site apparently "simply ignored" the 12-month stopping rule.

OVERALL CONCLUSIONS/RECOMMENDATIONS:

- The sponsor has submitted this supplemental NDA for "Long-term Treatment of Bipolar I Disorder". I do not believe the data from HGHL support the use of olanzapine for long-term use in bipolar I patients who responded to olanzapine initially, unless one

accepts several fundamental concepts: 1) patients were adequately "remitted" before randomization therefore the large relapse of the placebo group demonstrates efficacy of the drug and 2) long-term treatment is defined in weeks to a few months. Although I am not sure that concept number one is true, if it is, then the difference in the times to attrition of 50%, 55 days or so for the treatment group and 20 days or so for the placebo group (35-40 days longer for the treatment group than the placebo group), may be statistically significant, but still has limited clinical implication when viewed within the need for chronic treatment in this illness. This extended time perhaps is beyond acute stabilization, but in my opinion, does not arise to maintenance as long-term treatment. I am unsure what this time period should be called. Additionally, although I cannot speak for the psychiatric clinical community, I think it is reasonable to say that most clinicians would not consider this difference representative of a long-term treatment effect.

- If one does not accept that stopping treatment at two weeks is clinically useful and that further, this could have contributed to relapse, then this data becomes less interpretable. Again, one can look at the olanzapine group and see that this group even on medication, did not stay in the study very long after randomization for various reasons. This does not allow me to frame this as a long-term (maintenance) option for treatment. Perhaps this reflects how ill this population was and/or how well the drug in and of itself did or did not work in this group. Whether any drug could have done better in that specific population is unknown. Perhaps in ill patients, few drugs could be used in monotherapy and both keep patients in the study and keep them well.

- With regard to the HAM-D sub-item analysis, the suicidality analysis does not indicate a suggest this drug increases the risk within the time frame this data can address. The depression data may indicate that the drug may not protect from depressive "relapse". Any future trials of long term duration should incorporate monitoring for depression as to better characterize this admittedly difficult task given the population.

- I recommend we ask the sponsor to incorporate monitoring in all trials, with HGL and LDL measures as well as have a change in the level of cholesterol considered PCS (currently it is 600mg/dL).

- It appears that the sponsor should re-evaluate the way disposition tables are designed with regard to the categories of discontinuation and that perhaps PIs should receive instruction in choosing the discontinuation category to increase standardization.

- The sponsor's hyperlinked the document well. This is appreciated.

Teresa A. Podruchny, M.D., January 12, 2004
Medical Reviewer,
FDA CDER ODE1 DNDP HFD 120

cc: IND
HFD 120
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P Andreason
D Bates
T Laughren
T Podruchny

**APPENDIX TO FOLLOW**

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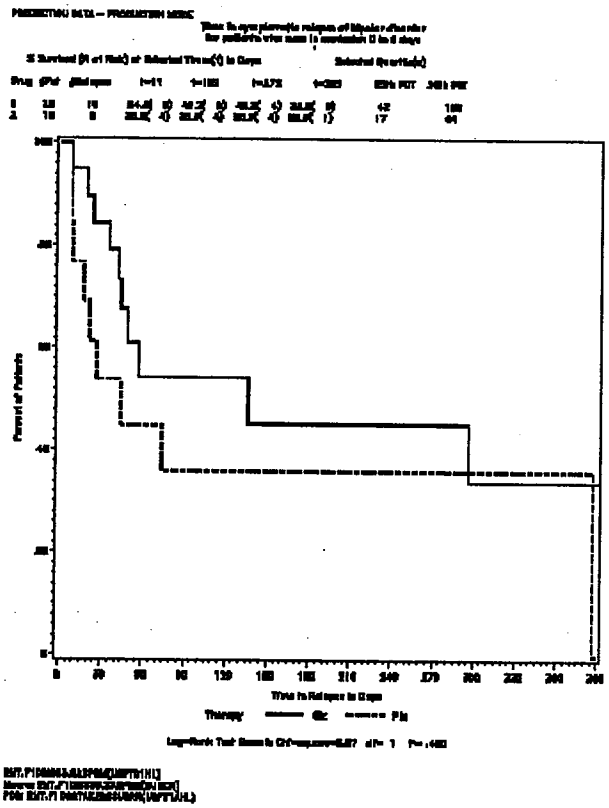

Figure 3fg.3. Time to symptomatic relapse of bipolar disorder for patients who were in remission for 0 to 6 days before randomization.

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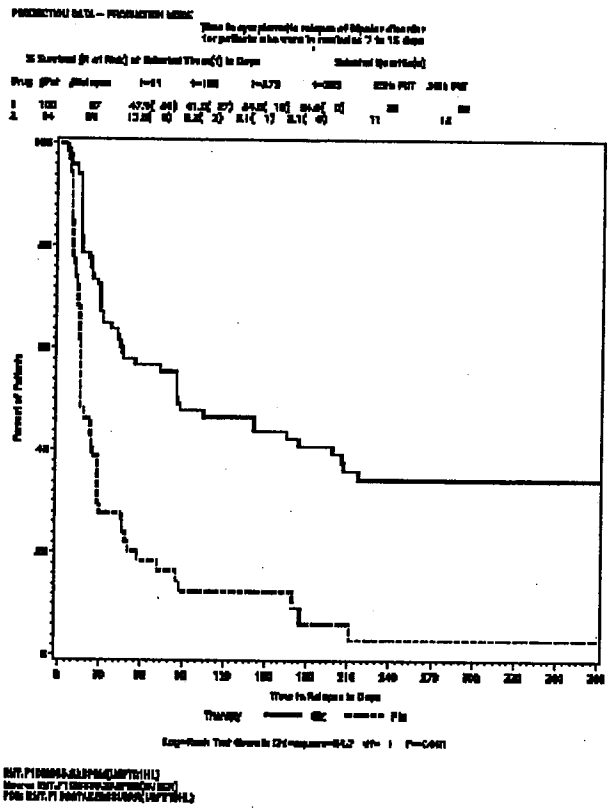

Figure 3fig.4. Time to symptomatic relapse of bipolar disorder for patients who were in remission for 7 to 13 days before randomization.

