CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-592/S-006

Name: Zyprexa Oral Tablets

Generic Name: olanzapine

Sponsor: Eli Lilly and Company

Approval Date: 03/17/2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-006

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 20-592/S-006
NDA 20-592/S-008

Food and Drug Administration
Rockville MD 20857

Eli Lilly and Company, Inc.
Attention: Greg Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285

MAR 17 2000

Dear Dr. Brophy:

Please refer to your resubmitted supplemental new drug application (S-006) dated December 22, 1999, received December 23, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzepine) tablets, 2.5, 5, 7.5, 10 and 15 mg. This submission constituted a complete response to our October 28, 1999 action letter. We also acknowledge receipt of your submissions dated November 23, 1999, February 18, 2000, February 25, 2000 and February 29, 2000. In addition we refer to discussions which have taken place between representatives of your firm and this Agency on February 22, 2000 (teleconference), February 23, 2000 (meeting), and February 28, 2000 (teleconference).

Please also refer to your supplemental application S-008, submitted August 26, 1998, received August 27, 1998.

Supplemental application S-006 proposes the use of olanzapine in the treatment of manic or mixed episodes in bipolar disorder. Supplemental application S-008 provides for revisions to the "Geriatric Use" subsection of the package insert for ZYPREXA® (olanzapine) Tablets in compliance with the Federal Register Notice of August 27, 1997.

We have completed the review of resubmitted supplemental application S-006 as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text (please refer to the enclosed package insert text). Accordingly, supplemental application S-006 is approved, effective on the date of this letter.

Please note that your acceptance, and our approval, of the agreed upon labeling text for S-006 includes labeling changes in the "Geriatric Use" subsection which relate to 008. We therefore consider S-008 to be superseded by the approval of S-006; we will not review this application, but it will be retained in our files. We note your concurrence with this action as indicated by your communication of February 29, 2000 cited above.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL, as soon as it is available, in no case more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved sNDA number 20-592/S-006". Approval of this submission by FDA is not required before the labeling is used.

Please also submit one market package of the drug product when it is available.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product in the newly approved indication. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this supplemental NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

You have been advised that the Pediatric Final Rule (63 FR 66632) requires that 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 note that your Proposed Pediatric Study Request was submitted to this supplemental NDA on February 25, 2000 and received February 28, 2000. A formal Written Request will be forwarded to you under separate cover.

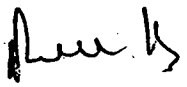
Also, as you know, on February 2, 1999, the financial disclosure rule, published in the Federal Register of February 2, 1998, became effective. Although your supplemental NDA was submitted before this rule was in effect, for any covered clinical studies submitted after February 2, 1999 which relate to this supplement, the regulations require financial information on clinical investigators conducting those trials. Please note that this requirement also applies to pediatric studies conducted in accordance with the Pediatric Final Rule. For further information about this requirement, you may

contact Ms. Linda Carter, Associate Director, Regulatory Affairs, Office of Drug Evaluation I at 301.594.6758.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions concerning this supplemental NDA, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 594-5536.

Sincerely yours,



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

Attachment (agreed-upon package insert text)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-006

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 20-592/S-006

Food and Drug Administration
Rockville MD 20857

Eli Lilly and Company, Inc.
Attention: Greg Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285

OCT 28 1999

Dear Dr. Brophy:

Please refer to your resubmitted supplemental new drug application dated April 12, 1999, received April 13, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ZYPREXA® (olanzapine) Tablets, 2.5, 5, 7.5, and 10 mg.

We also acknowledge receipt of your submission dated May 4, 1999.

The supplemental application proposes the use of olanzapine in the treatment of manic or mixed episodes in bipolar disorder.

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

CLINICAL

Labeling

Accompanying this letter (ATTACHMENT) is the Agency's proposal for the revised labeling of Zyprexa. We believe it presents a fair summary of the information available on the benefits and risks of Zyprexa. Please use the proposed text verbatim.

We have proposed a number of changes to the draft labeling resubmitted in your April 12, 1999 submission, and explanations for these changes are provided in the bracketed comments embedded within the proposed text. Division staff would be happy to discuss these proposed changes in detail, and we would be happy to meet with you to discuss any disagreements you might have with any part of the proposed labeling format or content.

Pediatric Studies

Be advised that as of April 1, 1999, all applications for new active ingredients, new dosage forms, 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 (63FR66632). Since it is likely that ZYPREXA will be used in children and adolescents with bipolar disorder, we ask that you commit to conducting, subsequent to approval, studies in these populations as

provided for in 21 CFR 314.55, in order to provide the safety and efficacy data needed to support such use. A useful starting point would be to obtain some pharmacokinetic data in children and adolescents suffering from this disorder. The Division will be happy to collaborate with your clinical and statistical staff in your design of such a program. Please provide a pediatric drug development plan within 120 days of the date of this letter, with proposed completion dates for Phase 4 studies you agree to conduct.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). Please refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity*, available on our Web site at www.fda.gov.cder/pediatric, for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to the pediatric development plan described above. If the request is not submitted within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity; however, you should still submit a pediatric drug development plan. Please note that satisfaction of the requirements of 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Requests for Additional Information for Studies HGEH and HGEW

These two studies enrolled patients meeting DSM-IV criteria for acute manic or mixed episodes associated with bipolar I disorder. Please provide information for each study regarding the breakdown of the number of patients enrolled in each by type of episode, i.e., manic or mixed.

Apparently a rule was used in the analysis of data from these trials requiring that the total score for the YMRS (Young Mania Rating Scale) was treated as missing for any particular visit if any of the items from that scale were missing for that visit. Please provide a table, for each study, of the patients and visits for which the total scores were treated as missing.

FINAL PRINTED LABELING

In addition, it will be necessary for you to submit 20 copies of the printed labels and other labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

PROMOTIONAL MATERIALS

In addition, please submit three copies of the introductory promotional materials that

you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products (HFD-120), and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 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 such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, 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. The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions concerning this NDA, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 594-5536.

Sincerely yours,

10/28/99

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

Attachment (draft labeling)

26 page(s) of draft labeling has been removed from this portion of the review.

Approvable Letter

cc:
NDA 20-592/S006: Archival NDA
NDA 20-592/S006: Division File
HFD-002/ORM
HFD-95/DDMS
HFD-101/ADRA(Carter)
HFD-100/Temple
HFD-120/Katz
/Laughren/Hearst/Andreason
/Fitzgerald
/Seevers
/Bates
HFD-710/Jin/He
HFD-860/Tammara
HFD-40/DDMAC (with draft labeling)
DISTRICT OFFICE

Drafted by: djb/06OCT99
Revised by: tpl/06OCT99
initialed by: see above
Final:
Doc N:\laughren\zyplabl\ltrae0.doc

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-006

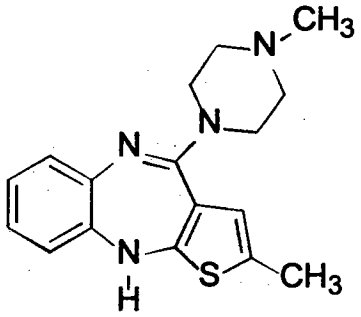
FINAL PRINTED LABELING

FINAL LABELING

ZYPREXA®
(Olanzapine)

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), or 15 mg (48 µmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths) and FD&C Blue No. 2 Aluminum Lake (15 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.

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_{1-4} (K_i=11-31 nM), muscarinic M_{1-5} (K_i=1.9-25 nM), histamine H_1 (K_i=7 nM), and adrenergic α_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 α_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.

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 α_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).

Clinical Efficacy Data:

Schizophrenia

The efficacy of olanzapine in the management of the manifestations of psychotic disorders 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 psychosis. 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.

Bipolar Mania

The efficacy of olanzapine in the treatment of acute manic 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 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.

INDICATIONS AND USAGE

Schizophrenia

ZYPREXA is indicated for the management of the manifestations of psychotic disorders.

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

The effectiveness of ZYPREXA in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, 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

ZYPREXA is indicated for the short-term treatment of acute 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).

The effectiveness of ZYPREXA for longer-term use, that is, for more than 4 weeks treatment of an acute episode, and for prophylactic use in mania, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use ZYPREXA for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

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

WARNINGS

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. 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.

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 α_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 Illnesses--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).

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.

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 (e.g., fluvoxamine) could potentially inhibit olanzapine elimination. Because olanzapine is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease olanzapine clearance.

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.

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.

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.

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.

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 $\geq$2 mg/kg/day and in female rats dosed at $\geq$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 4189 patients with approximately 2665 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) 1316 patients from 43 additional clinical trials as of May 1, 1997.

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 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 Trials--The following findings are based on the short-term, placebo-controlled premarketing trials for schizophrenia and bipolar mania and a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease.

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

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

Table 1 continued
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)**
Respiratory System		
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.

Additional Findings Observed in Premarketing Clinical Trials --The following findings are based on premarketing clinical trials in schizophrenia.

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			
	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 (4189 patients, 2665 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 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, flu syndrome, intentional injury, and suicide attempt; *Infrequent:* abdomen enlarged, chills, chills and fever, face edema, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, and photosensitivity reaction; *Rare:* hangover effect and sudden death.

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

Digestive System--*Frequent:* increased salivation, thirst; *Infrequent:* dysphagia, eructation, fecal impaction, fecal incontinence, flatulence, 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, esophageal ulcer, esophagitis, glossitis, ileus, intestinal obstruction, liver fatty deposit, and tongue discoloration.

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

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

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

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

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

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

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

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

Urogenital System--*Frequent:* amenorrhea*, hematuria, metrorrhagia*, and vaginitis*; *Infrequent:* abnormal ejaculation*, breast pain, cystitis, decreased menstruation*, dysuria, female lactation, glycosuria, impotence*, increased menstruation*, menorrhagia*, polyuria,

premenstrual syndrome*, pyuria, urinary frequency, urinary retention, urination impaired, uterine fibroids enlarged*, and vaginal hemorrhage*; *Rare:* albuminuria, gynecomastia, mastitis, oliguria, and urinary urgency.

*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: 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.

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. 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.

Antipsychotic efficacy 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 maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on olanzapine, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Bipolar Mania

Usual 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.

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

Maintenance Treatment--There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with olanzapine. While it is generally agreed that pharmacological

treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of olanzapine in such longer-term treatment (i.e., beyond 3-4 weeks).

HOW SUPPLIED

All tablets are film-coated and are identified with LILLY and the tablet number. The 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink. The 15 mg tablets are elliptical, blue, and debossed. They are available as:

	TABLET STRENGTH				
	2.5 mg	5 mg	7.5 mg	10 mg	15 mg
Tablet No.	4112	4115	4116	4117	4415
Identification	LILLY 4112	LILLY 4115	LILLY 4116	LILLY 4117	LILLY 4415
NDC Codes:					
Bottles 30	-----	-----	-----	-----	NDC-0002-4415-30
Bottles 60	NDC-0002-4112-60	NDC-0002-4115-60	NDC-0002-4116-60	NDC-0002-4117-60	----
Blisters – ID* 100	-----	NDC-0002-4115-33	NDC-0002-4116-33	NDC-0002-4117-33	NDC-0002-4415-33

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

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.

[Will carry actual revision date]

Eli Lilly and Company
Indianapolis, IN 46285, USA

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-006

MEDICAL REVIEW(S)

Orig NDA
20-592/S006

26.1

REVIEW AND EVALUATION OF CLINICAL DATA

SEP 11 1998

Application Information

NDA:	20-592
Sponsor:	Lilly
Clock Date:	12/3/97

Drug Name

Generic Name	olanzapine
Trade Name	Zyprexa

Drug Characterization

Pharmacological Category: Antipsychotic
Proposed Indication: Acute Treatment of Bipolar Disorder
NDA Classification: 1S
Dosage Forms, Strengths, and Routes of Administration:
Oral Tablets 2.5mg, 5mg, 7.5mg, and 10mg

Reviewer Information

Clinical Reviewer: Earl D. Hearst, M.D.
Review Completion Date:8/21/98

1.0 Material Reviewed

This NDA supplement received on 12/3/97 contains 52 volumes and includes a CDROM disk which is a exact copy of the paper submission. I have reviewed all narratives for patients meeting the criteria for adverse events leading to discontinuation, serious adverse events and the sponsor's potentially clinically significant adverse events including vital signs and weight, laboratory analytes, and ECG intervals and heart rate. I have also reviewed case report forms for patients HGEH-004-1159, HGEH-004-1168 and HGEH-013-1655. These are the three patients on olanzapine who discontinued due to an adverse event. The case report forms are consistent with the narratives and clinical summaries provided by the sponsor.

There is a 1 volume 4 month safety-update submitted on 4/1/98 which has also been reviewed.

There is no information in INDs 28,705 [ ] [ ] [ ] b(4)

2.0 Background

2.1 Indication

The sponsor proposes using olanzapine in the treatment of the manic or mixed episodes in bipolar disorder. The effectiveness of ZYPREXA for long-term use in mania, i.e., more than [ ] weeks, has not been systematically evaluated in controlled clinical trials. b(4)

2.2 Related INDs and NDAs

Olanzapine has also been submitted under IND 28,705 for schizophrenia [ ] [ ] b(4)

2.3 Administrative History

Protocol F1D-MC-HGEH was initiated in October 1996 to investigate the efficacy and safety of olanzapine in the treatment of patients with a manic or mixed episode associated with bipolar I disorder. In February 1997, the sponsor submitted to the FDA the clinical development plans for olanzapine in the treatment of

bipolar mania. The Sponsor submitted a request to the FDA for a pre-NDA meeting in May 1997. In June 1997, a pre-NDA meeting was held between the Sponsor and the FDA where the study design and submission data requirements were discussed.

2.4 Directions for Use

The sponsor proposes directions as indicated in italics below.

Bipolar Mania

b(4)

2.5 Foreign Marketing

Olanzapine has not been marketed in any country for the treatment of acute manic and mixed episodes in bipolar I disorder.

3.0 Chemistry

The same formulations currently available are proposed for the new indication. Eli Lilly and Company claims the Categorical Exclusion from the requirement for an environmental assessment to support the approval of Zyprexa (olanzapine) for the treatment of

bipolar mania.

4.0 Preclinical Pharmacology

Nonclinical pharmacology and toxicologic information regarding this section has been previously reported in NDA 20-592 and has not changed other than below.

The sponsor has provided the following new studies summary which I have truncated in italics.

Absorption, Distribution, Metabolism, and Excretion (ADME)

In vitro studies using human liver microsomes were conducted to examine valproate as a potential inhibitor of the oxidative routes of olanzapine metabolism and to determine whether olanzapine significantly inhibits the glucuronidation of valproate. Based on the results of these studies, valproate co-administration in vivo with olanzapine is not expected to affect the oxidative metabolism of olanzapine, and it is highly unlikely that olanzapine will affect valproate plasma concentrations in patients when both drugs are used concurrently.

Examination of the Potential Interactions of Valproate on Olanzapine Oxidative Metabolism and Human CYP1A2

In summary, valproate, at concentrations ranging from sub-therapeutic to above therapeutic levels, was found to only minimally affect the oxidative metabolism of olanzapine. Since olanzapine oxidative metabolism is mediated by CYP1A2, CYP2D6, and the flavin containing monooxygenases (Ring et al. 1996), these results suggest that valproate does not inhibit metabolism mediated by these enzymes. Valproate was also shown to only minimally affect the CYP1A2 mediated formation of acetaminophen from phenacetin, further confirming that valproate does not significantly inhibit CYP1A2 mediated metabolism. Therefore, valproate co-administration in vivo with olanzapine is not expected to affect the oxidative metabolism of olanzapine.

Effect of Olanzapine on Valproate Glucuronidation by Human Liver Microsomes

In vitro studies using human liver microsomes examined olanzapine as a potential inhibitor of the oxidative routes of valproate metabolism. Based on the Km values obtained for the formation of valproate glucuronide, valproate concentrations of 1, 2.5, 5, and 10 mM were evaluated (three valproate substrate concentrations below the average Km and one above). Based upon preliminary studies, olanzapine concentrations of 0, 0.1, 0.25, 0.5,

and 1 mM were evaluated.

Olanzapine was found to competitively inhibit the formation of valproate glucuronide at olanzapine concentrations considerably higher than those found in patients clinically. Using the method described by Ring et al. (1996), at a valproate concentration of 500 μM, Km of 5.9 mM, Ki of 884 μM, olanzapine concentration of 0.2 μM (equivalent to 40 ng/mL, the peak concentration observed in patients chronically treated with a 17.5 mg/day dose), the predicted in vivo inhibition by olanzapine on the glucuronidation of valproate was 0.02%. Therefore it is highly unlikely that olanzapine will affect valproate plasma concentrations in patients when both drugs are used concurrently.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

The use of olanzapine in the treatment of patients diagnosed with manic or mixed episode associated with bipolar I disorder has been studied in a double-blind placebo-controlled, multicenter trial (F1D-MC-HGEH) and two single-site open-label trials F1D-UT-HGES and F1D-MC-HGET which were conducted under the US IND for olanzapine (IND 28,705).