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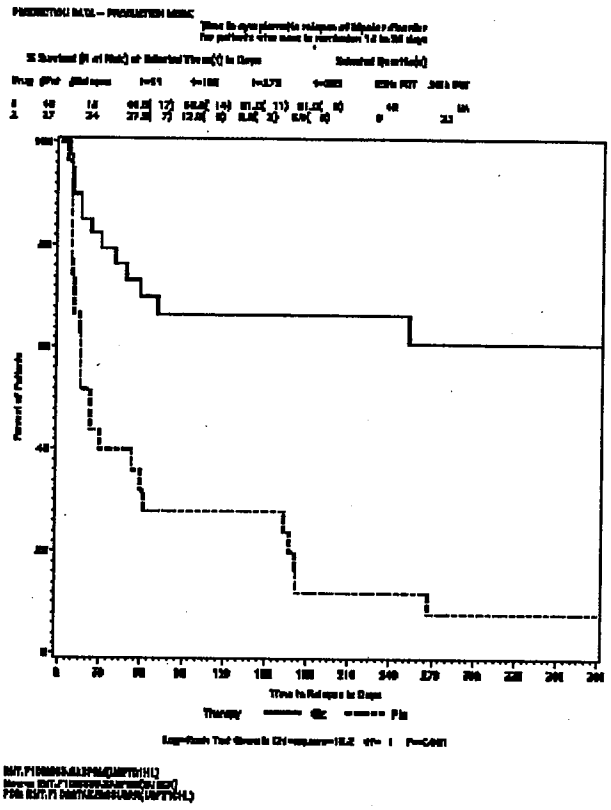

Figure 3fig.5. Time to symptomatic relapse of bipolar disorder for patients who were in remission for 14 to 28 days before randomization.

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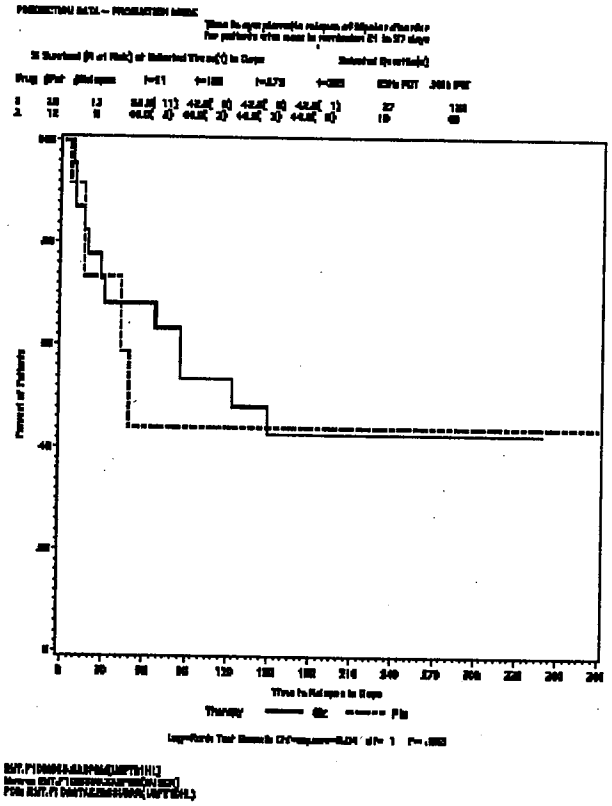

Figure 31g.8. Time to symptomatic relapse of bipolar disorder for patients who were in remission for 21 to 27 days before randomization.

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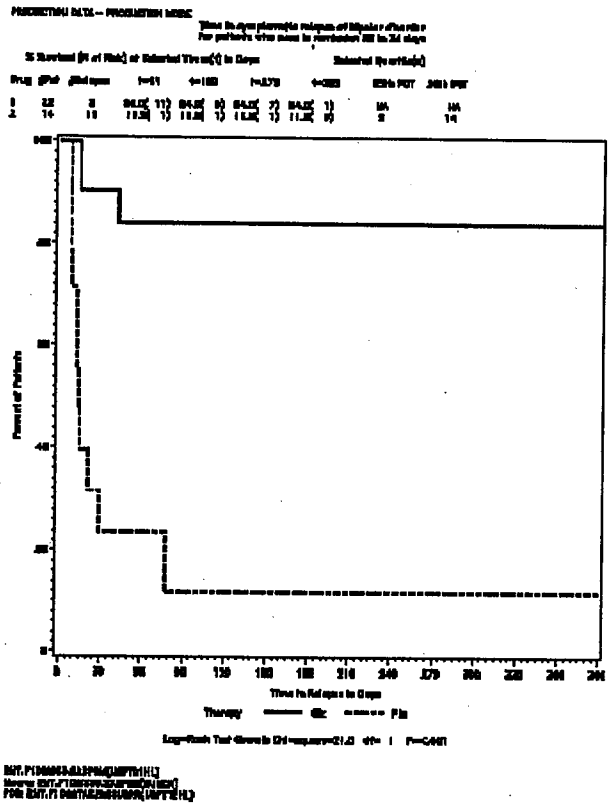

Figure 3fig.7. Time to symptomatic relapse of bipolar disorder for patients who were in remission for 28 to 34 days before randomization.

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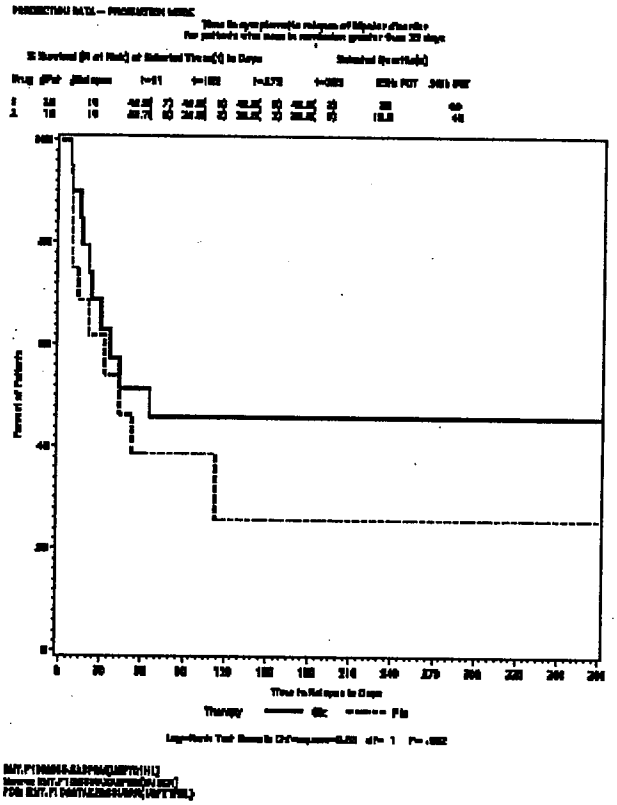

Figure 3fg.8. Time to symptomatic relapse of bipolar disorder for patients who were in remission for at least 35 days before randomization.

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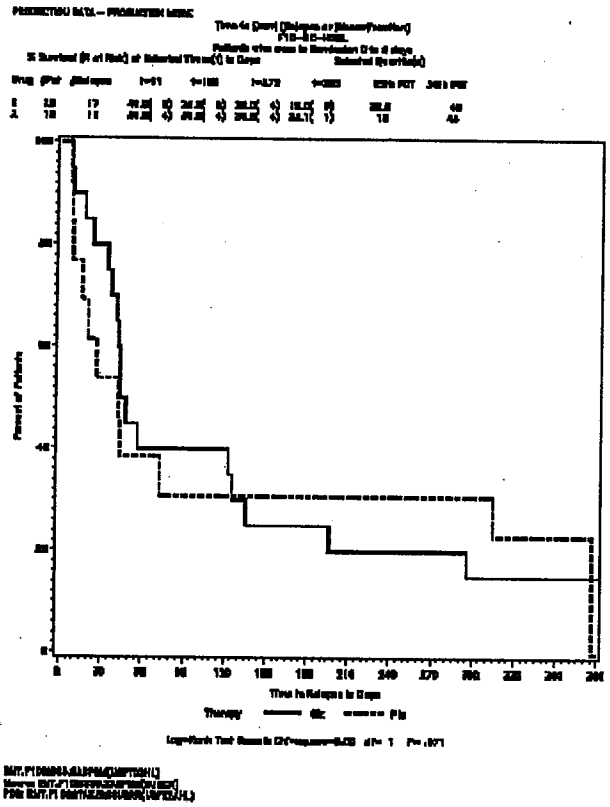

Figure 3fg.11. Time to event (relapse or discontinuation) for patients who were in remission for 0 to 6 days before randomization.

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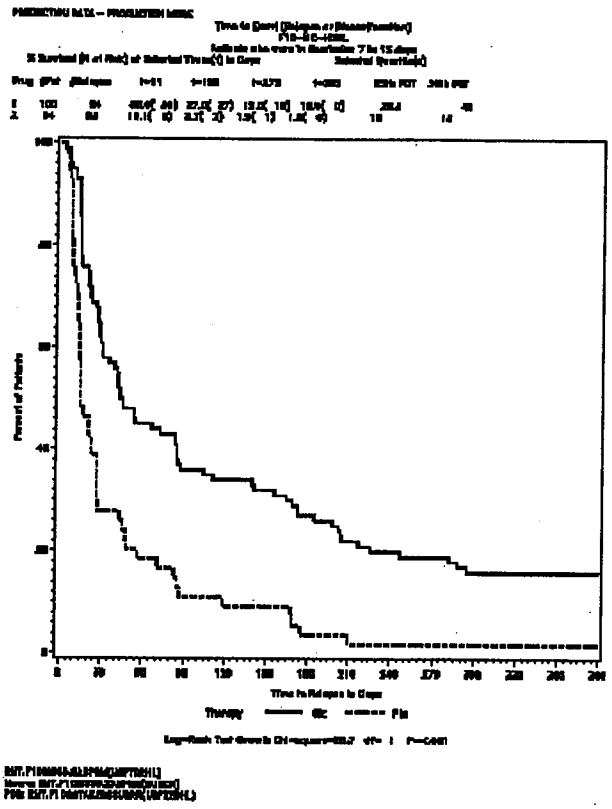

Figure 31g.12. Time to event (relapse or discontinuation) for patients who were in remission for 7 to 13 days before randomization.

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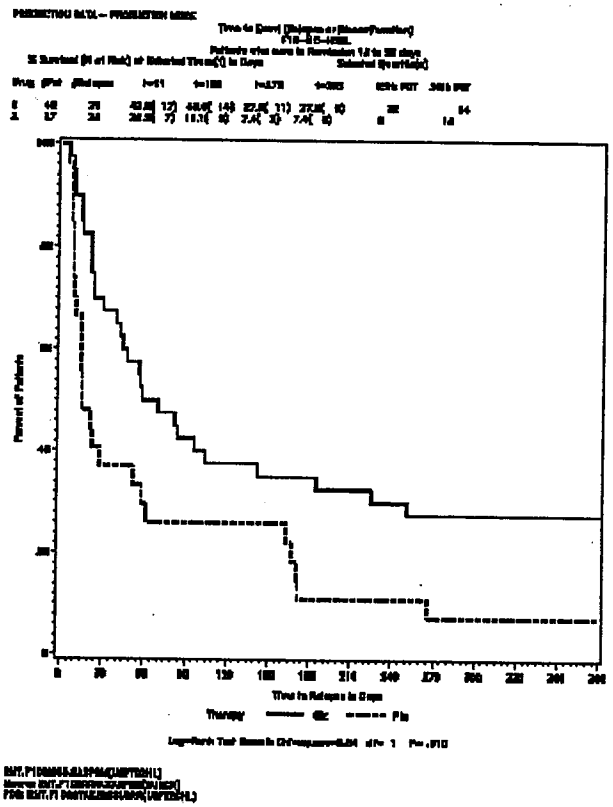

Figure 3g.13. Time to event (relapse or discontinuation) for patients who were in remission for 14 to 28 days before randomization.

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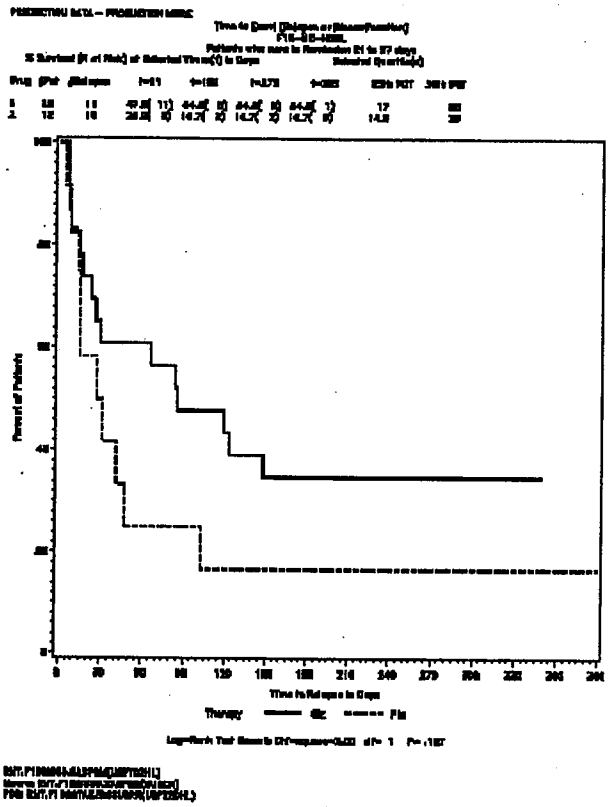

Figure 3fig.14. Time to event (relapse or discontinuation) for patients who were in remission for 21 to 27 days before randomization.