F1D-MC-HGEH, Olanzapine Versus Placebo in the Treatment of Mania Associated with Bipolar I Disorder, was conducted at 16 investigative sites in the United States (see complete list in appendix). The trial included 139 patients with a DSM-IV diagnosis of bipolar I disorder displaying an acute manic or mixed episode (with or without psychotic features) as determined by the SCID-P. This trial compared olanzapine (5, 10, 15, or 20 mg/day) with placebo.

F1D-UT-HGES, Olanzapine in Treatment Refractory Bipolar or Schizoaffective Disorder, was conducted at 1 investigative site in Netherlands in 2 patients with a DSM-IV diagnosis of bipolar I disorder with manic episode. This trial consisted of open-label olanzapine treatment in the doses of 5, 10, 15, or 20 mg/day.

F1D-MC-HGET, Open-Label Olanzapine, was a compassionate-use open-label trial conducted in the United States in 1 patient with a DSM-IV diagnosis of bipolar I disorder. This trial consisted of open-label olanzapine treatment in the doses of 5, 10, 15, 20 or

25 mg/day.

Data from the three trials (HGEH, HGES, and HGET) have been combined to comprise the integrated safety database. In these 3 trials, 122 patients were assigned to receive at least one dose of olanzapine.

The integrated primary safety database includes pooled data from the acute and open-label phases of study HGEH (119 patients, 70 patients randomized to olanzapine and 49 patients randomized to placebo who subsequently received olanzapine in the open-label phase), the 2 patients from study HGES, and the 1 patient from study HGET.

Patient Enumeration by Database, Study Type, and Study Design

	Treatment Group	
Database/Study Type/Study Design	**Olanzapine**	**Placebo**
Placebo-Controlled Studies		
Dose-Ranging	70	69
Uncontrolled Studies		
All	101 (49)[a]	
Total	122	69

[a] Number in parentheses (49) represents olanzapine-treated patients participating in open-label extension studies, but already counted in the Olanzapine column under Placebo-Controlled

The primary data cutoff date for the summary of safety information was 01 May 1997 for studies HGES and HGET and 01 July 1997 for HGEH. The second data cutoff date for information about deaths and serious adverse events was 01 August 1997.

The table below lists and summarizes all studies in which olanzapine was administered to patients diagnosed with bipolar disorder, begun on or before 01 August 1997.

Table of Studies

F1D-MC-HGEH	Olanzapine Versus Placebo in the Treatment of Mania Associated with Bipolar I Disorder, was conducted at 16 investigative sites in the United States. The trial included 139 patients with a DSM-IV diagnosis of bipolar I disorder displaying an acute manic or mixed episode (with or without psychotic features) as determined by the SCID-P. This trial compared olanzapine (5, 10, 15, or 20 mg/day) with placebo.
F1D-UT-HGES	Consisted of open-label olanzapine treatment in the doses of 5, 10, 15, 20 or 25 mg/day. Olanzapine in Treatment Refractory Bipolar or Schizoaffective Disorder, was conducted at 1 investigative site in Netherlands in 2 patients with a DSM-IV diagnosis of bipolar I disorder with manic episode. This trial consisted of open-label olanzapine treatment in the doses of 5, 10, 15, or 20 mg/day.
F1D-MC-HGET	Open-Label Olanzapine, was a compassionate-use open-label trial conducted in the United States in 1 patient with a DSM-IV diagnosis of bipolar I disorder. This trial consisted of open-label olanzapine treatment in the doses of 5, 10, 15, 20 or 25 mg/day.

5.1.2 Demographics

Patients were evenly divided between those over and those under 40 years of age. 74.6% of the patients were Caucasian and 52.5% were male. Please see the table below. Demographic comparisons with placebo patients were provided only for study HGEH and are included in the study appendix.

Table ISS.2.1. Patient Characteristics
Bipolar Overall Integrated Database

Variable	Olz (N=122)
Sex: No. (%)	
No. Patients	122
Male	64 (52.5)
Female	58 (47.5)
Origin: No. (%)	
No. Patients	122
Caucasian	91 (74.6)
African Descent	24 (19.7)
Hispanic	6 (4.9)
Other Origin	1 (0.8)
Age: yrs.	
No. Patients	122
Mean	39.15
Median	39.73
Standard Dev.	10.83
Minimum	18.15
Maximum	64.48
Age: yrs.	
No. Patients	122
<40	61 (50.0)
40 - <65	61 (50.0)

5.1.3 Extent of Exposure (dose/duration)

The total exposure in this database is 8099 days. The maximum duration of single patient exposure was 229 days as of 1 July 1997. In addition, four patients had been treated with olanzapine for at least 6 months (183 days). The median and mean modal daily doses of olanzapine were 15.0 mg/day and 14.9 mg/day, respectively. The maximum dose of olanzapine permitted in any of these studies was 25 mg/day in study HGET. For studies HGEH and HGES, the maximum dose of olanzapine permitted was 20 mg/day. Patient exposure to olanzapine in the studies included in the overall integrated database, based on modal daily dose, is summarized in the exposure table below. In this table 64% of patients received between 15-20 mg/day. 43.4% of patients had an exposure > than 60 days.

Table ISS.2.2. Patient Exposure to Olanzapine Therapy
Modal Daily Dose
Bipolar Overall Integrated Database

Duration (Days)	Dosage Range <10 mg	10 - <15 mg	15 - <20 mg	20 - <25 mg	>=25 mg	Total	(%)
<=14	1	6	4	10	0	21	(17.2%)
14< - 31	2	3	8	8	0	21	(17.2%)
31< - 61	1	7	8	11	0	27	(22.1%)
61< - 91	2	7	6	7	0	22	(18.0%)
91< - 183	2	12	1	12	0	27	(22.1%)
>183	0	1	1	2	0	4	(3.3%)
Total	8	36	28	50	0	122	
(%)	(6.6%)	(29.5%)	(23.0%)	(41.0%)			

Total patient days of exposure: 8099

5.1.4 Disposition

7.4% of patients discontinued because of lack of efficacy and 2.5% because of adverse effects. See table below. Disposition comparisons with placebo are provided in HGEH study appendix.

Table ISS.2.3. Patient Disposition
Bipolar Overall Integrated Database

Reason for Discontinuation	Olz (N=122) n (%)
Protocol Complete	1 (0.8)
Adverse Event	3 (2.5)
Lack of Efficacy	9 (7.4)
Lost to Follow-up	5 (4.1)
Patient Decision	21 (17.2)
Criteria not met / Compliance	7 (5.7)
Ongoing	74 (60.7)
Physician Decision	2 (1.6)

5.2 Secondary Sources

5.2.1 Non-IND Studies

There are no Non-IND studies with which the sponsor has been associated.

5.2.2 Post-Marketing Experience

There is post-marketing experience with olanzapine used in Bipolar disorders and this is described in section 8.5.1.3 of this review.

5.2.3 Literature

The sponsor compared safety data from completed and ongoing worldwide clinical studies through a cutoff date of 01 May 1997 with safety data initially submitted to the FDA for the indication of psychotic disorders on 22 September 1995 (NDA 20-592). The sponsor feels the additional literature search for olanzapine reflected in the current database reveals no substantial change in the safety profile from that of the original submission. The databases used for this search are: Medline Derwent Drug File SciSearch, Embase PsycINFO Biosis. I did not see any literature reports in the 41 articles in the sponsor's bibliography reviewed by title that would be directly relevant to this review.

5.3 Adequacy of Clinical Experience

I have concerns about the adequacy of the clinical experience with regard to the homogeneity of the treated population. My concern is that the patients actually used in the efficacy trials do not represent a true sample of the indication being studied. These concerns are presented in the subgroup analysis in section 7.3.1. The exposure to olanzapine appears to be of an adequate duration and dosage and the clinical experience is otherwise satisfactory.

5.4 Data Quality and Completeness

The data quality appears to be adequate and complete in that the specified scales and tests were appropriate, performed, with results collected and analyzed.

6.0 Summary of Human Pharmacokinetics

There are no changes in this section outside of the two drug interaction studies summarized in section 8.9.3 on drug-drug interactions presented later in this review.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

There are three studies in the ISS but only one is relevant to efficacy. This study has two parts with identical design.

F1D-MC-HGEH (Study 1) was conducted at 8 study sites in the United States in 72 patients with a DSM-IV diagnosis of manic or mixed episode associated with bipolar I disorder. This study compared olanzapine (5.0 to 20.0 mg/day) with placebo.

F1D-MC-HGEH (Study 2) was conducted at 8 study sites in the United States in 67 patients with a DSM-IV diagnosis of manic or mixed episode associated with bipolar I disorder. This study compared olanzapine (5.0 to 20.0 mg/day) with placebo.

7.2 Summary of Studies Pertinent to Efficacy

Study F1D-MC-HGEH

This trial compared olanzapine (5.0 to 20.0 mg/day) with placebo. The protocol was designed as 2 randomized, double-blind, placebo-controlled, parallel studies. The design of the two parallel studies is presented in this section whereas the results are presented in individual sections.

Investigators/Sites

F1D-MC-HGEH was conducted at 16 study sites in the United States in 139 patients with a DSM-IV diagnosis of manic or mixed episode associated with bipolar I disorder. Investigators were divided into 2 separate studies prior to beginning the studies (Study 1 and Study 2). Please see complete list in appendix.

Objectives

The primary objective of this trial was to assess the efficacy of olanzapine in a dose range of 5.0, 10.0,

15.0, or 20.0 mg/day compared with placebo in the treatment of patients diagnosed with manic or mixed episode associated with bipolar I disorder in improving overall symptomatology as measured by reductions from baseline of the Young-Mania Rating Scale (Y-MRS) total score after 3 weeks of therapy.

Secondary objectives included assessing the safety of acute treatment as well as the efficacy of long-term treatment. In addition, the use of adjunctive fluoxetine and lithium during long-term open-label treatment was assessed as were the effects of long-term treatment with olanzapine on patients' quality of life.

Study Population

Male and female patients between the ages of 18 and 65 were eligible if they had a diagnosis of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) bipolar I disorder and displayed an acute manic or mixed episode (with or without psychotic features) as determined by SCID-P. This included the following diagnoses: 296.4x, Bipolar I Disorder, Most Recent Episode Manic; 296.6x, Bipolar I Disorder, Most Recent Episode Mixed; and 296.0x, Bipolar I Disorder, Single Manic Episode. Patients must have had experienced the current manic or mixed episode for at least 2 weeks prior to Visit 1. Patients must have had an initial score (at Visits 1 and 2) on the Y-MRS total score of at least 20. Patients were excluded if they had a diagnosis of a psychotic disorder other than bipolar I disorder, an organic mental disorder, or a substance-use disorder. Other exclusionary criteria included serious and unstable non-psychiatric medical disorders.

Study Design

This was a double-blind placebo controlled multi-center study. After a 2- to 4-day screening period (Study Period I), patients who were experiencing a manic or mixed episode associated with bipolar I disorder were randomly allocated to one of two treatment groups: placebo or olanzapine (5.0 to 20.0 mg/day). During Study Period II, patients began double-blind therapy (Visit 2) with either

olanzapine (10.0mg/day, two 5.0-mg tablets) or placebo (two tablets) given once per day. Following one day on 2 tablets/day, investigators could titrate the dose up by one increment or down by multiple increments within the allowed dosage range to optimize clinical benefit. Patients were required to be hospitalized for a minimum of 1 week following Visit 2. Patients who showed no improvement from baseline (Visit 2) on the Y-MRS total score after at least 1 week (or 1 visit interval) of double-blind therapy and all patients who completed therapy in the 3-week acute phase (Study Period II) had the opportunity to receive open-label olanzapine (5.0 to 20.0 mg/day) for up to 53 weeks (Study Period III). Please see schedule of study events in the appendix.

Rating Scales

The primary efficacy scales used in the controlled clinical studies are defined below.

Y-MRS (Young-Mania Rating Scale): The Y-MRS (Young 1978) consists of 11 items. Items 5, 6, 8, and 9 are rated on a scale from 0 (symptom not present)to 8 (symptom extremely severe). The remaining items are rated on a scale from 0(symptom not present) to 4 (symptom extremely severe). Items 5, 6, 8, and 9(irritability, speech, content and disruptive-aggressive behavior) are given twice the weight of the remaining 7 in order to compensate for the poor condition of severely ill patients. The Y-MRS total score ranges from 0 to 60 and is the primary efficacy parameter.

PANSS (Positive and Negative Syndrome Scale): The PANSS (Kay et al. 1986) is used to assess overall psychopathology, specific positive symptoms, specific negative symptoms, and general psychopathology (nonspecific, frequently associated symptoms) specifically associated with schizophrenia and related disorders. The scale consists of 30 items. Each item is rated on a scale from 1(symptom not present) to 7 (symptoms extremely severe). The PANSS total score is the sum of all 30 items, and the score ranges from 30 to 210. The PANSS positive score and PANSS negative score each consists of 7 unique items from the 30 total items, and the scores range from 7 to 49. The PANSS general

psychopathology score includes 16 of the 30 items, and the score ranges from 16 to 112. Only PANSS total, positive, and negative scores were presented in the sponsor's summary.

HAMD-21 (Hamilton Psychiatric Rating Scale for Depression, 21-item): The HAMD-21(Hamilton 1967) is a observational rating measure of depression severity. The 21-item version of this scale (HAMD-21) was administered to assess the severity of depression and its improvement during the course of therapy.

CGI-BP Severity (Clinical Global Impressions Bipolar Version - Severity of Illness): CGI Severity (Guy 1976) is used by the clinician to record the severity of illness at the time of the assessment. The CGI-BP severity is a measure of illness severity especially adapted for bipolar illness. It allows rating of mania, depression, and overall illness. CGI-BP severity is used by the clinician to record the severity of illness at the time of assessment. The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).

SF-36 Health Status Survey: The SF-36 Health Status Survey was used to assess general quality of life. The SF-36 consists of 36 questions covering the following eight health domains (subscales): physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. Each subscale is scored by summing the individual items and transforming the scores into a 0 to 100 scale, with higher scores indicating better health status or functioning (Ware et al. 1993). No overall total score is calculated. More recently, two summary scores, the physical component summary (PCS) and the mental component summary (MCS), have been constructed based on the eight SF-36 subscales. The equations are provided in SF-36 Physical and Mental Health Summary Scales: A User's Manual (Ware et al. 1994). The two summary scores represent independent (orthogonal) indices based on a factor analysis of SF-36 scale scores using Medical Outcomes Study data.

The Y-MRS, PANSS, HAMD-21, CGI-BP, Barnes Akathisia,

Simpson-Angus, and AIMS rating scales were assessed at each visit. The SF-36 was assessed at each visit in Study Period II and Visit 307, Visit 311, and Visit 315 (or the final visit) during Study Period III.

Analysis

The primary efficacy analysis was the LOCF comparison of mean change from baseline to endpoint in Y-MRS total score. All analyses were done on an intent-to-treat basis.

In the analysis of LOCF change from baseline to endpoint, patients were included in the analysis only if a patient had a baseline and a postbaseline measure. The baseline measure was the Visit 2 observation, unless it was missing, then it was the Visit 1 measure. The endpoint measure was the last measure in the acute phase. All total scores from rating scales and subscales were derived from individual items. If any of the items were missing, the total score was treated as missing except for the SF-36 scale.

ANOVA models were used to evaluate continuous data; for analysis of proportions, Fisher's Exact test was used. If there were less than 2 patients per treatment group within an investigative site, those data were pooled with data from other small investigative sites within the same study. Investigators 005 and 006 and 001 and 015 were combined. All tests of hypotheses were tested at a two-sided a level of 0.05.

Treatment-by-investigator interactions and heterogeneity across investigative sites were tested at an a level of 0.10. The primary efficacy variable was the Y-MRS total score. LOCF change from baseline to Week 3 of therapy (acute phase) in Y-MRS total scores was the primary efficacy measure. Treatment groups were compared with respect to LOCF changes from baseline to Week 3 of double-blind therapy (Study Period II) in the secondary efficacy rating scales and subscales (HAMD-21 total score; PANSS total, positive, and negative scores; and CGI-BP severity of mania, depression, and overall).

An observed and LOCF visitwise analysis of Y-MRS total

score; PANSS total, positive, and negative scores; HAMD-21 total, and CGI-BP severity of mania, depression, and overall bipolar illness were performed.

A patient was considered a responder if the Y-MRS total score had decreased by 50% or more from baseline to endpoint. Response rates were analyzed using Fisher's Exact test. Time to response was analyzed using Kaplan-Meier estimated survival curves and the curves compared using the log-rank test.

Treatment groups were compared with regard to LOCF change from baseline to endpoint in the eight domain subscores of the SF-36 and the two summary scores (PCS and MCS),using an ANOVA model which included terms for treatment, investigator, and treatment-by-investigator interaction.

Study Outcome

Study F1D-MC-HGEH (Study 1)

Patient Disposition

In the acute phase of Study 1, 36 patients were randomized to receive olanzapine and 36 to placebo. Please see appendix tables showing patient disposition and completion rates. 63.9% of olanzapine patients completed week 3 but only 38.9% on placebo completed week 3. 44.4% of placebo patients dropped out due to lack of efficacy as compared to 25% on olanzapine.

Demographics

Patients had a mean age of 38.77 years with olanzapine patients at 41.67 and placebo at 35.87 years. 79.2% were Caucasian, olanzapine 83.3% an placebo 75%; 50.0% were male with olanzapine 47.2% and placebo 52.8%. Please see study 1 demographic appendix table.

Dosing Information

The sponsor reports that patients were highly compliant with study medications. The mean and median modal doses of olanzapine were 16.3 mg/day and 17.5 mg/day, respectively. 50% of olanzapine patients received the highest modal dose (20mg) in this study. Please see dosing table in the appendix.

Concomitant Medications

The sponsor reports that at study entry there were no statistically significant differences in the use of any medications to treat bipolar disorder. There were no statistically significant differences in the use of anticholinergic medication, benzodiazepines, or any other concomitant medications during the study.

Concomitant psychotropic medication was restricted to benzodiazepine and anticholinergic compounds in the acute phase. There were no statistically significant differences noted in the concomitant use of benzodiazepines or anticholinergic compounds between the olanzapine and placebo treatment groups.

Concomitant use of lithium and/or fluoxetine was allowed during Study Period III, as clinically appropriate. Of all patients, 86.3% took at least one dose of benzodiazepines, and 9.4% took at least one dose of anticholinergic medication.

The sponsor reports that there was a significant difference between treatment groups in the mean daily benzodiazepine use analysis (p=.002), with placebo-treated patients having a higher mean daily dose (1.681 mg/day) compared with olanzapine-treated patients (1.123 mg/day). Please see concomitant medication table in appendix.

Analysis

The primary efficacy analysis was the LOCF comparison of mean change from baseline to end point in Y-MRS total score. Please see full description of analysis methodology at the beginning of the efficacy section.

Efficacy Results

Please see efficacy tables for study 1 in the efficacy appendix.

The LOCF and OC analyses of the weekly change from baseline in the **Y-MRS** were not significant at any week.

The LOCF and OC weekly change from baseline in the **CGI-BP Severity of Overall Bipolar Illness** was not significant at any week.

The LOCF and OC weekly change from baseline in the **CGI-BP Severity of Mania Scale** was not significant at any week.

The LOCF and OC analyses of the **HAMD-21** total score were not significant at any week.

The **PANSS** total score LOCF analysis was positive at week 2 and 3. The PANSS total score OC analysis was positive at week 1 and 2.

EFFICACY CONCLUSION STUDY I

The sponsor feels that the lack of statistical significance may be explained by the large placebo response reported in this patient population. In only one of the 8 study sites, placebo demonstrated a greater response than olanzapine. When the data from this study site (016) is removed, the mean change from baseline to endpoint in Y-MRS total scores becomes -3.75 for placebo and -11.42 for olanzapine (p=.068). The sponsor argues that when the data from study site 016 is removed, the **response rate** of the olanzapine treatment group becomes 51.6% compared to 21.4% for the placebo treatment group, a statistically significant difference (p=.030) despite the reduced sample size.

This measure however was not the primary efficacy variable, the Y-MRS was. The Y-MRS does not become significant even when study site 16 is removed. The sponsor's explanation also does not explain why Olanzapine

was effective in psychotic symptoms (PANSS) but not in manic symptoms (Y-MRS and CG-BP Severity of Mania and CG-BP Severity of Overall Bipolar Illness) in study 1 with all sites included. I do not believe a high placebo response rate explains the significant response in the PANNS but not in the YMRS. I could however suspect from this data that olanzapine is more efficacious in psychotic symptoms than in manic symptoms.

This study does not support the claim that olanzapine is effective in mania.

Study F1D-MC-HGEH (Study 2)

Patient Disposition

In the acute phase of study II, 34 patients were randomized to receive olanzapine and 33 to placebo. The percentage completing week three was 58.8% for olanzapine and 30.3% for placebo. The percentage dropping out due to lack of efficacy was 51.6% on placebo and 32.2% on olanzapine. Please see tables in appendix with disposition and completion data.

Demographics

Patients had a mean age of 40.27 years with olanzapine 38.75 and placebo 41.83%; 65.7% were Caucasian with olanzapine 67.6% and placebo 63.6%; 53.7% were male with olanzapine 52.9% and placebo 54.5%. Please see table in appendix.

Dosing

The sponsor reports that patients were highly compliant with study medications. The mean and median modal dose of olanzapine were 13.5 mg/day and 15.0 mg/day, respectively. Only 26.5% of olanzapine patients in this study received the highest modal dose of 20mg/day. Please see dosing table in appendix.

Concomitant Medication

The sponsor reports that at study entry there were no statistically significant differences in any medications that are used to treat bipolar disorder. There was a significant

difference in the use of tiotixene (thiothixene) prior to study entry; however, it is not believed that such prior history would affect treatment outcome. There were no statistically significant differences in the frequency of use of anticholinergic medication, benzodiazepines, or any other concomitant medications during the study. Of all patients, 85.1% took at least one dose of benzodiazepines, and 9.0% took at least one dose of anticholinergic medication. However, there was a significant difference between treatment groups in the mean daily use of benzodiazepines analysis (p=.003), with placebo-treated patients having a higher mean daily dose (2.004 mg/day) compared with olanzapine-treated patients (1.010 mg/day).

Overall, patients were highly compliant with study medications. The mean and median modal dose of olanzapine were 13.5 mg/day and 15.0 mg/day, respectively.

Please see concomitant medication table in appendix.

Analysis

The primary efficacy analysis was the LOCF comparison of mean change from baseline to end point in Y-MRS total score. Please see full description of analysis methodology at the beginning of the efficacy section.

Efficacy Results

Please see efficacy tables in appendix.

In study 2 the LOCF weekly change from baseline in the **Y-MRS total score** was significant at weeks 2 and 3. The OC weekly change from baseline was not significant at any week.

In study 2 the LOCF weekly change from baseline in the **CGI-BP Severity of Mania Scale** was significant on weeks 1, 2 and 3. The OC weekly change from baseline was significant only at week 1.

In study 2 the LOCF weekly change from baseline in the **CGI-BP Severity of Overall Bipolar Illness** was significant only at week 1. The OC weekly change from baseline was significant only at week 1.

In study 2 the LOCF and OC weekly change from baseline in the **PANSS Total Score** was not significant at any week.

In study 2 the LOCF and OC weekly change from baseline in the **HAMD-21 Total Score** was not significant at any week.

EFFICACY CONCLUSION-STUDY 2

The LOCF analyses in study 2 offer some support that olanzapine is effective in the treatment of mania. The OC analyses do not support this conclusion. Overall this study, at face value, could be viewed as somewhat supportive to the claim of efficacy in Mania, however I will raise doubts about the validity of this claim in review sections 7.3.1 and 7.3.2.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

There was no attempt to find a dose-response relationship since this was a dose ranging study design.

The sponsor performed subgroup analyses to examine the consistency of treatment effects over the strata of various demographic populations. The subgroups analyzed were gender, racial origin (Caucasian, other), age (less than 40 years, at least 40 years), bipolar mixed versus bipolar manic, psychotic versus non-psychotic features, presence or absence of a rapid cycling course, concomitant benzodiazapine use, previous episodes of mania in the last 12 months (less than 3, at least 3), previous lithium use, previous valproate use, and previous antipsychotic use. A subgroup was analyzed only if the number of patients in each strata was 10 or more.

I have reviewed the tables of subgroup analysis vol 7, (262-313) and believe that some trends emerge. There are not many p values that are significant on the p=.05 level. We could expect some of these to be positive just by chance because many were performed. Most of them are not positive, however, I am struck by how often significant p values show up as related to prior use of medication.

No previous exposure in the prior two years to lithium predicts a statistically significant or almost significant greater decrease in the following scales for olanzapine patients compared to placebo-- CGI-Severity of Mania (p=.005), CGI-Severity of Overall Bipolar Illness(p=.032), PANNS positive(p=.068), Y-MRS(p=.052), and PANNS Total(p=.012). None of these scales are positive or have P values close to the p=.05 level in the subgroup previously treated with lithium in the prior two years. No previous exposure in the prior two years to valproate predicts a statistically significant decrease in the PANNS Total for olanzapine treated patients compared to placebo(p=.01). This same comparison is not positive in the subgroup treated previously with valproate.

Previous exposure in the prior two years to antipsychotics predicts a statistically significantly greater decrease in the following scales-- CGI-BP Severity of Mania(p=.027), PANNS positive(p=.036), PANNS Total(p=.025). The subgroup without prior two year exposure to antipsychotics does not show a statistically significant decrease in any of these scales.

This suggests to me a striking pattern that patients who are thought over the prior two years to be psychotic (treated with antipsychotics) and not bipolar (no treatment with lithium or valproate) are much more likely to respond to olanzapine. It would seem from their prior treatment over the previous two years that many of these patients were not considered bipolar until they entered this trial.

In addition, factor analysis using maximum likelihood was used by the sponsor to create factors from the individual YMRS items using changes from baseline to endpoint. Their analysis produced the following two clusters using eiganvalue greater than one and a varimax rotation.

Factor-I: YMRS items Y4 + Y5 +Y6 + Y7 +YS +Y9 + Y10 + Y11 (sleep, irritability, speech, language-thought disorder, content, disruptive-aggressive behavior, appearance insight)

Factor-2: YMRS items Y1 + Y2 + Y3 (elevated mood, increased motor activity, and sexual interest).

Differences were found between treatment groups favoring olanzapine for Factor-I with a p=.013 and the difference between treatment groups favoring olanzapine for Factor-2 was p=.096.

My judgment of these two factors are that Factor 1 has items that are more common in psychoses whereas Factor II has items more likely to be seen in bipolar, manic patients. This factor analysis (by the sponsor's own method) also indicates that olanzapine is numerically more effective with psychotic symptoms that bipolar symptoms.

7.3.2 Size of Treatment Effect

The sponsor has provided the table below indicating the size of the treatment effect.

Efficacy Scores
95% Confidence Intervals of Least-Squares Mean Treatment Difference (Olanzapine - Placebo)
F1D-MC-HGEH, Acute Phase Combined Studies

Score	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Y- MRS Total	-10.31	-0.93
HAMD- 21 Total	-2.34	2.75
CGI- BP severity of Mania	-1.22	-0.11
CGI- BP severity of Depression	-0.11	0.78
CGI- BP severity of Overall Bipolar Illness	-0.87	0.14
PANSS Total	-15.27	-1.38
PANSS Positive	-5.43	-0.12
PANSS Negative	-2.46	0.98

The sponsor reports that the Olanzapine treatment group experienced a statistically significantly greater mean improvement in Y-MRS total score than the placebo treatment

group (p=.019) when the two studies are combined. This mean difference of 5.38 point decrease compared to placebo had a 95% confidence interval of the least-squares mean difference of (-10.31,-0.93).

I compared this mean improvement difference in the Y-MRS of 5.38 points (compared to placebo) to the similar measure seen in the depakote for mania NDA trials which showed a mean improvement in the YMRS of 9.2. I understand that a direct comparison over 2 different trials has a number of methodological problems, however, by this rough comparison, depakote had a treatment effect 70% larger than olanzapine.

7.3.3 Choice of Dose

The modal dose for an individual patient is displayed in the table below. This table is consistent with the treatment dose being in the range of 10-20 mg/day. Doses above 20mg/day were not evaluated.

Modal Drug Dosage
F1D-MC-HGEH, Acute Phase

Olanzapine
Number of Patients (%)
0.0 mg 2 (2.9%)
5.0 mg 1 (1.4%)
10.0 mg 20 (28.6%)
15.0 mg 20 (28.6%)
20.0 mg 27 (38.6%)
Total 70
Dosage (mg)
Mean 14.9
Median 15.0
Std. Dev. 5.0

No drug concentration information was collected.

7.3.4 Duration of Treatment

There is insufficient data to support any efficacy claim
b(4) beyond [ ] weeks of treatment.

7.4 Conclusions Regarding Efficacy Data

Only two of the eleven items (disregarding power issues) on the primary efficacy scale (Y-MRS) were significant at the p=.05 level in the combined double-blind study. These two items were irritability and sleep which are not unique symptoms to mania.

It is not surprising that there was a mean decrease of 5.38 in the Y-MRS across the double blind studies since many symptoms in the Y-MRS are seen frequently in psychoses whether associated with schizophrenia or mania.

The two studies presented do not make a persuasive argument that olanzapine is effective in the treatment of mania. It can be argued from the subgroup analysis that many of these patients were treated for schizophrenic related illnesses rather than bipolar disorder in the two years prior to study entry. Their response to olanzapine is statistically related to their prior drug treatment and presumably their diagnosis prior to trial entry. It appears that only at study entry were they rediagnosed as bipolar patients.

I believe the efficacy data presents an argument that olanzapine alleviates some nonspecific symptoms in this group of patients which are 52.2% psychotic at baseline. There is no compelling evidence that olanzapine does anything specific for bipolar patients.

An independent statistical review was done by Kooros Mahjoob, Ph.D. of the FDA and his conclusion is also that the case for efficacy was not made.

8.0 Safety Findings

8.1 Methods

This safety review derives from 3 clinical trials, F1D-MC-HGEH (N=139), F1D-UT-HGES (N=2), and F1D-MC-HGET (N=1), for the treatment of mania associated with bipolar I disorder. The data cutoff date for information included in this integrated summary of safety was 1 May 1997 for HGES and HGET and 1 July 1997 for the open-label phase of HGEH. All acute phase data for patients in HGEH is included. The final acute phase visit for HGEH occurred on 22 August 1997. The second data cutoff date for information about deaths and alert events was 1 August 1997 for HGES, HGET, and the open-label phase of HGEH.

The more commonly encountered adverse experiences were assessed using data from the placebo-controlled trials. Less frequent, but more grave adverse experiences were investigated by examining any death, reasons for premature discontinuation from clinical trials and the sponsor's safety reports of potentially serious adverse events from all studies.

8.2 Deaths

There were no deaths which occurred during or within 30 days of study discontinuation or poststudy (greater than 30 days following study discontinuation) for HGEH, HGES, or HGET.

8.3 Assessment of Dropouts

8.3.1 Overall Pattern of Dropouts

Only three patients (all in the open phase) on olanzapine dropped out due to an adverse event while 9 dropped out due to lack of efficacy. Please see table below.

Table ISS.2.3. Patient Disposition
Bipolar Overall Integrated Database

Reason for Discontinuation	Olz (N=122) n (%)
Protocol Complete	1 (0.8)
Adverse Event	3 (2.5)
Lack of Efficacy	9 (7.4)
Lost to Follow-up	5 (4.1)
Patient Decision	21 (17.2)
Criteria not met / Compliance	7 (5.7)
Ongoing	74 (60.7)
Physician Decision	2 (1.6)

8.3.2 Adverse Events Associated with Dropout

The sponsor reports that of the 122 patients included in the overall integrated database, 3 patients (2.5%) discontinued from the trials because of an adverse event. The adverse events reported as the reason for discontinuation by olanzapine-treated patients are summarized in Table ISS.3.2. I have reviewed the narratives and case report forms for the patients who had these three events and they are accurately represented and consist of one accidental injury, one case of hostile agitation and one hyperglycemia (in a previously known diabetic).

Table ISS.3.2. Adverse Events Reported as Reason for Discontinuation
Bipolar Overall Integrated Database

Event Classification	Olz (N=122) n (%)	PT #	age	sex
PATIENTS DISCONTINUED	3 (2.5)			
ACCIDENTAL INJURY	1 (0.8)	004-1159	40	M
HOSTILITY	1 (0.8)	014-1655	46	F
HYPERGLYCEMIA	1 (0.8)	004-1168	35	F

8.4 Search for Serious Adverse Events

Serious adverse events were defined as any experience that was fatal or life threatening, incapacitating, permanently disabling, required hospitalization, or resulted in a prolongation of hospitalization, or was a congenital anomaly, cancer, or an overdose.

There were 70 serious adverse events which occurred in 16 patients. They are listed in the safety appendix. I have reviewed this list and find no new or worrisome events that differ from the serious adverse events in the original submission.

Dropouts and deaths have been discussed in previous sections. Laboratory abnormalities, overdoses, withdrawal phenomena and pregnancy related events will be discussed in subsequent sections of this review.

8.5 Other Safety Findings

8.5.1 ADR Incidence Tables

8.5.1.1 Appropriateness of Adverse Event Categorization and Preferred Terms

The sponsor has modified the list of COSTART term and provided reasons for the alterations in their modified COSTART list. I have reviewed this list and find the organization to be reasonable. This table lists all COSTART classification terms reflecting a treatment-emergent adverse event in the primary database (N=3938, [3816 non-bipolar, 122 bipolar]) for olanzapine.

8.5.1.2 Incidence in Controlled Clinical Trials

The sponsor has provided tables of TESS by frequency and TESS by body system. I have reviewed these listings and find that statistically significant increases in favor of olanzapine compared to placebo were seen for the following events: Somnolence p=.05, dry mouth p=.012, dizziness p=.007, and weight gain p=.033.

Events occurring twice as often in olanzapine as placebo and greater than 5% include: dry mouth 25.7% vs 8.7%, dizziness 22.9% vs 5.8%, asthenia 18.6% vs 7.2%, constipation 11.4% vs 2.9%, pain 11.4% vs 4.3%, weight gain 11.4% vs 1.4%, and dyspepsia 8.6% vs 2.9%.