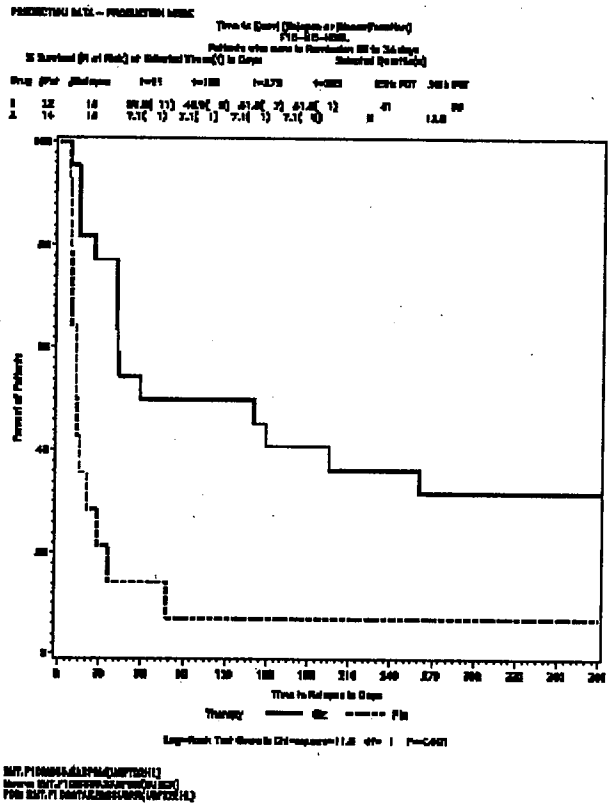

Figure 3fig.15. Time to event (relapse or discontinuation) for patients who were in remission for 28 to 34 days before randomization.

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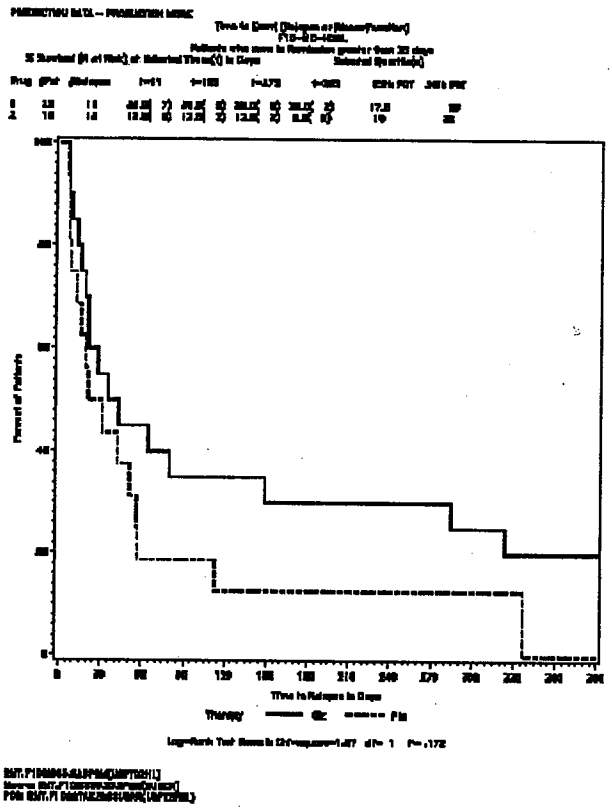

Figure 31g.16. Time to event (relapse or discontinuation) for patients who were in remission for at least 35 days before randomization.

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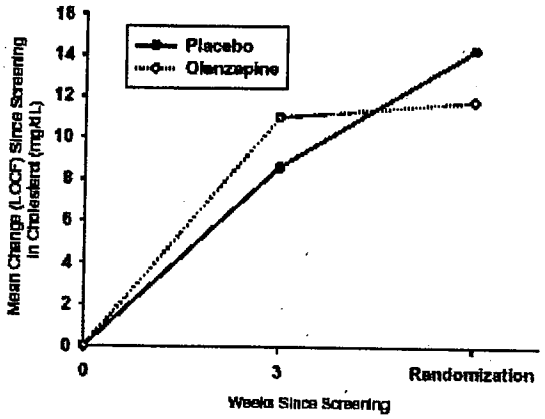


**Figure 3hl.1.** **Mean change in cholesterol (LOCF) in the open-label lead-in phase for Study HGHL (with Visit 2 as baseline).**

**Table 3hl.13.** **Visitwise Mean Change in Cholesterol (LOCF) with Visit 2 as Baseline**
**Study HGHL, Open-Label Lead-in Phase**

| | | | Baseline | | Change to Endpoint | | | P-value*2 | |
|---|---|---|---|---|---|---|---|---|---|
| Visit | Therapy | N | Mean | (Std) | Mean | (Std) | w/in P*1 | Intrctn | Therapy |
| 5 | Placebo | 126 | 191.1 | (35.40) | 8.6 | (24.60) | <.001 | .951 | .969 |
| | Olz | 215 | 198.9 | (46.38) | 11.0 | (30.09) | <.001 | | |
| Rand | Placebo | 136 | 191.2 | (36.34) | 14.3 | (29.67) | <.001 | .078 | .907 |
| | Olz | 224 | 198.2 | (46.53) | 11.9 | (27.58) | <.001 | | |

N - Number of patients having both baseline and endpoint.
*1 - Within group P-values are from t-test on mean change.
*2 - P-values are from Type III Sum of Squares ANOVA.

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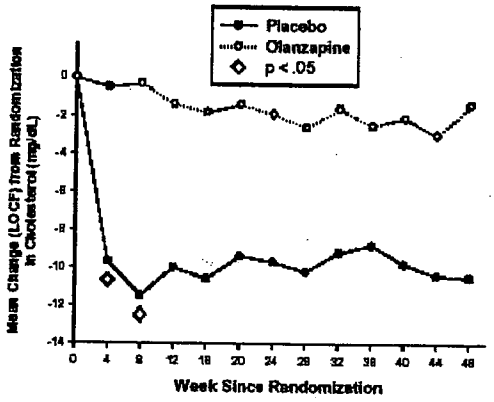


**Figure 3hi.4.** **Mean change in cholesterol (LOCF) in the double-blind treatment phase for Study HGHL (with randomization as baseline).**

**Table 3hi.17.** **Summary of Outcomes for Patients with PCS High Cholesterol at Any Time Study HGHL**

| Number of Patients | Not Rand. | Olanzapine | Placebo | Total |
|---|---|---|---|---|
| With PCS values[a] at any time | 8 | 32 | 11 | 51 |
| Returned to within 10 mg/dL of V1 or V2 values | 1 (12.5%) | 4 (12.5%) | 4 (36.4%) | 9 (17.6%) |
| PCS values at < half of remaining visits[b] | 0 ( 0.0%) | 13 (40.6%) | 3 (27.3%) | 16 (31.4%) |
| PCS values for ≥half of remaining visits[b] | 1 (12.5%) | 12 (37.5%) | 2 (18.2%) | 15 (29.4%) |
| First PCS value at last or second to last visit | 6 (75.0%) | 3 ( 9.4%) | 2 (18.2%) | 11 (21.6%) |

Abbreviations: PCS = potentially clinically significant; Rand = randomized; V = visit.