The most commonly reported (incidence > 10%) treatment-emergent adverse events among olanzapine-treated patients were somnolence (34.4%), depression (24.6%), dry mouth (24.6%), asthenia (22.1%), weight gain (21.3%), headache (18.0%), increased appetite (18.0%), agitation (16.4%), anxiety

(15.6%), dizziness (14.8%), rhinitis (13.9%), constipation (12.3%), pain (12.3%), and insomnia (10.7%).

8.5.1.3 Post Marketing Spontaneous Reports

The sponsor had provided an analysis of postmarketing use of olanzapine for bipolar patients. It is reproduced in truncated form in italics below.

In order to assess whether spontaneous adverse event reports for olanzapine in the treatment of bipolar disorder contribute information regarding the safety of olanzapine that is new or different from information already known, the [ ] database was searched for spontaneous adverse event reports involving patients who may have been treated with olanzapine for bipolar disorder. This search was conducted electronically by the Lilly Global Safety Monitoring Team (GMT) responsible for the [ ] database. The identification of adverse event reports temporally associated with the use of olanzapine in the treatment of bipolar disorder was performed by Lilly personnel and reviewed by a physician board-certified in psychiatry. All olanzapine entries in the [ ] database through 30 June 1997 were searched. b(4) b(4) b(4)

After the electronic search and the reviews were conducted, a list was prepared of all Coding Symbol and Thesaurus for Adverse Reaction Terms (COSTART) that appeared in spontaneous adverse event reports in bipolar patients, along with the number of reports of each event term and the percentage of the total events reported in patients with a bipolar disorder diagnosis.

Based on the detailed clinical review of spontaneous adverse event reports for patients considered to have been treated with olanzapine for bipolar disorder and the comparison of the relative frequencies of COSTART classification terms for bipolar versus nonbipolar patients, it cannot be concluded that bipolar patients are at increased risk for any adverse event or any unique adverse events relative to their nonbipolar counterparts.

Similarly, a review of the spontaneous adverse event reports was conducted to evaluate reports from patients who received mood stabilizers concomitantly with olanzapine. The mood stabilizers included in the search were lithium and valproate as well as the

anticonvulsants, used by clinicians as mood stabilizers, carbamazepine, gabapentin, and lamotrigine. There was no conclusive indication that patients treated concomitantly with mood stabilizers are at increased risk for any adverse event or unique adverse events compared with patients not treated concomitantly with mood stabilizers.

Furthermore, spontaneous events that have been reported by bipolar patients and by patients both treated and not treated concomitantly with mood stabilizers are adequately described in the product labeling for olanzapine.

8.5.2 Laboratory Findings

The following sections will provide proportions of patients in the double-blind placebo-controlled trial who met arbitrarily defined criteria for changes in laboratory variables of possible clinical significance. There will also be comparisons of olanzapine versus placebo regarding mean changes in baseline parameters of laboratory values and a listing of patients who discontinued due to laboratory abnormalities.

The sponsor's laboratory program was adequate to evaluate patients in this database. During the acute phase, laboratory tests were performed at each visit. The tests included clinical chemistry, hematology, electrolytes, and urinalysis. A urine drug screen was performed at Visits 1 and the last visit of the acute phase (Visit 3, 4, or 5). A hepatitis screen was performed at Visit 1 and repeated as necessary based on the investigator's clinical judgment. A serum pregnancy test (women only) was performed at Visit 1 and repeated at any time deemed necessary by the investigator. A thyroid-stimulating hormone (TSH) test was performed on all patients at Visit 1.

8.5.2.1 Clinical Chemistry Findings

The chemistry criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial fell outside the defined criteria for changes and the table of change in mean baseline for this section.

There were no statistically significant changes in the proportions of patients exceeding defined criteria. Three olanzapine patients had elevated ALTs while no placebo patient did.

The following items were significant among mean baseline changes; Creatinine (Olan<Pla p=.02), Cholesterol (Olan>Pla p=.046), Albumen (Olan<Pla p=.003), with ALT (Olan>Pla almost significant at p=.053). The ALT mean level across groups was almost doubled in Olanzapine patients.

There was one drop out because of an adverse event associated with hyperglycemic change in an olanzapine-treated patient, but this did not occur during the acute phase of treatment. This patient had diabetes prior to randomization.

8.5.2.2 Hematology Findings

The hematology criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the criteria for changes and the table of change in mean baseline for this section.

There were no statistically significant changes in the proportions of patients exceeding defined criteria.

The following items were significant among mean baseline changes with the Olanzapine mean value decreasing in all cases; HGB p=.012, MCHC p=.032, MCH p=.001.

There were no drop outs because of adverse events associated with hematologic change for olanzapine-treated patients.

8.5.2.3 Urinalysis

The urinalysis criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the defined criteria for changes and the table of change in mean baseline for this section.

There were no statistically significant changes in the proportions of patients exceeding defined criteria.

There were no drop outs because of adverse events associated with urinalysis change for olanzapine-treated patients.

There were no changes is urinary mean values reported.

8.5.3 Vital Signs

The vital sign criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the defined criteria for changes and the table of change in mean baseline for this section.

There were no statistically significant changes in the proportions of patients exceeding defined criteria. Only one patient had a weight gain > 20% and this gain was 35.1%. A weight gain (>10% from baseline) was experienced by 17.6% of olanzapine-treated patients. No vital sign had a change greater than or equal to 10% in olanzapine-treated patients.

The following items were significant among mean baseline changes; weight (Olan > Pla p=.001), standing pulse (Olan > Pla p=.012), pulse-ortho (Olan > Pla p=.035), standing diastolic BP (Olan < Pla p=.026).

There were no drop outs because of adverse events associated with vital sign or weight change for olanzapine-treated patients.

8.5.4 ECGs

The ECG criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the arbitrarily defined criteria for changes and the table of change in mean baseline for this section.

There were no statistically significant changes in the proportions of patients exceeding defined criteria, however olanzapine outnumbered placebo 16.7% vs 7.1% among QTc prolongers in the acute phase of HGEH. See EKG appendix table.

There were no significant parameters among mean baseline changes.

There were no drop outs because of adverse events associated with ECG change for olanzapine-treated patients.

I have reviewed the sponsors table of EKG changes from baseline and the most frequently observed EKG change in olanzapine-treated patients in the integrated database was an increase in the corrected QT interval (23.7%). I have reviewed the line listing of reports of these 14 patients, only 2 experienced a QTc increase to >450 msec, 476 and 463 msec respectively.

There was also an increase in the QRS interval for 13.4% of the patients shown in the sponsor's table of EKG changes. I have reviewed the line listing of reports of the 9 patients with QRS prolongation, 1 patient had a QRS prolongation of 160 msec and the remaining 8 had QRS prolongations equal to 100 msec. There were no potentially clinically significant changes for the remaining ECG intervals and heart rate. Olanzapine-treated patients experienced a statistically significant within-group increase (4.10 bpm) from baseline to endpoint in heart rate.

8.5.5 Special Studies

None done.

8.5.6 Withdrawal Phenomena/Abuse Potential

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. There is no significant change from previous data and recommendations in this section.

8.5.7 Human Reproduction Data

There are no adequate and well-controlled trials with olanzapine in pregnant females. There is no significant change from previous data and recommendations in this section.

8.6 Overdose Experience

There is no significant change from previous data and recommendations in this section.

8.7 Summary of Important Events Considered Drug Related

Weight:

Only one patient had a weight gain > 20% and this gain was 35.1%. A weight gain (>10% from baseline) was experienced by 17.6% of olanzapine-treated patients.

The following items were significant among mean baseline changes; weight (Olan > Pla p=.001).

There were no drop outs because of adverse events associated with weight change for olanzapine-treated patients.

Liver Functions:

Three olanzapine patients had elevated ALTs while no placebo patient did. The ALT mean level across groups was almost doubled in Olanzapine patients with ALT (Olan>Pla) almost significant at p=.053.

EKG:

There were no statistically significant changes in the proportions of patients exceeding defined criteria, however olanzapine outnumbered placebo 16.7% vs 7.1% among QTc prolongers in the acute phase of HGEH. See EKG appendix table.

There were no significant parameters among mean EKG baseline changes.

There were no drop outs because of adverse events associated with ECG change for olanzapine-treated patients.

8.8 Important Events Considered Not Drug Related

Certain events have been discussed elsewhere in this document and have been excluded from this list (i.e., deaths, overdoses, dropouts and changes in laboratory values).

The rest of the serious adverse events are considered not drug related and they are displayed in the Appendix of serious adverse events.

8.9 Summary of Drug Interactions

8.9.1 Drug-Demographic Interactions

The sponsor feels there were no statistically significant treatment-by-subgroup interactions. Subgroup analyses were

performed to examine the consistency of treatment effects over the strata of various demographic populations. The subgroups that were candidates for analysis were gender, racial origin (Caucasian, other), and age (less than 40 years, 40 years or older). A subgroup was analyzed only if the number of patients in each strata was 10 or more. The incidence of treatment-emergent adverse events and treatment-emergent abnormal high or low laboratory values, as well as mean change in vital signs, weight, and ECG heart rate and intervals were examined. A few statistically significant treatment-by-subgroup differences were noted, but none were considered clinically relevant.

8.9.2 Drug-Disease Interactions

There are no new precautions regarding drug-disease interactions.

The sponsor continues to urge cautious use 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). 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 by the sponsor in patients with significant hepatic disease

8.9.3 Drug-Drug Interactions

The sponsor describes two drug interaction studies.

The first study was designed to evaluate the influence of fluoxetine on the pharmacokinetic characteristics of olanzapine. A brief summary provided by the sponsor is presented in italics below.

F1D-MS-HGCI: Pharmacokinetic Interaction of Fluoxetine on Olanzapine

Fifteen healthy, non-smoker volunteers (11 males, 4 females), aged 23 to 40 years, completed an interaction study designed to determine the pharmacokinetics, safety, and potential interaction of a single oral dose of olanzapine 5 mg following a single dose or multiple doses of fluoxetine 60 mg. Plasma concentrations for both drugs, sampled up to 120 hours postdose, were measured by either HPLC/EC (olanzapine) or GC/EC (fluoxetine). Safety was assessed by means of clinical examinations, laboratory tests, and the record of symptoms.

Results: *A small (about 16%) increase in olanzapine Cmax and a small (about 16%) decrease in olanzapine plasma clearance was observed when olanzapine was given with fluoxetine. This result may reflect the known inhibition of CYP2D6 by fluoxetine, and the small magnitude of change thus reflects the minor role of CYP2D6 in the overall metabolic scheme of olanzapine. There were no serious or unexpected adverse events. The most frequent symptoms were dry mouth (6 reports by 2 subjects) and asthenia (4 reports by 2 subjects). At each period, there was a statistically significant time effect for blood pressure and pulse (in supine position); mean blood pressure and pulse in supine position 4 hours after the administration of olanzapine was lower in all periods. There were no clinically significant changes in laboratory data obtained 5 days after olanzapine dosing. No clinically significant changes were observed during the study in liver enzymes (AST, ALT, and GGT).*

Conclusions: *The small pharmacokinetic changes observed in olanzapine Cmax and plasma clearance were statistically significant, but unlikely to be clinically important, and fluoxetine does not modify the safety of olanzapine.*

The sponsor gives a preliminary report on an on-going 2nd study of valproate and olanzapine which is summarized below in italics.

Low-dose valproate (£ 1000 mg daily) administered alone and together with 10 mg olanzapine was safe in each patient enrolled in the study. The pharmacokinetic profile of olanzapine in this study was similar to that captured in the clinical pharmacology data base. No alterations in the pharmacokinetic profile of

olanzapine or in the steady-state concentrations of valproate were apparent. The study is ongoing, and recruitment efforts are continuing.

9.0 Safety Update

The sponsor has provided a safety update of patient data from 01 Jul 97 through a cutoff date of 08 Dec 97. The Bipolar Mania Safety Database for the 4-Month Safety Update comprises 9,526 additional days of olanzapine exposure from the open-label extension of the multicenter study (F1D-MC-HOEH: Olanzapine Versus Placebo In The Treatment Of Mania Associated With Bipolar I Disorder). They also included summaries for patients with serious adverse events, patients discontinued due to adverse events and patients with potentially clinically significant changes in laboratory analytes, vital signs, weight or electrocardiograms (ECG' s) occurring between 01 Jul 97 and 08 Dec 97. All calculations were performed using the last visit before initiation of open-label olanzapine therapy as baseline.

Deaths

There were no deaths reported in the safety update.

Dropouts

There were 3 new dropouts due to depression, drug dependence and unintended pregnancy.

Serious Adverse Events

There were 11 new SAEs reported. 10 were due to psychiatric symptoms worsening and one was for elevated liver function tests which returned to baseline after the patient dropped out.

Significant Laboratory Findings

Sections on laboratory values and vital signs were updated without significant change from the 10/3/97 submission. Of note 5 new patients had elevated QTc ranging from 442--461 msec.

I reviewed the narratives provided for all patients with significant findings listed above. There are no narratives of particular interest.

10.0 Labeling Review

I will go through the new labeling section by section with comments about changes.

CLINICAL EFFICACY DATA: BIPOLAR MANIA
INDICATIONS AND USAGE:

I believe these sections are not appropriate in their conclusion. The studies could be described with appropriate language regarding the homogeneity of the population treated and the subgroup analysis. The weak nature of the response to treatment would also need to be stressed.

THE EFFECT OF OTHER DRUGS ON OLANZAPINE

The two new drug interaction studies have been appropriately described.

ADVERSE REACTIONS

This section is updated for the increased database with certain disclaimers for analyses done only for the psychotic database and believed to be generally applicable to the bipolar patients. Tables have been updated with the bipolar patients added.

ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATIONS

This section is updated correctly with the bipolar data.

MOST COMMON TREATMENT EMERGENT ADVERSE EVENTS

This section is updated correctly with the bipolar data.

b(4)

DOSAGE

The section now has a bipolar mania dosage section.

There are minor corrections of the text in other places which are technical in nature and not of clinical significance.

11.0 Conclusions

Olanzapine is safe when used in patients seen in this database. The efficacy of olanzapine in bipolar patients is not established due to concerns that the patients in these studies are not a true group of homogeneous bipolar patients (see 7.3.1 subgroup analysis) and associated evidence that olanzapine does not treat anything other than non-specific symptoms seen in these patients. The treatment effect is minimal (see 7.3.2) and the factor analysis of the YMRS items also indicates that olanzapine is most effective with general psychotic symptoms. One study is arguable mildly positive while an identically designed study is negative showing only a statistically significant effect on the PANNS but not on the primary efficacy variable (Y-MRS).

12.0 Recommendations

I recommend that olanzapine not be approved for the acute treatment of bipolar mania or mixed episodes.

Earl D. Hearst, M.D. 8/24/98

Earl D. Hearst, M.D.
Medical Reviewer

9-11-98
I agree that this supplement is nonapprovable. No memo to file for detailed comments.
J. Laughren, MD
TL, DAP

cc: Orig NDA 20-592/S-006
HFD-120/Div File
HFD-120/TLaughren
EHearst
DBates

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Table 1 **Investigator List**
Study F1D-MC-HGEH

Investigator #	Patient Block	Investigator/Address
1	1001-1050	Lori L. Altshuler, M.D.
		Director, Mood Disorders Research
		Department of Veterans Affairs Medical Center
		11301 Wilshire Blvd.
		Bldg. 158, Room 202 B-116/A12
		Los Angeles, CA 90073
2	1051-1100	Richard Wang, M.D., Ph.D.
		MedStream Inc.
		4608 W. Burleigh Street
		Milwaukee, WI 53210
3	1101-1150	K. N. Roy Chengappa, M.D.
		Western Psychiatric Institute and Clinic
		U of Pittsburgh Medical Center
		3811 O'Hara St.
		Pittsburgh, PA 15213-2593
		Mayview State Hospital
		1601 Mayview Road
		Bridgeville, PA 15017
		Aliquippa Hospital MH Services
		178 Virginia Avenue
		Rochester, PA 15074
4	1151-1200	David G. Daniel, M.D.
		Washington Clinical Research Center
		Neuro-Psychiatric Services, Greater Washington
		6404-P Seven Corners Place
		Falls Church, VA 22044
5	1201-1250	Jan Fawcett, M.D.
		Rush Institute for Mental Well-Being
		1725 West Harrison St., Suite 955
		Chicago, IL 60612-3824

Table 1 **Investigator List**
Study F1D-MC-HGEH

Investigator	Patient Block	Investigator/Address
6	1251-1300	Alan J. Gelenberg, M.D. University of Arizona Arizona Health Sciences Center Dept. of Psychiatry, Room 7402 1501 N. Campbell Tucson, AZ 85724-5002
7	1301-1350	James Russell, M.D. Dept. of Psychiatry and Behavioral Sciences The University of Texas Medical Branch at Room 1.200 Graves Building 301 University Boulevard Galveston, TX 77555-0428
8	1351-1400	Philip G. Janicak, M.D. The Psychiatric Institute UIC Department of Psychiatry 1601 West Taylor Street, M/C 912 Chicago, IL 60612-4397
9	1401-1450	Robert Levine, M.D. 1236 Park Avenue New York, NY 10128
10	1451-1500	Susan L. McElroy, M.D. Director, Biological Psychiatry Program University of Cincinnati College of Medicine 231 Bethesda Avenue, Suite 7005 Cincinnati, OH 45267
11	1501-1550	Frederick Petty, M.D., Ph. D. Veterans Administration Medical Center Building 1 Room 143, (116A) 4500 South Lancaster Road Dallas, TX 75216