[a] PCS cholesterol was ≥50 mg/dL greater than baseline (V2) value, in patients with baseline <200 mg/dL.

[b] "Remaining visits" comprised visits following the first visit with a PCS value. For nonrandomized and olanzapine-treated patients, all visits and study periods were included. For placebo-treated patients, visits during the open-label rescue phase were not included.

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/s/
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Teresa Podruchny
1/12/04 01:06:23 PM
MEDICAL OFFICER

Paul Andreason
1/12/04 01:44:59 PM
MEDICAL OFFICER
I disagree with Dr. Podruchny's recommendation for a Not Approved action. I recommend a second approvable action-please see my memo to file dated January 12, 2004.

**Bates, Doris J**

**From:** Bates, Doris J
**Sent:** Monday, November 24, 2003 3:09 PM
**To:** 'Sharp_Michele@lilly.com'
**Cc:** Bates, Doris J
**Subject:** RE: Zyprexa NDA 20-592 S019

Good afternoon Michele

This e-mail confirms that your submission of November 13, 2003 to NDA 20-592 / S-019, received November 14, 2003, is a complete, class 1 response to our action letter of September 22, 2003.

Because this submission was received on November 14, 2003, its two month action due date is January 14, 2004. At this time, we have no additional questions related to your resubmission.

We also note the request for a meeting to discuss labeling, which was included in the submission. Because we are now obligated to accept or deny all meeting requests within 14 calendar days of their receipt, and because we have not yet had an opportunity to review your revised labeling in depth, we must technically deny your request at this time. However, we have noted your desire to discuss the labeling with us, and we presently intend to initiate such a discussion with you prior to our next action on this submission.

Please feel free to contact me at 301-594-5536 or by return email if you have any questions.

Sincerely,

*Doris J. Bates, Ph.D.*
*Regulatory Project Manager*
*Division of Neuropharmacological Drug Products*
*Office of Drug Evaluation I*
*Center for Drug Evaluation and Research*

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/s/

Doris Bates
11/24/03 03:14:35 PM

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Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

November 13, 2003

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

**COMPLETE RESPONSE TO APPROVABLE LETTER**

**Re: Zyprexa® (olanzapine) - NDA 20-592 (S019)**
**Complete Response to Approvable Letter**

We are providing the following complete response to your September 22, 2003 approvable letter for the referenced supplemental NDA. Please note our September 29, 2003 submission to the referenced NDA notifying you of our intent to amend the referenced supplement.

We request that you review our complete response as a PDUFA Class 1 resubmission. Additionally, we request a meeting or teleconference to finalize labeling and any other steps to approval.

The complete response is provided on one CD Rom with a submission size of approximately 1 megabyte. All electronic media have been checked by representatives of Lilly Information Technology and have been verified to be free of known viruses. The virus checking software was Norton AntiVirus Corporation Edition version 7.51.847 using Virus Definitions 51105g created on November 5, 2003.

Please call me at (317) 277-8382 if you require any additional information or if there are any questions. Alternatively, you may contact Dr. Gregory T. Brophy, Ph.D., Director, U.S. Regulatory Affairs at (317) 277-3799. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Michele Sharp, PharmD
Regulatory Research Scientist
U.S. Regulatory Affairs

# Note to Reviewers

## Zyprexa (olanzapine)
## NDA 20-592 S019
## Complete Response to Approvable Letter

## Background

On November 20, 2002, Lilly submitted a supplemental new drug application to NDA 20-592 for the use of Zyprexa in the long-term treatment of bipolar I disorder. The Division of Neuropharmacological Products granted an approvable letter on September 22, 2003. Lilly notified FDA of our intent to amend the application on September 29, 2003. On October 7 and October 27, 2003, teleconferences were held between representatives of FDA and Lilly to clarify the clinical questions raised in the approvable letter. Meeting minutes for the teleconferences were submitted to NDA 20-592 on November 4, 2003.

Lilly considers this submission to constitute a Complete Response to the approvable letter. We believe that all questions and comments noted by FDA in the approvable letter are addressed in our complete response. Additionally, Lilly requests that FDA review this response under PDUFA as a Class 1 resubmission since this response provides the following:

- draft labeling
- minor re-analysis of data previously provided in the application which relates to labeling, and
- other minor clarifying information requested by the FDA.

## Response to Comments and Requests in the Approvable Letter

We provide an overview of our responses in the order addressed in the approvable letter.

### *Clinical Questions*

In Item 8, we address FDA's comments and requests for clinical information as outlined in Questions 1 through 3(a-l) of the approvable letter.

### *Labeling (Package Insert)*

Draft labeling with responses to FDA proposed revisions are presented in Item 2 of this response. We used the FDA label from the approvable letter as a starting point for our counter-proposals. Revisions are marked and highlighted in yellow for ease of identification. We retained the FDA explanations for proposed changes and have added Lilly's responses to the proposals within text boxes.

## *Promotional Materials*

Lilly has not yet completed development of introductory promotional materials. Pursuant to 21 CFR 314.81, Lilly will submit these materials at the time of first use.

November 4, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

**General Correspondence**
**Meeting Minutes Enclosed**

**Re: Zyprexa® (olanzapine) - NDA 20-592 (S019)**
**Minutes from Teleconferences on October 7 and October 27, 2003**

Lilly is enclosing our minutes of the October 7 and October 27, 2003 teleconferences between representatives of Lilly and the Division. Based on these discussions, we are proceeding with our plans to submit our complete response to the approvable letter (received on September 22, 2003). Accordingly, we would appreciate your prompt review to assure that the Division is in agreement with our enclosed minutes.

Thank you for the opportunity to discuss the questions from the approvable letter. We appreciate your responsiveness and assistance with obtaining clarity on these questions. Please call me at (317) 277-8382 if you require any additional information or if there are any questions. Alternatively, you may contact Dr. Gregory T. Brophy, Ph.D., Director, U.S. Regulatory Affairs at (317) 277-3799.