Table 1 **Investigator List**
Study F1D-MC-HGEH

Investigator	Patient Block	Investigator/Address
12	1551-1600	Charles B. Nemeroff, M.D. Emory University School of Medicine Department of Psychiatry 1701 Uppergate Drive 4th floor, Room 408 Atlanta, GA 30322
		Fox Recovery Services Dekalb Mental Health Center 3100 Clifton Springs Road Decatur, GA 30034
13	1601-1650	S. Craig Risch, M.D. Medical University of South Carolina Clin. Neuro. Pharm. Research Program Institute of Psychiatry, 502N 171 Ashley Avenue Charleston, SC 29425-0742
14	1651-1700	Norman Sussman, M.D. Department of Psychiatry NYU Medical Center 550 First Avenue NB 19-North New York, NY 10016
15	1701-1750	Alan C. Swann, M.D. U of Texas Mental Sciences Institute 1300 Moursund Avenue, Room 270 Houston, TX 77030
16	1751-1800	Franca Centorrino, M.D. Bipolar and Psychotic Disorders Program McLean Hospital 115 Mill Street Belmont, MA 02178-9106

Table 2 Investigator List
Study F1D-UT-HGES

Principal Investigator	W.A. Nolen, M.D., Ph.D. General Psychiatric Hospital Willem Arntsz Huis Vrouwjuttenhof 18 3512 PZ Utrecht The Netherlands
Sub-investigators	b(4)

Table32 Investigator List
Study F1D-MC-HGET

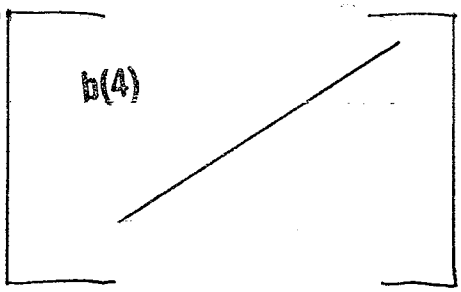
Principal Investigator	Philip Wilner, M.D. Assistant Professor of Psychiatry New York Hospital Payne Whitney Clinic 525 E. 68th Street Box 147 New York, NY 10021 Phone: (212) 821-0792 FAX: (212) 821-0987
Sub-investigators	b(4) 
Study Coordinator	b(4) New York Hospital Payne Whitney Clinic 525 E. 68th Street Box 147 New York, NY 10021 b(4) FAX: (212) 821-0792 Home: b(6)

Table HGEH.9.4. Schedule of Events
F1D-MC-HGEH

Schedule of Events: F1D-MC-HGEH

Description of Data	V1	V2	V3	V4	V5	V301	V302	V303	V304	V305	V306	V307	V308	V309	V310	V311	V312	V313	V314	315/ Final	Follow-up (501)
Weeks until next visit	2-4d	1	1	1	1	2	2	2	2	4	4	4	4	4	4	4	4	4	4	4[a]	
Informed consent, demographics, height	X																				
Kit number assigned		X																			
Weight, temperature, blood pressure, heart rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Psychiatric examination	X																				
Physical examination and electrocardiography	X		X[f]	X[f]	X[f]								X						X	X	
Preexisting conditions and adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Historical illnesses and previous medications	X																				
Habits	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug dispensed		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[a]	
Concomitant medications	X	X	X	X	X	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	X	X	X	X	X	
Adverse event follow-up, if necessary																					X
Patient summary, including comments																				X	
Clinical chemistry	X	X	X	X	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X[b]	X[b]	X[b]	X[b]	X[b]	X	X	
Electrolyte group, hematology, urinalysis	X	X	X	X	X								X						X	X	
Thyroid function, hepatitis[c], pregnancy screen[d]	X																				
Urine drug screen[e]	X		X[f]	X[f]	X[f]			X		X	X	X	X	X	X	X	X	X	X	X	

(continued)

Table HGEH.9.4. (Concluded) Schedule of Events F1D-MC-HGEH

Schedule of Events: F1D-MC-HGEH

Description of Data	V1	V2	V3	V4	V5	V301	V302	V303	V304	V305	V306	V307	V308	V309	V310	V311	V312	V313	V314	315/ Final	Follow-up (501)
Weeks until next visit	2-4d	1	1	1	1	2	2	2	2	4	4	4	4	4	4	4	4	4	4	4[a]	
Y-MRS, PANSS, HAMD-21, CGI-BP severity	X	X	X	X	X	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	X	X	X	X	X	
SF-36, Resource Utilization questionnaire		X	X[f]	X[f]	X[f]							X				X				X	

Abbreviations: d = days; V = Visit.

a Following Visit 315 (1 year of open-label olanzapine therapy), if olanzapine was not commercially available, patients could continue in the study until olanzapine became commercially available.

b At these visits, unless clinically indicated by the physician, only the following laboratory tests were performed: AST/SGOT, ALT/SGPT, total bilirubin, alkaline phosphatase, and GGT.

c Any patient whose AST/SGOT, ALT/SGPT, GGT, total bilirubin, or alkaline phosphatase value exceeded the upper limit of the reference range established by Eli Lilly and Company could have had the following tests performed: IgM anti-HAV, HBsAg, and anti-HCVab.

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

e Also was performed at any time a patient relapsed (see Section 9.5.3 for the definition of symptomatic relapse).

f Final visit of Study Period II (Visit 3, 4 or 5).

Table HGEH.11.51. Physical Characteristics
F1D-MC-HGEH Study 1, Acute Phase

Variable	Placebo (N=36)	Olz (N=36)	Total (N=72)	p-Value
Sex: No. (%)				
No. Patients	36	36	72	.814*
Male	19 (52.8)	17 (47.2)	36 (50.0)	
Female	17 (47.2)	19 (52.8)	36 (50.0)	
Origin: No. (%)				
No. Patients	36	36	72	.767*
Caucasian	27 (75.0)	30 (83.3)	57 (79.2)	
African Descent	8 (22.2)	5 (13.9)	13 (18.1)	
Hispanic	1 (2.8)	1 (2.8)	2 (2.8)	
Age:yrs.				
No. Patients	36	36	72	.668**
Mean	35.87	41.67	38.77	
Median	35.77	41.38	39.03	
Standard Dev.	10.41	12.21	11.64	
Minimum	18.88	20.78	18.88	
Maximum	62.58	64.48	64.48	

RMP.F1DP.JCLLIB(ASBSAEH)
RMP.F1DP.SASMACRO(SBASEA)
* Frequencies are analyzed using a Fisher's exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=investigator, treatment, and interaction.
XDES0001

Patient Completion Rates

F1D-MC-HGEH Acute Phase, Study 1

Treatment Group	N	n[a]	Number (%) of Patients Completing[b]		
			Week 1	Week 2	Week 3
Placebo	36	33	36 (100.0)	21 (58.3)	14 (38.9)
Olz	36	36	36 (100.0)	26 (72.2)	23 (63.9)

a Number of patients with baseline and postbaseline Y-MARS total score

b Number of patients with a visit in the corresponding week or the number of patients designated as completing the acute phase

Table HGEH.10.8. Patient Disposition
F1D-MC-HGEH Study 1, Acute Phase

Reason for Discontinuation	Placebo (N=36) n (%)	Olz (N=36) n (%)	Total (N=72) n (%)	p-Value*
Reporting Interval Complete	14 (38.9)	23 (63.9)	37 (51.4)	.059
Adverse Event	2 (5.6)	0	2 (2.8)	.493
Lack of Efficacy	16 (44.4)	9 (25.0)	25 (34.7)	.137
Lost to Follow-up	1 (2.8)	0	1 (1.4)	1.00
Patient Decision	1 (2.8)	4 (11.1)	5 (6.9)	.357
Sponsor Decision	1 (2.8)	0	1 (1.4)	1.00
Physician Decision	1 (2.8)	0	1 (1.4)	1.00

Patients included in the reasons discontinued, Reporting Interval Complete and Lack of Efficacy, may have continued into the next reporting interval or discontinued from the study.
RMP.F1DP.SASMACRO(SPATDA)
RMP.F1DP.JCLLIB(ASPTDAEH)
* Frequencies analyzed using the Fisher's Exact Test
XRDS0001

Table HGEH.10.9. Patient Disposition by Visit
F1D-MC-HGEH Study 1, Acute Phase

Treatment Group: Placebo
Number of patients in the therapy group: (N=36)

Reason for Discontinuation	Visit 3 n (%)	Visit 4 n (%)	Visit 5 n (%)
Reporting Interval Complete	0	0	14 (38.9)
Adverse Event	1 (2.8)	1 (2.8)	0
Lack of Efficacy	10 (27.8)	6 (16.7)	0
Lost to Follow-up	1 (2.8)	0	0
Patient Decision	1 (2.8)	0	0
Sponsor Decision	1 (2.8)	0	0
Physician Decision	1 (2.8)	0	0
Patients continuing	21 (58.3)	14 (38.9)	0

Patients included in the reasons discontinued, Reporting Interval Complete and Lack of Efficacy, may have continued into the next reporting interval or discontinued from the study.
RMP.F1DP.JCLLIB(ASPTDBEH)
RMP.F1DP.SASMACRO(SPATDB)
XRDS0002

Treatment Group: Olz
Number of patients in the therapy group: (N=36)

Reason for Discontinuation	Visit 3 n (%)	Visit 4 n (%)	Visit 5 n (%)
Reporting Interval Complete	0	0	23 (63.9)
Lack of Efficacy	7 (19.4)	2 (5.6)	0
Patient Decision	3 (8.3)	1 (2.8)	0
Patients continuing	26 (72.2)	23 (63.9)	0

Patients included in the reasons discontinued, Reporting Interval Complete and Lack of Efficacy, may have continued into the next reporting interval or discontinued from the study.
RMP.F1DP.JCLLIB(ASPTDBEH)
RMP.F1DP.SASMACRO(SPATDB)
XRDS0002

Table HGEH.11.98. Modal Drug Dosage
F1D-MC-HGEH Study 1, Acute Phase

	Olanzapine
Number of Patients (%)	
5.0 mg	1 (2.8%)
10.0 mg	7 (19.4%)
15.0 mg	10 (27.8%)
20.0 mg	18 (50.0%)
Total	36
Dosage (mg)	
Mean	16.3
Median	17.5
Std. Dev.	4.4

RMP.F1DP.HGEHJCL(ASMDB2EH)
RMP.F1DP.SASMACRO(SMEDSB)

Table HGEH.11.55. Concomitant Medications Reported by at Least 10% of Patients F1D-MC-HGEH Study 1, Acute Phase

Drug Name	Placebo (N=36) n (%)	Olz (N=36) n (%)	Total (N=72) n (%)	p-Value*
PATIENTS WITH >= 1 DRUG	36 (100)	34 (94.4)	70 (97.2)	.493
PATIENTS WITH NO DRUGS	0	2 (5.6)	2 (2.8)	.493
IBUPROFEN	8 (22.2)	3 (8.3)	11 (15.3)	.189
LEVOTHYROXINE SODIUM	3 (8.3)	6 (16.7)	9 (12.5)	.478
LORAZEPAM	31 (86.1)	32 (88.9)	63 (87.5)	1.00
PARACETAMOL	17 (47.2)	22 (61.1)	39 (54.2)	.344

P-value obtained from the Fisher's exact test
RMP.F1DP.JCLLIB(ASMDFEH)
RMP.F1DP.SASMACRO(SMEDSF)
XDTS0001

Table HGEH.11.82. Y-MRS Total Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-4.36	10.50	36	-6.33	10.27
4	2	33	-4.15	11.00	36	-7.03	13.89
5	3	33	-4.55	11.57	36	-9.94	14.62

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.795	.962
4	2	.550	.469
5	3	.177	.461

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

Table HGEH.11.74. Y-MRS Total Score
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-4.36	10.50	36	-6.33	10.27
4	2	21	-9.14	9.75	26	-11.19	13.81
5	3	14	-14.29	8.87	23	-18.48	10.20

p-Values*1

Visit	Week	Overall
3	1	.513
4	2	.507
5	3	.202

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.86. CGI-BP Severity of Overall Bipolar Illness
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-0.58	1.15	36	-0.44	0.97
4	2	33	-0.61	1.22	36	-0.56	1.21
5	3	33	-0.58	1.32	36	-0.86	1.51

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.831	.898
4	2	.839	.150
5	3	.629	.400

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

HGEH.11.78. CGI-BP Severity of Overall Bipolar Illness
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-0.58	1.15	36	-0.44	0.97
4	2	21	-1.14	1.20	26	-0.96	1.15
5	3	14	-1.50	1.34	23	-1.70	1.22

p-Values*1

Visit	Week	Overall
3	1	.535
4	2	.714
5	3	.530

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.84. CGI-BP Severity of Mania
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 1, Acute Phase

Visit	Week	Placebo (1) n	Mean	SD	Olz (2) n	Mean	SD
3	1	33	-0.48	1.00	36	-0.36	0.96
4	2	33	-0.52	1.25	36	-0.61	1.32
5	3	33	-0.45	1.42	36	-1.03	1.68

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.573	.985
4	2	.789	.175
5	3	.276	.403

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

HGEH.11.76. CGI-BP Severity of Mania
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-0.48	1.00	36	-0.36	0.96
4	2	21	-1.00	1.30	26	-1.08	1.23
5	3	14	-1.36	1.69	23	-1.96	1.30

p-Values*1

Visit	Week	Overall
3	1	.470
4	2	.819
5	3	.168

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.83. HAMD-21 Total Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	32	-2.22	5.60	35	-3.37	4.87
4	2	32	-1.66	6.06	35	-2.80	5.91
5	3	32	-1.88	6.01	35	-2.17	6.11

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.780	.484
4	2	.843	.201
5	3	.972	.606

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

HGEH.11.75. HAMD-21 Total Score
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	32	-2.22	5.60	35	-3.37	4.87
4	2	21	-2.00	5.85	26	-3.81	6.34
5	3	14	-3.14	5.17	23	-3.61	6.26

p-Values*1

Visit	Week	Overall
3	1	.430
4	2	.393
5	3	.771

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.87. PANSS Total Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	31	-1.35	15.14	36	-8.25	11.81
4	2	31	1.97	14.94	36	-7.81	15.32
5	3	31	1.68	17.34	36	-9.64	16.06

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.162	.740
4	2	.038	.230
5	3	.028	.380

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

HGEH.11.79. PANSS Total Score
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	31	-1.35	15.14	36	-8.25	11.81
4	2	21	-1.10	15.39	26	-11.46	15.58
5	3	14	-4.43	21.86	23	-16.22	15.27

p-Values*1

Visit	Week	Overall
3	1	.033
4	2	.028
5	3	.079

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.88. PANSS Positive Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	31	-1.16	6.69	36	-3.11	5.14
4	2	31	-0.90	6.81	36	-2.94	6.61
5	3	31	-0.74	7.09	36	-4.06	7.07

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.486	.599
4	2	.331	.099
5	3	.150	.127

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

HGEH.11.80. PANSS Positive Score
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	31	-1.16	6.69	36	-3.11	5.14
4	2	21	-2.52	6.79	26	-4.19	7.01
5	3	14	-4.00	8.08	23	-7.13	6.45

p-Values*1

Visit	Week	Overall
3	1	.166
4	2	.421
5	3	.175

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.89. PANSS Negative Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	31	0.03	2.94	36	-1.17	2.38
4	2	31	1.39	3.89	36	-1.33	3.00
5	3	31	0.90	4.55	36	-1.25	3.18

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.077	.793
4	2	.009	.665
5	3	.034	.889

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

HGEH.11.81. PANSS Negative Score
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	31	0.03	2.94	36	-1.17	2.38
4	2	21	1.38	4.07	26	-1.65	3.02
5	3	14	0.00	5.63	23	-1.35	3.37

p-Values*1

Visit	Week	Overall
3	1	.083
4	2	.010
5	3	.499

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.85. CGI-BP Severity of Depression
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-0.27	0.94	36	0.11	0.57
4	2	33	-0.24	1.17	36	0.19	0.95
5	3	33	-0.27	1.23	36	0.19	0.98

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.248	.704
4	2	.344	.574
5	3	.345	.752

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

HGEH.11.77. CGI-BP Severity of Depression
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 1, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-0.27	0.94	36	0.11	0.57
4	2	21	-0.38	1.40	26	0.23	1.07
5	3	14	-0.57	1.70	23	0.04	0.82

p-Values*1

Visit	Week	Overall
3	1	.031
4	2	.129
5	3	.160

The following investigators were pooled: (005, 006)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.99. Physical Characteristics
F1D-MC-HGEH Study 2, Acute Phase

Variable	Placebo (N=33)	Olz (N=34)	Total (N=67)	p-Value
Sex: No. (%)				
No. Patients	33	34	67	1.00*
Male	18 (54.5)	18 (52.9)	36 (53.7)	
Female	15 (45.5)	16 (47.1)	31 (46.3)	
Origin: No. (%)				
No. Patients	33	34	67	.900*
Caucasian	21 (63.6)	23 (67.6)	44 (65.7)	
African Descent	7 (21.2)	8 (23.5)	15 (22.4)	
Hispanic	4 (12.1)	3 (8.8)	7 (10.4)	
Other Origin	1 (3.0)	0	1 (1.5)	
Age:yrs.				
No. Patients	33	34	67	.603**
Mean	41.83	38.75	40.27	
Median	41.76	38.24	41.30	
Standard Dev.	9.49	10.88	10.26	
Minimum	20.63	18.15	18.15	
Maximum	62.43	60.49	62.43	

RMP.F1DP.JCLLIB(ASBSAEH)
RMP.F1DP.SASMACRO(SBASEA)
* Frequencies are analyzed using a Fisher's exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=investigator, treatment, and interaction.
XDES0001

Patient Completion Rates

F1D-MC-HGEH Acute Phase, Study 2

Treatment Group	N	n[a]	Number (%) of Patients Completing[b]		
			Week 1	Week 2	Week 3
Placebo	33	33	33 (100.0)	17 (51.1)	10 (30.3)
Olz	34	34	34 (100.0)	26 (76.5)	20 (58.8)

a Number of patients with baseline and postbaseline Y-MARS total score

b Number of patients with a visit in the corresponding week or the number of patients designated as completing the acute phase

Table HGEH.10.13. Patient Disposition
F1D-MC-HGEH Study 2, Acute Phase

Reason for Discontinuation	Placebo (N=33) n (%)	Olz (N=34) n (%)	Total (N=67) n (%)	p-Value*
Reporting Interval Complete	10 (30.3)	20 (58.8)	30 (44.8)	.027
Lack of Efficacy	17 (51.5)	11 (32.4)	28 (41.8)	.141
Patient Decision	3 (9.1)	2 (5.9)	5 (7.5)	.673
Criteria not met / Compliance	1 (3.0)	1 (2.9)	2 (3.0)	1.00
Sponsor Decision	2 (6.1)	0	2 (3.0)	.239

Patients included in the reasons discontinued, Reporting Interval Complete and Lack of Efficacy, may
have continued into the next reporting interval or discontinued from the study.
RMP.F1DP.SASMACRO(SPATDA)
RMP.F1DP.JCLLIB(ASPTDAEH)
* Frequencies analyzed using the Fisher's Exact Test
XRDS0001

Table HGEH.10.14. Patient Disposition by Visit
Olz Treatment Group
F1D-MC-HGEH Study 2, Acute Phase

Treatment Group: Placebo
Number of patients in the therapy group: (N=33)

Reason for Discontinuation	Visit 3 n (%)	Visit 4 n (%)	Visit 5 n (%)
Reporting Interval Complete	0	0	10 (30.3)
Lack of Efficacy	12 (36.4)	5 (15.2)	0
Patient Decision	1 (3.0)	2 (6.1)	0
Criteria not met / Compliance	1 (3.0)	0	0
Sponsor Decision	2 (6.1)	0	0
Patients continuing	17 (51.5)	10 (30.3)	0

Patients included in the reasons discontinued, Reporting Interval Complete and Lack of Efficacy, may have continued into the next reporting interval or discontinued from the study.
RMP.F1DP.JCLLIB(ASPTDBEH)
RMP.F1DP.SASMACRO(SPATDB)
XRDS0002

Treatment Group: Olz
Number of patients in the therapy group: (N=34)

Reason for Discontinuation	Visit 3 n (%)	Visit 4 n (%)	Visit 5 n (%)
Reporting Interval Complete	0	0	20 (58.8)
Lack of Efficacy	6 (17.6)	5 (14.7)	0
Patient Decision	1 (2.9)	1 (2.9)	0
Criteria not met / Compliance	1 (2.9)	0	0
Patients continuing	26 (76.5)	20 (58.8)	0

Patients included in the reasons discontinued, Reporting Interval Complete and Lack of Efficacy, may have continued into the next reporting interval or discontinued from the study.
RMP.F1DP.JCLLIB(ASPTDBEH)
RMP.F1DP.SASMACRO(SPATDB)
XRDS0002

Table HGEH.11.146. Modal Drug Dosage
F1D-MC-HGEH Study 2, Acute Phase

	Olanzapine	
Number of Patients (%)		
0.0 mg	2	(5.9%)
10.0 mg	13	(38.2%)
15.0 mg	10	(29.4%)
20.0 mg	9	(26.5%)
Total	34	
Dosage (mg)		
Mean	13.5	
Median	15.0	
Std. Dev.	5.3	

RMP.F1DP.HGEHJCL(ASMDB2EH)
RMP.F1DP.SASMACRO(SMEDSB)

Table HGEH.11.103. Concomitant Medications Reported by at Least 10% of Patients F1D-MC-HGEH Study 2, Acute Phase

Drug Name	Placebo (N=33) n (%)	Olz (N=34) n (%)	Total (N=67) n (%)	p-Value*
PATIENTS WITH >= 1 DRUG	32 (97.0)	33 (97.1)	65 (97.0)	1.00
PATIENTS WITH NO DRUGS	1 (3.0)	1 (2.9)	2 (3.0)	1.00
IBUPROFEN	5 (15.2)	9 (26.5)	14 (20.9)	.369
LORAZEPAM	27 (81.8)	30 (88.2)	57 (85.1)	.512
PARACETAMOL	13 (39.4)	13 (38.2)	26 (38.8)	1.00

P-value obtained from the Fisher's exact test
RMP.F1DP.JCLLIB(ASMDFEH)
RMP.F1DP.SASMACRO(SMEDSF)
XDTS0001

Table HGEH.11.130. Y-MRS Total Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-5.79	10.62	34	-10.38	9.32
4	2	33	-4.97	11.18	34	-10.38	12.19
5	3	33	-5.21	11.87	34	-10.59	12.25

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.169	.738
4	2	.046	.112
5	3	.046	.239

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

HGEH.11.122. Y-MRS Total Score
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-5.79	10.62	34	-10.38	9.32
4	2	16	-10.50	10.58	26	-12.35	12.34
5	3	10	-16.10	8.58	19	-18.26	7.44

p-Values*1

Visit	Week	Overall
3	1	.086
4	2	.488
5	3	.553

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.132. CGI-BP Severity of Mania
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-0.42	1.20	34	-1.00	1.13
4	2	33	-0.45	1.23	34	-1.12	1.43
5	3	33	-0.52	1.35	34	-1.12	1.53

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.030	.068
4	2	.006	.001
5	3	.020	.034

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

HGEH.11.124. CGI-BP Severity of Mania
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-0.42	1.20	34	-1.00	1.13
4	2	17	-1.12	1.05	26	-1.35	1.41
5	3	10	-1.70	1.25	18	-1.67	1.03

p-Values*1

Visit	Week	Overall
3	1	.043
4	2	.653
5	3	.893

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.134. CGI-BP Severity of Overall Bipolar Illness
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-0.48	1.00	34	-1.00	0.98
4	2	33	-0.55	1.18	34	-0.94	1.30
5	3	33	-0.61	1.30	34	-0.91	1.26

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.030	.068
4	2	.052	.012
5	3	.101	.077

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

HGEH.11.126. CGI-BP Severity of Overall Bipolar Illness
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-0.48	1.00	34	-1.00	0.98
4	2	17	-1.18	1.19	26	-1.12	1.31
5	3	10	-1.90	1.29	18	-1.39	0.70

p-Values*1

Visit	Week	Overall
3	1	.035
4	2	.724
5	3	.278

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.135. PANSS Total Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-8.67	17.72	34	-12.15	16.82
4	2	33	-7.94	18.82	34	-13.18	18.58
5	3	33	-7.58	18.43	34	-12.56	18.02

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.600	.882
4	2	.228	.296
5	3	.271	.519

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

Table HGEH.11.127. PANSS Total Score
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-8.67	17.72	34	-12.15	16.82
4	2	16	-17.56	16.97	25	-17.36	16.06
5	3	10	-23.30	16.22	19	-21.37	11.97

p-Values*1

Visit	Week	Overall
3	1	.498
4	2	.895
5	3	.685

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.136. PANSS Positive Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-3.33	6.63	34	-4.50	5.25
4	2	33	-3.58	7.08	34	-5.38	6.27
5	3	33	-3.18	7.01	34	-5.32	6.04

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.476	.554
4	2	.118	.020
5	3	.146	.289

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

le HGEH.11.128. PANSS Positive Score
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-3.33	6.63	34	-4.50	5.25
4	2	16	-6.31	6.72	25	-6.24	5.33
5	3	10	-8.00	7.27	19	-7.84	4.11

p-Values*1

Visit	Week	Overall
3	1	.657
4	2	.982
5	3	.685

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.137. PANSS Negative Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-1.42	3.66	34	-1.56	4.67
4	2	33	-1.42	3.71	34	-1.12	5.47
5	3	33	-1.21	3.68	34	-0.53	5.18

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.795	.901
4	2	.622	.883
5	3	.362	.769

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

le HGEH.11.129. PANSS Negative Score
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-1.42	3.66	34	-1.56	4.67
4	2	16	-3.38	3.32	25	-1.64	5.94
5	3	10	-3.30	4.32	19	-1.63	4.88

p-Values*1

Visit	Week	Overall
3	1	.984
4	2	.326
5	3	.623

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.131. HAMD-21 Total Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-3.88	5.58	34	-5.35	6.36
4	2	33	-3.82	5.66	34	-3.94	7.26
5	3	33	-4.09	5.86	34	-3.65	7.35

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.453	.789
4	2	.736	.890
5	3	.845	.955

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

le HGEH.11.123. HAMD-21 Total Score
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-3.88	5.58	34	-5.35	6.36
4	2	16	-6.06	5.94	26	-4.92	8.01
5	3	10	-9.60	5.70	19	-6.21	6.30

p-Values*1

Visit	Week	Overall
3	1	.285
4	2	.791
5	3	.384

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.11.133. CGI-BP Severity of Depression
Visitwise Change from Baseline (LOCF)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-0.24	0.79	34	-0.47	0.79
4	2	33	-0.30	1.02	34	-0.29	1.06
5	3	33	-0.33	1.08	34	-0.09	1.33

p-Values*1

Visit	Week	Overall	Inter-action
3	1	.344	.938
4	2	.879	.342
5	3	.262	.244

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction for the interaction and overall p-Value.

e HGEH.11.125. CGI-BP Severity of Depression
Visitwise Change from Baseline (OC)
F1D-MC-HGEH Study 2, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	33	-0.24	0.79	34	-0.47	0.79
4	2	17	-0.59	1.12	26	-0.35	1.20
5	3	10	-1.00	1.41	18	-0.06	1.51

p-Values*1

Visit	Week	Overall
3	1	.326
4	2	.565
5	3	.190

The following investigators were pooled: (001, 015)
RMP.F1DP.JCLLIB(ASEFBEH3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table HGEH.14.239. Listing of Adverse Events Reported as Reason for Discontinuation F1D-MC-HGEH, Open-Label Phase

Drug *1	Study	Inv.	Patient	Age *2	Sex	Visit	Event Onset Date	Dose *3	Days on Drug	Event Classification Term
OLANZAPINE	HGEH	004	1159	40	M	309	1997-06-25	5	171	ACCIDENTAL INJURY
OLANZAPINE	HGEH	004	1168	35	F	306	1997-06-13	20	70	HYPERGLYCEMIA
OLANZAPINE	HGEH	014	1655	46	F	301	1997-03-21	10	4	HOSTILITY

*1 Drug taken at Event Onset
*2 Age at Study Admission
*3 Dose taken at Event Onset

RMP.F1DP.JCLLIB(NLSFA1EH)

Table HGEH.14.240. Listing of Potentially Clinically Significant Adverse Events F1D-MC-HGEH, Open-Label Phase

Drug *1	Study	Inv.	Patient	Age *2	Sex	Visit	Event Onset Date	Dose *1 *3	Days on Drug	Event Classification Term
OLANZAPINE	HGEH	004	1157	38	M	301	1997-01-06	10.0	28	DELIRIUM

*1 at Event Onset
*2 at Study Admission, *3 W=Washout

RMP.F1DP.JCLLIB(NLSFB5EH)
RMP.F1DP.SASMACRO(LSAFEB5)

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Table ISS.9.4. Listing of Serious Adverse Events Sorted by Patient Bipolar Overall Integrated Database

Drug at Event Onset	Event Classification Term	Study	Inv.	Patient	Age[a]	Sex	Dose at event onset[b] (mg/day)	Days on Drug at Event Onset	Event Onset Date[c]	Randomization Date
Olanzapine	Accidental Overdose	HGEH	003	1101	28	M	20	71	1997-02-15	1996-12-07
Olanzapine	Euphoria	HGEH	003	1101	28	M	20	71	1997-02-15	1996-12-07
Olanzapine	Insomnia	HGEH	003	1101	28	M	20	71	1997-02-15	1996-12-07
Olanzapine	Thinking Abnormal	HGEH	003	1101	28	M	20	71	1997-02-15	1996-12-07
Olanzapine	Thinking Abnormal	HGEH	003	1101	28	M	20	71	1997-02-15	1996-12-07
Olanzapine	Accidental Overdose	HGEH	003	1104	43	F	20	21	1997-02-25	1997-01-24
Olanzapine	Agitation	HGEH	003	1104	43	F	20	20	1997-02-24	1997-01-24
Olanzapine	Agitation	HGEH	003	1104	43	F	20	81	1997-04-26	1997-01-24
Olanzapine	Delusions	HGEH	003	1104	43	F	20	81	1997-04-26	1997-01-24
Olanzapine	Hostility	HGEH	003	1104	43	F	20	81	1997-04-26	1997-01-24
Olanzapine	Insomnia	HGEH	003	1104	43	F	20	21	1997-02-25	1997-01-24
Olanzapine	Nervousness	HGEH	003	1104	43	F	20	20	1997-02-24	1997-01-24
Olanzapine	Personality Disorder	HGEH	003	1104	43	F	20	81	1997-04-26	1997-01-24
Olanzapine	Thinking Abnormal	HGEH	003	1104	43	F	20	81	1997-04-26	1997-01-24
Olanzapine	Thinking Abnormal	HGEH	003	1104	43	F	20	81	1997-04-26	1997-01-24
Olanzapine	Thinking Abnormal	HGEH	003	1104	43	F	20	81	1997-04-26	1997-01-24
Olanzapine	Twitching	HGEH	003	1104	43	F	20	81	1997-04-26	1997-01-24
Olanzapine	Depression	HGEH	003	1105	39	F	20	25	1997-03-22	1997-02-06
Olanzapine	Emotional Lability	HGEH	003	1105	39	F	20	25	1997-03-22	1997-02-06
Olanzapine	Hallucinations	HGEH	003	1105	39	F	20	27	1997-03-24	1997-02-06
Olanzapine	Personality Disorder	HGEH	003	1105	39	F	20	25	1997-03-22	1997-02-06
Olanzapine	Thinking Abnormal	HGEH	003	1105	39	F	20	25	1997-03-22	1997-02-06
Olanzapine	Abdominal Pain	HGEH	004	1152	30	F	20	45	1997-01-26	1996-11-22

(continued)

Table ISS.9.4. (Continued) Listing of Serious Adverse Events Sorted by Patient Bipolar Overall Integrated Database

Drug at Event Onset	Event Classification Term	Study	Inv.	Patient	Age[a]	Sex	Dose at event onset[b] (mg/day)	Days on Drug at Event Onset	Event Onset Date[c]	Randomization Date
Olanzapine	Cholecystitis	HGEH	004	1152	30	F	20	45	1997-01-26	1996-11-22
Olanzapine	Surgical Procedure[d]	HGEH	004	1152	30	F	20	49	1997-02-05	1996-11-22
Olanzapine	Addiction	HGEH	004	1157	38	M	10	26	1997-01-04	1996-12-10
Olanzapine	Agitation	HGEH	004	1157	38	M	10	26	1997-01-04	1996-12-10
Olanzapine	Confusion	HGEH	004	1157	38	M	10	26	1997-01-04	1996-12-10
Olanzapine	Accidental Injury	HGEH	004	1159	40	M	5	171	1997-06-25	1996-12-20
Olanzapine	Anxiety	HGEH	004	1159	40	M	5	171	1997-06-25	1996-12-20
Olanzapine	Sleep Disorder	HGEH	004	1159	40	M	15	166	1997-06-20	1996-12-20
Olanzapine	Agitation	HGEH	004	1161	36	M	15	108	1997-04-19	1997-01-02
Olanzapine	Alcohol Intolerance	HGEH	004	1161	36	M	15	108	1997-04-19	1997-01-02
Olanzapine	Confusion	HGEH	004	1161	36	M	15	108	1997-04-19	1997-01-02
Olanzapine	Intentional Injury	HGEH	004	1161	36	M	15	108	1997-04-19	1997-01-02
Olanzapine	Depression	HGEH	004	1167	34	F	20	37	1997-05-13	1997-03-17
Olanzapine	Depression	HGEH	004	1167	34	F	20	37	1997-05-13	1997-03-17
Olanzapine	Psychosis	HGEH	004	1167	34	F	20	37	1997-05-13	1997-03-17
Olanzapine	Thinking Abnormal	HGEH	004	1167	34	F	20	37	1997-05-13	1997-03-17
Olanzapine	Anxiety	HGEH	004	1168	35	F	NR	NR	1997-03-21	1997-03-25
Olanzapine	Increased Appetite	HGEH	004	1168	35	F	20	8	1997-04-11	1997-03-25
Olanzapine	Insomnia	HGEH	004	1168	35	F	NR	NR	1997-03-21	1997-03-25
Olanzapine	Nervousness	HGEH	004	1168	35	F	NR	NR	1997-03-21	1997-03-25
Olanzapine	Thinking Abnormal	HGEH	004	1168	35	F	20	50	1997-05-23	1997-03-25
Olanzapine	Thirst	HGEH	004	1168	35	F	20	8	1997-04-11	1997-03-25
Olanzapine	Depression	HGEH	004	1171	52	M	10	41	1997-05-28	1997-04-18