Sincerely,
ELI LILLY AND COMPANY

Michele Sharp, PharmD
Regulatory Research Scientist
U.S. Regulatory Affairs

Enclosure

**Minutes from Teleconference with FDA**
**Zyprexa Bipolar Maintenance NDA 20-592 S019**

Date: October 7, 2003
FDA Participants: Paul Andreason, Teresa Podruchny, and Doris Bates
Lilly Participants: Mauricio Tohen, Cherri Miner, Sara Corya, Greg Brophy, Michele Sharp, Rick Risser, Tammy Forrester, Giedra Campbell, and Krisann Van Hoosen

Proposals correspond to Questions from Approvable Letter (dated September 22, 2003)

3a) We had initially interpreted this analysis request for "time-to-event" as time to bipolar relapse, the primary endpoint of the study. However, when we received the clarification for item 3g regarding your intended meaning of "time-to-event", we would like to clarify that the request for a formal analysis of "time-to-event" analysis excluding sites 34 [ ] should include discontinuations for any reason including meeting relapse criteria. We would also like to understand why you have requested excluding site[ ]. b(4)

**Response**: FDA requested analysis of time to discontinuation for any reason (including relapse) as well as analysis of time to relapse, excluding sites 34 [ ] from HGHL. b(4)
[ ]

3b) We would like to confirm that you are requesting an analysis of patients with scores of 0-2 on HAM-D items 1 *and* 3 (ie low on both items) and then are high with scores of 3 or 4 on either item.

**Response**: FDA indicated that the intent was to duplicate the analysis previously completed for Prozac. FDA indicated that they preferred two separate analyses (ie one for item 1 and one for item 3).

3cde) We believe that the source of the apparent discrepancies is that relapse was not considered a formal reason for discontinuation in the study. Our response will detail out this difference.

**Response**: FDA provided examples of patients where they have identified discrepancies and indicated that discrepancies were found in the[ ]files (summary text). These patients were 201, 233, 455, 560, 563, 564, and 603. b(4)

3f) We believe that the apparent discrepancy with protocol-specified randomization criteria is due to patients like patient 455 who were not randomized as early as they were eligible (ie they were in remission longer than the protocol-specified 2 consecutive visits). Our response will detail out results of protocol-compliant patients versus those who were in remission longer.

**Response**: FDA agreed with the approach to this question.

3g) As we discussed with question 3a, we understand "time-to-event" to mean discontinuation for any reason including meeting relapse criteria and will provide this

analysis. We would like to clarify that our interval cut-offs were 21-27 days (not 28) and ≥ 35 days and confirm that is acceptable.

**Response**: FDA agreed with the approach to this question.

3h) With respect to the re-analysis of cholesterol, we would like to confirm that a normal baseline measurement is <200 mg/dL and thus we will provide an analysis of patients who had baselines of <200 and then had measurements over 250 mg/dL or had a change of 50 mg/dL.

**Response**: FDA agreed with the approach to this question.

3i) For studies HL, HQ, HD and HT (double-blind extension studies), we are intending to provide presentations of mean change, treatment-emergent high/lows using Lilly reference ranges and potentially clinically significant changes for each of the analytes requested using the end of screening as baseline and capturing all open-label and double-blind visits associated with olanzapine exposure. Does this address your question?

**Response**: FDA will get back to us on question.

3k) For Studies HL, HQ and HT (active-controlled databases), we searched for adverse events related to syncope and ECG findings in the listings for SAE, discontinuations due to AEs, and potentially clinically significant AEs. We will be providing all vital signs and ECGs for these identified patients.

**Response**: FDA agreed with the approach to this question.

3j) and 3l) Nothing to clarify

**Minutes from Teleconference with FDA**
**Zyprexa Bipolar Maintenance NDA 20-592 S019**

Date: October 27, 2003
FDA Participants: Paul Andreason, Teresa Podruchny, and Doris Bates
Lilly Participants: Mauricio Tohen, Sara Corya, Greg Brophy, Michele Sharp, Rick Risser, Giedra Campbell, and Krisann Van Hoosen

Discussion during teleconference was in response to request for clarifications on Questions 3b, 3a, 3h and 3i from Approvable Letter (dated September 22, 2003). Request for clarifications were communicated to FDA via e-mail on October 16 and October 21.

Clarification #1
With respect to question 3b from approvable letter (question re: treatment-emergent suicidality), we have interpreted this request as asking for 2 analyses. One analysis evaluating treatment-emergent adverse events and the other analysis evaluating HAM-D Item 1 and 3. We received clarity during our teleconference on Oct. 7 regarding HAM-D analysis, but did not ask for clarity regarding adverse event analysis.

We are preparing an analysis of treatment-emergent adverse events possibly suggestive of suicidality by searching for the following MedDRA terms: completed suicide, suicidal ideation, suicide attempt, self-mutilation, intentional self injury, self-injurious ideation, self-injurious behavior, depression suicidal, accidental overdose, non-accidental overdose, overdose NOS, multiple drug overdose. We will provide an analysis for open-label period (olanzapine only) and for double-blind period (olanzapine vs placebo). Does this approach seem acceptable to address your concern?

Response during October 27 teleconference
Proposal is acceptable.

Clarification #2
During Oct. 7 teleconference, we were seeking clarification on why you have requested Site [redacted]

b(4)

Response during October 27 teleconference
FDA indicated that they were not able to provide us additional information.

Clarification #3

We have reviewed the clarification received last Friday, October 17 regarding clinical questions [c,d,e,h and i] in the Zyprexa bipolar maintenance approvable letter. We appreciate your responsiveness and assistance with obtaining clarity on these questions. We believe that we understand your clarification regarding questions c, d and e. However, for questions h and i, we still have some concerns. To ensure that we understand the clarifications given for these questions, we have provided an analysis plan that we believe adequately addresses your request. We would appreciate confirmation that you agree that this analysis plan will adequately respond to questions h and i.

Would you please confirm that:

1) we have correctly identified the study periods to be considered ("Periods Considered" column) and the corresponding therapies considered ("Therapies Considered" column) for each analysis

2) the analysis requested for question 3h is accurately described in the attached analysis plan under the HGHL analyses for cholesterol (ie last analysis under Analyses Performed)?

To address your request in the Oct. 17 clarification for question i ["Please perform this analysis on the pivotal trial and all databases with placebo- controlled double blind monotherapy treatment."], we have identified the additional placebo-controlled bipolar studies that have double-blind olanzapine monotherapy treatment periods (Studies HGEH, HGGW and HGGY) and included them in the attached analysis plan. Each of these studies is an acute study of varying length (ie 3, 4 or 8 week) with no open label lead-in periods. In Study HGEH, 70 patients were randomized to olanzapine and 69 patients to placebo. In Study HGGW, 55 patients were randomized to olanzapine and 60 patients to placebo. In Study HGGY, 370 patients were randomized to olanzapine and 377 patients to placebo. Please confirm that inclusion of analyses from these studies addresses your request.

Response during October 27 teleconference

FDA stated that we do not need to provide analyses for urine ketones, because we have already implemented the hyperglycemia and diabetes labeling request (submitted September 18, 2003). FDA indicated that we should continue to provide analyses for eosinophils, uric acid and cholesterol.

FDA indicated that they are interested in placebo-controlled double-blind analyses for patient exposures of at a minimum of 8 weeks. Therefore, we need to provide analyses from Studies HGHL and HGGY only and not from Studies HGEH and HGGW. The analyses should use baseline as the visit before treatment is initiated or the first day treatment is introduced and endpoint as the last visit in the double-blind phase. These analyses should be a comparison of olanzapine to placebo.

See Attachment A for the analysis plan that resulted from this discussion.

## ATTACHMENT A

### Analyses in Response to Questions 3h and 3i

| Databases | Periods Considered | Baseline and Evaluated Visits | Therapies Considered | Lab Measure | Analyses Performed: Mean Chg[1] | TE[2] | PCS[3] | ≥250 or ≥50 inc[4] |
|---|---|---|---|---|---|---|---|---|
| HGHL | Double-blind period (Study Period 3) compared to pre-exposure to olanzapine in the trial | BL: Visit 2 (if missing, Visit 1)<br>Evaluated: Visits 101-116 | olanzapine vs. placebo | Cholesterol | X | X | X | X |
| | | | | Uric Acid | X | X | X | |
| | | | | Eosinophils | X | X | X | |
| HGGY | From beginning of double-blind to end of double-blind (Study Period 2)[5] | BL: Visit 2 (if missing, Visit 1)<br>Evaluated: Visit 3 to 8<br>(Only includes patients who are in trial through Visit 8) | olanzapine vs. placebo | Cholesterol | X | X | X | X |
| | | | | Uric Acid | X | X | X | |
| | | | | Eosinophils | X | X | X | |

Abbreviations: BL = baseline; Chg = change; DB = double-blind; inc = increase; PCS = potentially clinically significant; TE = treatment-emergent.

[1] Mean change from baseline to endpoint

[2] Incidence of treatment-emergent abnormalities based on Lilly reference ranges

[3] Incidence of potentially clinically significant abnormalities (PCS values as specified in clinical study reports)

[4] Incidence of abnormalities with abnormal defined as a value ≥250 mg/dL or an increase ≥50 mg/dL, in either case among patients with values <200 at baseline

[5] For Study HGGY, SP2 is 8 weeks long and covers Visits 3 to 8.

**Bates, Doris J**

**From:** Bates, Doris J
**Sent:** Friday, October 17, 2003 3:41 PM
**To:** 'Sharp_Michele@lilly.com'
**Cc:** Bates, Doris J
**Subject:** RE: Zyprexa NDA 20-592 S019 -- Process-Related Info

Good afternoon Michele,

I have received the following information from Drs. Andreason and Podruchny. They are in agreement with the Lilly minutes of our October 7 teleconference, with the following points of clarifications added.

**********

With regard to clarification of items discussed in the teleconference of 10/07/03 with the Sponsor regarding 20592_s019:

**3I:** Please provide a presentation of the laboratory values eosinophils, uric acid, urine ketones, and cholesterol (<200 mg/dL at baseline and >250 mg/dL or a change of 50mg/dL) from the beginning of the open-label enrichment to the last visit of double blind and from the beginning of the double blind period to the end of the double blind period. Please perform this analysis on the pivotal trial and all databases with placebo- controlled double blind monotherapy treatment.

## Further clarification for 3c,d,e:

We request a revised patient disposition table. Although most of the following examples were corrected for the purpose of efficacy analysis, they do not appear to have been corrected in the disposition table. This internal inconsistency is what brought these cases to our attention.

Please explain what appear to be discrepancies seen in information (as seen in [ ] files) regarding disposition. Specifically, between what the text reads and how the disposition is coded. The patient numbers provided in the telecon were examples. Another example is patient 212. This patient was coded as a discontinuation at visit 110 for an AE when he/she relapsed at visit 101. Therefore to capture this patient in a disposition table as a discontinuation secondary to an AE was confusing to the reviewer. b(4)

Please verify that all patients who met relapse criteria were discontinued as relapsed and that this time was accurately coded for purposes of both efficacy analysis and disposition table construction.

Though this did not come up in the teleconference, please provide a definition for the term "Reporting Interval Completed" as used in the disposition tables in study HGHL.

**Further clarification for 3H.** baseline for the cholesterol evaluation = before olanzapine is initiated or the first day of the first introduction of olanzapine.

*Doris J. Bates, Ph.D.*
*Regulatory Project Manager*
*Division of Neuropharmacological Drug Products*
*Office of Drug Evaluation 1*

10/17/2003

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/s/
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Doris Bates
10/17/03 03:48:01 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

# CLINICAL INSPECTION SUMMARY

DATE: July 25, 2003

TO: Doris J. Bates, Ph.D., Regulatory Health Project Manager
Teresa A. Podruchny, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Khin Maung U, M.D., Branch Chief
Good Clinical Practice Branch I, HFD-46

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 20-592/SE1-019

APPLICANT: Eli Lilly and Company

DRUG: Zyprexa (olanzapine)

THERAPEUTIC CLASSIFICATION: Type S

INDICATION: Long-Term Treatment of Bipolar I Disorder

CONSULTATION REQUEST DATE: February 3, 2003

ACTION GOAL DATE: September 21, 2003

## I. BACKGROUND:

Olanzapine (Zyprexa) is an atypical antipsychotic agent. It is approved for use in treatment of schizophrenia and the short-term treatment of acute manic episodes associated with Bipolar I Disorder. In this application, the sponsor has requested the use of olanzapine in the long-term treatment of Bipolar I Disorder. The application is based on protocol F1D-MC-HGHL entitled "Olanzapine Versus Placebo in Prevention of Relapse in Bipolar Disorder."

The study is a randomized, double-blind, parallel study of subjects who have responded to acute open-label (6 yo 12 weeks) olanzapine treatment and are in symptomatic remission of an index manic, mixed or depressive episode (with or without psychotic features). Subjects with a DSM-

IV diagnosis of bipolar I disorder and display an index manic or mixed episode (with or without psychotic features) according to the SCID-I/P were included in the study. The primary objective of this study is to assess the efficacy of olanzapine compared with placebo in prevention of relapse into a manic or mixed episode among bipolar patients who have responded to acute open-label olanzapine treatment and are in symptomatic remission of an index manic or mixed episodes.