(continued)

Table ISS.9.4. (Continued) Listing of Serious Adverse Events Sorted by Patient Bipolar Overall Integrated Database

Drug at Event Onset	Event Classification Term	Study	Inv.	Patient	Age[a]	Sex	Dose at event onset[b] (mg/day)	Days on Drug at Event Onset	Event Onset Date[c]	Randomization Date
Olanzapine	Depression	HGEH	004	1171	52	M	10	69	1997-06-25	1997-04-18
Olanzapine	Depression	HGEH	004	1171	52	M	10	69	1997-06-25	1997-04-18
Olanzapine	Manic Reaction[e]	HGEH	007	1306	47	M	20	13	1997-04-04	1997-01-29
Olanzapine	Manic Reaction	HGEH	007	1307	31	F	20	29	1997-03-17	1997-02-17
Olanzapine	Manic Reaction[d]	HGEH	007	1307	31	F	20	79	1997-06-12	1997-02-17
Olanzapine	Libido Increased	HGEH	012	1557	27	F	NR	NR	1997-03-29	1997-05-10
Olanzapine	Manic Reaction	HGEH	012	1557	27	F	10	24	1997-06-02	1997-05-10
Olanzapine	Paranoid Reaction	HGEH	012	1557	27	F	NR	NR	1997-03-29	1997-05-10
Olanzapine	Personality Disorder	HGEH	012	1557	27	F	10	24	1997-06-02	1997-05-10
Olanzapine	Agitation	HGEH	013	1605	24	M	NR	NR	1996-11-10	1997-03-13
Olanzapine	Hallucinations	HGEH	013	1605	24	M	20	61	1997-05-20	1997-03-13
Olanzapine	Hostility	HGEH	013	1605	24	M	NR	NR	1996-11-10	1997-03-13
Olanzapine	Sleep Disorder	HGEH	013	1605	24	M	NR	NR	1996-11-10	1997-03-13
Olanzapine	Thinking Abnormal	HGEH	013	1605	24	M	NR	NR	1996-11-10	1997-03-13
Olanzapine	Anxiety	HGEH	014	1651	55	F	NR	NR	1950	1997-01-17
Olanzapine	Delusions	HGEH	014	1651	55	F	15	36	1997-02-21	1997-01-17
Olanzapine	Hallucinations	HGEH	014	1651	55	F	15	36	1997-02-21	1997-01-17
Olanzapine	Overdose	HGEH	014	1651	55	F	15	37	1997-02-22	1997-01-17
Olanzapine	Anxiety	HGEH	016	1752	41	M	15	8	1997-02-07	1997-01-24
Olanzapine	Hostility	HGEH	016	1752	41	M	15	8	1997-02-07	1997-01-24
Olanzapine	Libido Increased	HGEH	016	1752	41	M	15	8	1997-02-07	1997-01-24

(continued)

Table ISS.9.4. (Concluded) Listing of Serious Adverse Events Sorted by Patient Bipolar Overall Integrated Database

Drug at Event Onset	Event Classification Term	Study	Inv.	Patient	Age[a]	Sex	Dose at event onset[b] (mg/day)	Days on Drug at Event Onset	Event Onset Date[c]	Randomization Date
Olanzapine	Nervousness	HGEH	016	1752	41	M	15	6	1997-02-05	1997-01-24
Olanzapine	Personality Disorder	HGEH	016	1752	41	M	15	6	1997-02-05	1997-01-24
Olanzapine	Speech Disorder	HGEH	016	1752	41	M	15	8	1997-02-07	1997-01-24

Abbreviations: Inv. = investigator; M = male; F = female; NR = not reported.

a At time of study entry.

b At adverse event onset date. For adverse events which occurred after study discontinuation, dose and duration of study drug at the time of study discontinuation are listed. For events of overdose, dose patient was intended to receive is listed, rather than the total amount of study drug patient may have taken. For any patient who had missed a dose at the time of event onset, last non-zero dose received by patient is listed.

c Adverse event was not necessarily serious at the time of onset. Adverse event may have initially been non-serious and subsequently became serious. For adverse events that began prior to randomization dose and duration is listed as not reported.

d Table includes poststudy (within 30 days of discontinuation) serious adverse events reported to sponsor as of September 23, 1997 for those patients discontinued from open-label phase.

e Table includes poststudy (greater than 30 days of discontinuation) serious adverse events reported to sponsor as of September 23, 1997 for those patients discontinued from open-label phase.

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Table HGEH.12.5. Criteria for Identifying Patients with Individual Marked Abnormalities in Clinical Chemistry, Hematology, and Urinalysis Values (SI units)
F1D-MC-HGEH, Acute Phase

Analyte	Units	Low Limit	High Limit
AST/SGOT	U/L		150
ALT/SGPT	U/L		165
CPK: Female	U/L		507
Male	U/L		594
Alkaline Phosphatase	U/L		420
GGT: Female	U/L		135
Male	U/L		195
Urea Nitrogen	mmol/L		10.71
Creatinine	µmol/L		176.8
Calcium	mmol/L	1.7465	2.994
Phosphorous	mmol/L	0.48435	1.77595
Sodium	mmol/L	129	160
Total Protein	g/L	50	
Albumin	g/L	25	
Glucose (nonfasting)	mmol/L	2.4975	13.875
Uric Acid: Female	µmol/L		505.58
Male	µmol/L		624.54
Total Cholesterol	mmol/L		15.516
Total Bilirubin	µmol/L		34.2
Hematocrit: Female	1	0.32	0.50
Male	1	0.37	0.55
Hemoglobin: Female	mml/L (Fe)	5.8957	10.2399
Male	mml/L (Fe)	7.1369	11.4811
RBC	TI/L	3	6
WBC	GI/L	2.8	16.0
Platelet Count	GI/L	75	700
Neutrophils	% WBC	15	
Eosinophils	% WBC		10
UA-Specific Gravity		1.001	1.035
UA-pH		4.6	8.0
UA-RBC			increase ≥2 and score ≥3
UA-WBC			increase ≥2 and score ≥3
UA-Casts			increase ≥2 and score ≥3
UA-Protein			increase ≥2 and score ≥3
UA-Ketones			increase ≥2 and score ≥3
UA-Glucose			increase ≥2 and score ≥3

Abbreviations: SI = Systeme International; AST/SGOT = aspartate transaminase/serum glutamic oxaloacetic transaminase; ALT/SGPT = alanine transaminase/serum glutamic pyruvic transaminase; CPK = creatine phosphokinase; GGT = Gamma-glutamyl transferase; RBC = red blood cell; WBC = white blood cell; UA = urinary.

Table HGEH.12.4. Criteria for Identifying Patients with Potentially Clinically Significant Change in Vital Signs and Weight F1D-MC-HGEH, Acute Phase

Parameter	Low	High
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)[a]	--	≥101°F and increase ≥2
Weight (kg)	decrease ≥10%	increase ≥10%
Orthostatic hypotension (mm Hg)	≥30 mm Hg decrease in systolic BP (supine to standing)	--

[a] Converted to Celsius for analysis.

Table HGEH.12.6. Criteria for Identifying Patients with Potentially Clinically Significant Change in ECG Intervals and Heart Rate F1D-MC-HGEH, Acute Phase

Interval	Low	High
PR	--	200 msec
QRS	--	100 msec
QT	--	450 msec
QTc	--	430 msec
Heart rate	40 bpm	120 bpm

Table HGEH.12.10. Potentially Clinically Significant Change in Laboratory Analytes F1D-MC-HGEH, Acute Phase

Analyte	Direction	Placebo N	Placebo n	Placebo (%)	Olz N	Olz n	Olz (%)	Fisher's Exact p-Value
ALBUMIN	Low	62	0	0.0%	70	0	0.0%	
ALKALINE PHOSPHATASE	High	64	0	0.0%	70	0	0.0%	
ALT/SGPT	High	62	0	0.0%	70	3	4.3%	.247
AST/SGOT	High	63	0	0.0%	70	1	1.4%	1.00
BILIRUBIN, TOTAL	High	63	0	0.0%	68	0	0.0%	
CALCIUM	High	63	0	0.0%	70	0	0.0%	
	Low	63	0	0.0%	70	0	0.0%	
CHOLESTEROL	High	63	0	0.0%	70	0	0.0%	
CREATINE PHOSPHOKINASE	High	59	2	3.4%	65	1	1.5%	.604
CREATININE	High	63	0	0.0%	70	0	0.0%	
EOSINOPHILS	High	62	0	0.0%	66	0	0.0%	
ERYTHROCYTE COUNT	High	62	0	0.0%	67	0	0.0%	
	Low	62	0	0.0%	67	0	0.0%	
GGT(GGPT/SGGT/YGGT)	High	64	1	1.6%	69	0	0.0%	.481
GLUCOSE, NON-FASTING	High	61	1	1.6%	70	1	1.4%	1.00
	Low	61	0	0.0%	70	0	0.0%	

RMP.F1DP.JCLLIB(ASSFTLEH)
RMP.F1DP.SASMACRO(SSUMTAB)

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Table HGEH.12.10. (Continued) Potentially Clinically Significant Change in Laboratory Analytes F1D-MC-HGEH, Acute Phase

		Placebo			Olz			Fisher's Exact
Analyte	Direction	N	n	(%)	N	n	(%)	p-Value
HEMATOCRIT	High	60	0	0.0%	65	0	0.0%	
	Low	61	0	0.0%	64	0	0.0%	
HEMOGLOBIN	High	61	0	0.0%	67	0	0.0%	
	Low	62	0	0.0%	66	0	0.0%	
INORGANIC PHOSPHORUS	High	62	1	1.6%	70	0	0.0%	.470
	Low	63	0	0.0%	70	0	0.0%	
LEUKOCYTE COUNT	High	62	0	0.0%	67	0	0.0%	
	Low	62	2	3.2%	67	0	0.0%	.229
NEUTROPHILS, SEGMENTED	Low	62	0	0.0%	67	0	0.0%	
PLATELET COUNT	High	62	0	0.0%	66	0	0.0%	
	Low	62	0	0.0%	67	0	0.0%	
SODIUM	High	63	0	0.0%	69	0	0.0%	
	Low	63	1	1.6%	68	0	0.0%	.481
TOTAL PROTEIN	Low	63	0	0.0%	70	0	0.0%	
UA-CASTS, GRANULAR	Increase>=2	61	0	0.0%	68	0	0.0%	
UA-CASTS, HYALINE	Increase>=2	61	0	0.0%	68	0	0.0%	
UA-GLUCOSE	Increase>=2	60	0	0.0%	68	0	0.0%	

RMP.F1DP.JCLLIB(ASSFTLEH)
RMP.F1DP.SASMACRO(SSUMTAB)

Table HGEH.12.10. (Concluded) Potentially Clinically Significant Change in Laboratory Analytes F1D-MC-HGEH, Acute Phase

		Placebo			Olz			Fisher's Exact
Analyte	Direction	N	n	(%)	N	n	(%)	p-Value
UA-KETONES	Increase>=2	61	0	0.0%	68	0	0.0%	
UA-PH	High	61	0	0.0%	68	0	0.0%	
	Low	61	0	0.0%	68	0	0.0%	
UA-PROTEIN	Increase>=2	61	0	0.0%	68	0	0.0%	
UA-RBC	Increase>=2	59	0	0.0%	67	2	3.0%	.498
UA-SPECIFIC GRAVITY	High	61	0	0.0%	68	0	0.0%	
	Low	61	0	0.0%	68	0	0.0%	
UA-WBC	Increase>=2	60	0	0.0%	68	0	0.0%	
UREA NITROGEN	High	63	0	0.0%	70	0	0.0%	
URIC ACID	High	63	1	1.6%	70	0	0.0%	.474

RMP.F1DP.JCLLIB(ASSFTLEH)
RMP.F1DP.SASMACRO(SSUMTAB)

Table HGEH.12.12. Potentially Clinically Significant Change in Vital Signs and Weight
F1D-MC-HGEH, Acute Phase

Vital	Direction	Placebo N	Placebo n	Placebo (%)	Olz N	Olz n	Olz (%)	Fisher's Exact p-Value
Orthostatic Sys BP	Decrease	63	2	3.2%	68	3	4.4%	1.00
Standing Diastolic BP	High	62	2	3.2%	67	1	1.5%	.608
	Low	63	0	0.0%	69	1	1.4%	1.00
Standing Pulse	High	63	0	0.0%	69	2	2.9%	.497
	Low	63	1	1.6%	69	1	1.4%	1.00
Standing Systolic BP	High	63	0	0.0%	69	0	0.0%	
	Low	62	2	3.2%	69	3	4.3%	1.00
Supine Diastolic BP	High	63	2	3.2%	68	0	0.0%	.229
	Low	63	1	1.6%	69	2	2.9%	1.00
Supine Pulse	High	63	0	0.0%	69	0	0.0%	
	Low	63	1	1.6%	69	0	0.0%	.477
Supine Systolic BP	High	63	0	0.0%	69	0	0.0%	
	Low	63	1	1.6%	69	1	1.4%	1.00
Temperature (C)	High	63	0	0.0%	68	0	0.0%	
Weight (kg)	Gain	60	0	0.0%	69	0	0.0%	
	Loss	60	0	0.0%	69	0	0.0%	

RMP.F1DP.JCLLIB(ASSFTVEH)
RMP.F1DP.SASMACRO(SSUMTAB)

Table HGEH.12.14. Potentially Clinically Significant Change in ECG Interval and Heart Rate
F1D-MC-HGEH, Acute Phase

ECG Interval	Direction	Placebo N	Placebo n	Placebo (%)	Olz N	Olz n	Olz (%)	Fisher's Exact p-Value
ECG Heart Rate	High	53	0	0.0%	63	0	0.0%	
	Low	53	0	0.0%	63	0	0.0%	
ECG PR Interval	High	52	2	3.8%	61	0	0.0%	.210
ECG QRS Interval	High	45	7	15.6%	56	5	8.9%	.363
ECG QT corrected	High	42	3	7.1%	48	8	16.7%	.209
ECG QT Interval	High	53	1	1.9%	63	0	0.0%	.457

RMP.F1DP.JCLLIB(ASSFTEEH)
RMP.F1DP.SASMACRO(SSUMTAB)

Table HGEH.12.7. Laboratory Analyses
Mean Change from Baseline to Endpoint
F1D-MC-HGEH, Acute Phase

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)
HCT	1	Placebo	61	0.43	0.04	0.00	0.03	.344
		Olz	66	0.43	0.04	-0.01	0.03	(.464)
HGB	mml/L-Fe	Placebo	62	8.79	0.84	0.11	0.42	.012
		Olz	67	8.76	0.78	-0.10	0.42	(.675)
RBC	TI/L	Placebo	62	4.64	0.43	0.03	0.26	.719
		Olz	67	4.62	0.46	0.01	0.23	(.866)
MCHC	mml/L-Fe	Placebo	61	20.43	0.88	0.16	0.95	.032
		Olz	66	20.40	0.85	-0.15	0.82	(.102)
MCH	fmol(Fe)	Placebo	62	1.90	0.12	0.00	0.05	.001
		Olz	67	1.91	0.12	-0.03	0.05	(.416)
WBC	GI/L	Placebo	62	7.86	2.40	-0.45	1.83	.645
		Olz	67	7.95	1.90	-0.34	2.00	(.362)
POLYS	GI/L	Placebo	62	4.73	1.85	-0.23	1.42	.637
		Olz	67	4.99	1.41	-0.13	1.62	(.144)
LYMPHS	GI/L	Placebo	62	2.38	0.91	-0.12	0.78	.792
		Olz	67	2.22	0.81	-0.23	0.72	(.604)
MONOS	GI/L	Placebo	62	0.51	0.18	-0.04	0.20	.490
		Olz	67	0.53	0.17	-0.01	0.21	(.892)
EOSN	GI/L	Placebo	62	0.17	0.13	-0.03	0.09	.081
		Olz	67	0.15	0.11	0.02	0.13	(.533)
BASO	GI/L	Placebo	62	0.06	0.04	-0.01	0.04	.893
		Olz	67	0.06	0.03	-0.01	0.04	(.909)
MCV	fL	Placebo	61	93.31	4.86	-0.31	3.32	.253
		Olz	66	93.76	6.43	-1.08	3.92	(.063)
PLTCT	GI/L	Placebo	62	261.39	58.39	3.76	37.53	.398
		Olz	67	269.30	96.32	-4.12	54.19	(.910)

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Table HGEH.12.7. (Continued) Laboratory Analyses Mean Change from Baseline to Endpoint F1D-MC-HGEH, Acute Phase