This study was organized into four study phases:
1) screening (two visits over a 2-7 day period);
2) open-label treatment phase (seven visits over 6-12 weeks);
3) subjects in symptomatic remission were entered into the double-blinded test article versus placebo phase (12 months/16 visits); and
4) rescue phase for subjects that relapsed in phase 3 (maximum of six months not to exceed twelve months from the start of Phase 3).

Primary efficacy criteria was symptomatic relapse of mania and depression based on an increase in total scores of the Young Mania Rating Scale (Y-MRS) and Hamilton Psychiatric Rating Scale for Depression 21 items (Ham-D) during 12 months of therapy respectively. Symptomatic remission of mania was defined as achievement of a Y-MRS total scores of 12 or less at two consecutive visits. Symptomatic relapse of mania was based on achievement of a Y-MRS total score of at least 15 or hospitalization for mania associated with bipolar disorder after having met the criteria for symptomatic remission. Symptomatic remission of depression was defined as achievement of a Ham-D total scores of 8 or less at two consecutive visits. Symptomatic relapse of depression was based on achievement of a Y-MRS total score of at least 15 or hospitalization for depression associated with bipolar disorder after having met the criteria for symptomatic remission. Symptomatic relapse of bipolar was defined as meeting the criteria for relapse of either mania or depression after having met the criteria for remission or hospitalization for an affective (manic, mixed or depressed) episode associated with bipolar disorder. Symptomatic remission was assessed for all patients and symptomatic relapse was assessed for all patients who remitted.

Inspection assignment was issued in February 2003 for [ ] domestic sites: Drs. [ ] and Hartford because these investigators enrolled a [ ] number of subjects in the study. [ ] b(4)

[ ]

II. RESULTS (by site):

| NAME | Center # | Location | ASSIGNED DATE | EIR RECEIVED DATE | CLASSIFICATION |
|---|---|---|---|---|---|
| Dr. Hartford | 022 | Cincinnati, OH | 02-03-2003 | 06-19-2003 | NAI |
| [ ] | | | | | b(4) |

HARTFORD, M.D.

Hartford Research Group conducted this study at two geographic sites. 71 subjects were screened at the Cincinnati site and 21 subjects at the Dayton site (92 total). 69 subjects entered Phase 2; 23 subjects entered Phase 3. Those subjects who dropped out either experienced adverse events, were non-compliant or withdrew consent. Five subjects completed the study in Phase 3 or 4. An audit of 25 subjects' records was conducted; informed consents were verified for all 92 subjects. A one-item Form FDA 483 was issued. Twelve subjects signed informed consent (version 1/6/00) but did not sign modified informed consent (version 10/26/00) in a timely manner. The modified informed consent added additional risks of liver problems and high blood glucose. Overall, data appear acceptable.

b(4) b(7)

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For the study sites that were inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol and amendments at Dr. Hartford's site. Although Dr. Hardford did not reconsent 12 subjects with the revised informed consent in a timely manner, data from this center appear acceptable for use in support of supplemental NDA.

b(7)

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Khin Maung U, M.D, Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable

cc:
NDA 20-592/SE1-019
HFD-45/Division File/Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/U
HFD-46/Khin
HFD-46/Friend
HFD-46/George GCPB1 Files

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/s/
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MEDICAL OFFICER

Khin U
7/28/03 12:05:46 PM
MEDICAL OFFICER

Minutes of Meeting
NDA 20-592 / SE1-019: Zyprexa (olanzapine) Tablets, 2.5, 5, 7.5, 10, 15, 20 mg
Eli Lilly & Co.: Bipolar Disorder, Maintenance Therapy
Supplemental NDA *Virtual* Filing Meeting Minutes

**DATE:** January 17, 2003
**INPUT RECEIVED FROM:** R. Katz, P. Andreason, T. Podruchny, B. Rosloff, T. Oliver, S. McLamore, K. Jin, R. Kelly, R. Uppoor, V. Tandon, L. Stockbridge, N. Khin

**Background:** Olanzapine is currently approved in the treatment of acute manic episodes both as monotherapy (S-006) and is under review as adjunctive therapy with lithium or valproate (S-018. ***Post Meeting Note:*** S-018 was approved July 10, 2003). The original approved indication is schizophrenia. S-019 is a standard efficacy supplement proposing the use of olanzapine as monotherapy in the long-term treatment of Bipolar I Disorder.

**Summary:** The supplemental NDA is an all-electronic submission and was found fileable in all pertinent disciplines. It is classified 6S (approved chemical entity, new indication, standard priority). The receipt date was November 21, 2002; the filing date is January 20, 2003. The action due date is September 21, 2003. This action will require Dr. Katz' signature. All reviews should be completed by mid-August, 2003.

**Discussion: The formal meeting was cancelled due to inclement weather: these minutes summarize the online information collected in lieu of holding the meeting.**
*CMC:* Fileable for CMC; the CMC review has already been completed (EA categorical exclusion, approval recommendation).
*Pharm/Tox:* No P/T review is needed; no new pharm/tox data and no pharm/tox related additions or revisions to labeling are included in the supplement.
*Clin Pharm/Biopharmaceutics:* Fileable for Biopharmaceutics review, probably limited to labeling; there does not appear to be significant new information in this submission. Drug interactions are of most relevance for S-018; S-018 and –019 may be reviewed in tandem.
*Clinical:* Fileable for clinical review, with no significant issues identified.
*DSI:* A DSI audit will be performed for [ ] US sites [ ] b(4)
[ ]; also Dr. Hartford from Cincinnati, n = 93 entered, 22 randomized). Because these are domestic inspections, no formal consult request is needed.
*Statistics:* Fileable for statistics. A request for datasets (review issue) has been provided to the RPM for inclusion in the 74-day letter.
*DDMAC:* No filing issues were identified by DDMAC.
*Regulatory / Project Management (with Post Meeting Notes):* All team members have EDR access. User Fees were paid prior to supplement submission. The firm has previously requested a waiver of the requirement for pediatric studies, which was granted (May 30, 2002). The 74-day acknowledgement/filing letter for the supplement will address these points and include the statistics request for datasets.

There were no objections to filing the supplemental NDA. It was officially filed as of this date. The Lilly contact person, Ms. Michele Sharp, was telephoned at 12:50 p.m. and informed of the filing decision.

**Post Meeting Notes:** The 74-day letter was transmitted to the firm on Day 74, February 4, 2003 (e-mail).

Please see electronic signature page

Doris J. Bates, Ph.D.
Regulatory Project Manager
*For the attendees*

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/s/

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Doris Bates
7/22/03 03:39:14 PM