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)
U-SPGR	NO UNITS	Placebo	61	1.02	0.01	0.00	0.01	.728
		Olz	68	1.02	0.01	-0.00	0.01	(.062)
U-PH	U	Placebo	61	5.52	0.77	-0.15	0.96	.076
		Olz	68	5.71	0.85	-0.43	0.97	(.585)
AST	U/L	Placebo	63	25.22	14.08	2.17	12.72	.109
		Olz	70	21.17	7.36	10.51	25.61	(.584)
ALT	U/L	Placebo	63	31.13	27.64	3.30	15.19	.053
		Olz	70	24.53	19.27	23.01	52.98	(.629)
CPK	U/L	Placebo	62	150.29	177.71	96.55	349.19	.191
		Olz	70	135.71	139.28	10.46	142.15	(.659)
ALKPH	U/L	Placebo	64	69.75	18.48	1.52	10.76	.286
		Olz	70	66.21	16.62	0.90	10.03	(.492)
GGT	U/L	Placebo	64	31.39	29.11	4.14	28.40	.835
		Olz	70	33.00	60.43	4.89	32.26	(.512)
BUN	mmol/L	Placebo	63	4.73	1.33	-0.07	1.30	.251
		Olz	70	4.52	1.37	0.11	1.25	(.956)
CREAT	umol/L	Placebo	63	99.34	16.93	2.95	10.17	.020
		Olz	70	96.36	13.81	-2.15	9.80	(.326)
CALC	mmol/L	Placebo	63	2.34	0.12	0.00	0.09	.298
		Olz	70	2.32	0.10	-0.02	0.10	(.681)
PHOS	mmol/L	Placebo	63	1.24	0.24	-0.00	0.21	.353
		Olz	70	1.25	0.20	0.04	0.25	(.051)
SODIUM	mmol/L	Placebo	63	139.27	2.73	0.16	3.85	.345
		Olz	69	138.90	2.74	0.61	2.79	(.681)
POTAS	mmol/L	Placebo	63	4.32	0.40	-0.12	0.40	.247
		Olz	69	4.26	0.34	-0.02	0.33	(.970)

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Table HGEH.12.7. (Continued) Laboratory Analyses Mean Change from Baseline to Endpoint F1D-MC-HGEH, Acute Phase

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)
CHLOR	mmol/L	Placebo	63	104.67	3.19	-0.29	4.13	.046
		Olz	69	104.20	3.07	1.38	3.43	(.201)
TPROT	g/L	Placebo	63	71.38	5.52	1.48	4.79	.096
		Olz	70	71.47	5.10	-0.70	5.40	(.653)
ALBUM	g/L	Placebo	62	41.00	3.30	0.81	2.93	.003
		Olz	70	40.90	3.26	-1.19	3.02	(.839)
NFGLU	mmol/L	Placebo	62	5.73	1.97	-0.13	1.69	.826
		Olz	70	5.84	1.77	0.11	1.69	(.258)
UR AC	umol/L	Placebo	63	310.81	81.60	2.17	55.20	.097
		Olz	70	295.45	69.48	18.95	48.08	(.203)
CHOL	mmol/L	Placebo	63	4.85	1.09	0.19	0.93	.184
		Olz	70	4.64	1.01	0.39	0.95	(.987)
BICARB	mmol/L	Placebo	62	25.66	2.08	-0.56	2.18	.153
		Olz	69	25.23	2.52	-1.03	2.44	(.441)
T.BILI	umol/L	Placebo	63	9.17	4.03	-0.11	3.16	.418
		Olz	68	7.97	3.28	-0.60	3.63	(.128)

Reporting SI units
The following investigators were pooled: (001, 015) and (005 006)
RMP.F1DP.JCLLIB(ASSE8EH)
RMP.F1DP.SASMACRO(SSAFEE8)
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.
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Table HGEH.12.7. (Concluded) Laboratory Analyses Mean Change from Baseline to Endpoint F1D-MC-HGEH, Acute Phase

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

Table HGEH.12.11. Vital Signs and Weight
Mean Change from Baseline to Endpoint
F1D-MC-HGEH, Acute Phase

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)
WEIGHTKG	Placebo	60	87.29	21.88	-0.44	2.35	<.001
	Olz	69	81.70	14.25	1.65	2.54	(.344)
PULSE_ST	Placebo	63	85.94	9.81	-3.27	14.39	.012
	Olz	69	81.13	11.35	5.45	16.96	(.558)
TEMPCPO	Placebo	63	36.63	0.49	0.04	0.57	.553
	Olz	68	36.70	0.53	-0.05	0.64	(.879)
SYSBP_OR	Placebo	63	-0.40	9.74	0.97	14.83	.949
	Olz	68	-0.49	9.07	0.46	13.64	(.732)
PULSE_OR	Placebo	63	7.30	8.73	-2.21	10.34	.035
	Olz	68	5.38	9.90	2.87	14.84	(.839)
SYSBP_SU	Placebo	63	121.48	14.94	2.11	16.51	.282
	Olz	69	121.87	16.41	1.12	14.96	(.421)
DIABP_SU	Placebo	63	76.05	9.54	2.30	12.31	.071
	Olz	69	77.33	10.32	-1.12	12.53	(.593)
PULSE_SU	Placebo	63	79.38	8.98	-1.81	13.93	.232
	Olz	69	76.17	11.64	2.68	14.80	(.688)
SYSBP_ST	Placebo	63	122.16	14.37	0.86	16.67	.104
	Olz	69	122.72	15.77	-0.45	14.81	(.199)
DIABP_ST	Placebo	63	77.67	9.57	2.97	13.56	.026
	Olz	69	79.64	11.27	-0.81	14.25	(.602)

The following investigators were pooled: (001, 015) and (005, 006)
RMP.F1DP.JCLLIB(ASSFD1EH)
RMP.F1DP.SASMACRO(SSAFEC1)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.
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Table HGEH.12.11. (Concluded) Vital Signs and Weight Mean Change from Baseline to Endpoint F1D-MC-HGEH, Acute Phase

Research Project Code: F1D

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.

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Legend of Variable Abbreviations:

Abbrev.	Description
DIABP_ST	Diastolic Blood Pressure - Standing
DIABP_SU	Diastolic Blood Pressure - Supine
PULSE_OR	Pulse - Ortho
PULSE_ST	Pulse - Standing
PULSE_SU	Pulse - Supine
SYSBP_OR	Systolic Blood Pressure - Ortho
SYSBP_ST	Systolic Blood Pressure - Standing
SYSBP_SU	Systolic Blood Pressure - Supine
TEMPCPO	Temp in Centigrade Standardized to PO
WEIGHTKG	Weight in kg.

Table HGEH.12.13. ECG Intervals and Heart Rate Mean Change from Baseline to Endpoint F1D-MC-HGEH, Acute Phase

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)
ECGHR	Placebo	53	75.68	13.27	0.42	14.05	.457
	Olz	63	73.29	13.91	4.83	14.59	(.235)
INTPRSEC	Placebo	53	0.15	0.02	0.00	0.04	.923
	Olz	63	0.15	0.02	-0.00	0.02	(.542)
INTQRSEC	Placebo	53	0.08	0.01	0.00	0.01	.698
	Olz	63	0.09	0.04	-0.00	0.04	(.950)
INTQTC	Placebo	53	410.84	24.68	-0.62	25.25	.612
	Olz	63	408.77	26.64	2.82	20.44	(.471)
INTQTMSC	Placebo	53	367.98	27.19	-0.70	30.74	.280
	Olz	63	373.29	31.25	-10.81	29.59	(.037)
INTRRSEC	Placebo	53	0.81	0.14	0.00	0.16	.182
	Olz	63	0.85	0.17	-0.06	0.17	(.543)

The following investigators were pooled: (001, 015) and (005, 006)
RMP.F1DP.JCLLIB(ASSFD6EH)
RMP.F1DP.SASMACRO(SSAFEC1)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:
FULL4 - *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 interaction.
Note: Each investigator has at least one patient in each treatment group.
XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
ECGHR	Heart Rate Per Minute
INTPRSEC	Intervals PR / Second
INTQRSEC	Intervals QRS / Second
INTQTC	Intervals QT Corrected
INTQTMSC	Intervals QT / Msec
INTRRSEC	Intervals RR / Second

AUG 30 1999

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA: 20-592 / S-006
Sponsor: Lilly

Drug Name

Generic Name olanzapine
Trade Name Zyprexa

Drug Characterization

Pharmacological Category: Antipsychotic
Proposed Indication: Acute Treatment of Bipolar Disorder
Dosage Forms, Strengths, and Routes of Administration:
Oral Tablets 2.5mg, 5mg, 7.5mg, and 10mg

Reviewer Information

Clinical Reviewer: Earl D. Hearst, M.D.
Review Completion Date: 8/30/99

1.0 Material Reviewed

The sponsor has submitted an amendment to their 12/3/97 supplement consisting of a complete response to our not-approvable letter of 10/8/98 along with a new study HGGW and safety data for open label patients. This was submitted on a CDROM as well as on paper and word tables were supplied on floppy disks. I have not re-presented study HGEH which was contained in my review of the sponsor's previous bipolar submission.

2.0 Background

2.1 Indication

The sponsor proposes using olanzapine in the treatment of the manic or mixed episodes in bipolar disorder. The effectiveness of ZYPREXA for long-term use in mania, i.e., more than 4 weeks, has not been systematically evaluated in controlled clinical trials.

2.2 Related INDs and NDAs

Olanzapine has also been submitted under IND 28,705 for schizophrenia [ ] b(4)

2.3 Administrative History

The administrative history below is derived from sponsor provided material.

Protocol F1D-MC-HGEH was initiated in October 1996 to investigate the efficacy and safety of olanzapine in the treatment of patients with a manic or mixed episode associated with bipolar I disorder. In February 1997, the sponsor submitted to the FDA the clinical development plans for olanzapine in the treatment of bipolar mania. The Sponsor submitted a request to the FDA for a pre-NDA meeting in May 1997. In June 1997, a pre-NDA meeting was held between the Sponsor and the FDA where the study design and submission data requirements were discussed.

October 2, 1998
FDA sent a not approvable letter for S006 (NDA 20-592).

October 8, 1998
Lilly submitted intention to amend S-006 (NDA 20-592).

October 27, 1998
A briefing document to support a meeting to discuss the not approvable status was submitted to NDA 20-592.

November 6, 1998
Meeting to discuss the not approvable status.

November 10, 1998
FAX to Doris Bates (FDA Project Manager) of Y-MRS item 1 and 3 analysis from study HGEH, per request of Dr. Tom Laughren (FDA) in November 6 meeting.

November 16, 1998
Lilly's minutes for November 6 meeting were submitted to NDA 20-592.

December 3, 1998
FDA's minutes for the November 6 meeting were sent to Lilly.

December 10, 1998
Drs. Gary Tollefson and Al Webber (Eli Lilly) spoke via telephone with Dr. Tom Laughren (FDA).

January 11, 1999
Lilly FAXed patient list for study HGEH to Dr. Doris Bates.

January 13, 1999
Lilly submission stated that they would terminate study HGGW early.

January 14, 1999
In a telephone conversation, Dr. Bates and Dr. Webber discussed the appropriate number of HGEH patients for audit. The FDA asked for a number and Lilly suggested 15.

January 22, 1999
The Division FAXed to Dr. Al Webber comment on audit of certain patient records for study HGEH and requested to review the Lilly plan for this audit.

January 28, 1999
The Division sent letter regarding our plans for early termination of study HGGW.

February 5, 1999
Lilly submitted arguments in response to the January 28 letter from the Division.

February 8, 1999
FDA Project Manager Doris Bates informed Lilly's Al Webber that our plans for statistical evaluation of study HGGW were acceptable to the Division.

February 26, 1999
Lilly FAXed response to January 22 Division FAX, with plan for audit of certain patient records.

March 1, 1999
FDA Project Manager Doris Bates informed Lilly's Dr. Al Webber that the audit plan was acceptable.

March 5, 1999
Lilly submitted plan for electronic Item 11 for this amendment.

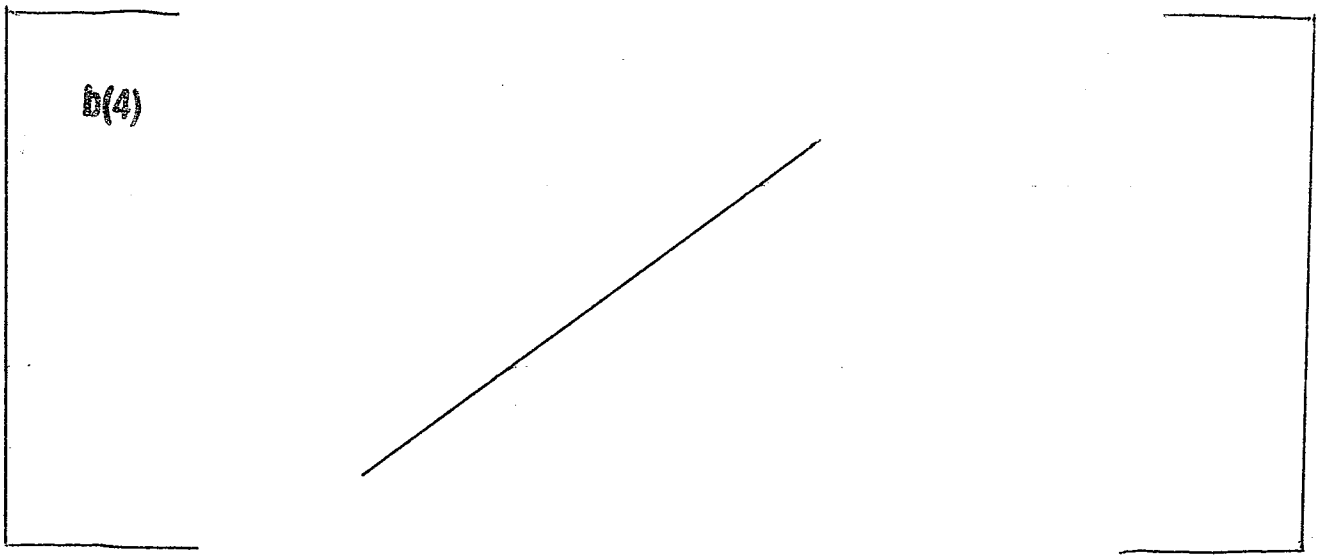
March 8, 1999
Division FAX of 1/22/99 and Lilly FAX of 2/26/99 were officially submitted.

April 2, 1999
FDA Project Manager Doris Bates agreed with Lilly's Steve Ward that an electronic copy of the complete NDA would not be submitted as a review aid with the submission but would be provided by Lilly if requested by the FDA at a later date.

2.4 Directions for Use

The sponsor proposes directions as indicated in italics below.

Bipolar Mania



b(4)

2.5 Foreign Marketing

Olanzapine has not been marketed in any country for the treatment of acute manic and mixed episodes in bipolar I disorder.

3.0 Chemistry

The same formulations currently available are proposed for the new indication. Eli Lilly and Company claims the Categorical Exclusion from the requirement for an environmental assessment to support the approval of Zyprexa (olanzapine) for the treatment of bipolar mania.

4.0 Preclinical Pharmacology

Nonclinical pharmacology and toxicologic information regarding this section has been previously reported in NDA 20-592 and has not changed other than below.

The sponsor has provided the following new studies summary which I have truncated in italics.

Absorption, Distribution, Metabolism, and Excretion (ADME)

In vitro studies using human liver microsomes were conducted to examine valproate as a potential inhibitor of the oxidative routes of olanzapine metabolism and to determine whether olanzapine significantly inhibits the glucuronidation of valproate. Based on the results of these studies, valproate co-administration in vivo with olanzapine is not expected to affect the oxidative metabolism of olanzapine, and it is highly unlikely that olanzapine will affect valproate plasma concentrations in patients when both drugs are used concurrently.

Examination of the Potential Interactions of Valproate on Olanzapine Oxidative Metabolism and Human CYP1A2

In summary, valproate, at concentrations ranging from sub-therapeutic to above therapeutic levels, was found to only minimally affect the oxidative metabolism of olanzapine. Since olanzapine oxidative metabolism is mediated by CYP1A2, CYP2D6, and the flavin containing monooxygenases (Ring et al. 1996), these results suggest that valproate does not inhibit metabolism mediated by these enzymes. Valproate was also

shown to only minimally affect the CYP1A2 mediated formation of acetaminophen from phenacetin, further confirming that valproate does not significantly inhibit CYP1A2 mediated metabolism. Therefore, valproate co-administration in vivo with olanzapine is not expected to affect the oxidative metabolism of olanzapine.

Effect of Olanzapine on Valproate Glucuronidation by Human Liver Microsomes

In vitro studies using human liver microsomes examined olanzapine as a potential inhibitor of the oxidative routes of valproate metabolism. Based on the Km values obtained for the formation of valproate glucuronide, valproate concentrations of 1, 2.5, 5, and 10 mM were evaluated (three valproate substrate concentrations below the average Km and one above). Based upon preliminary studies, olanzapine concentrations of 0, 0.1, 0.25, 0.5, and 1 mM were evaluated.

Olanzapine was found to competitively inhibit the formation of valproate glucuronide at olanzapine concentrations considerably higher than those found in patients clinically. Using the method described by Ring et al. (1996), at a valproate concentration of 500 μM, Km of 5.9 mM, Ki of 884 μM, olanzapine concentration of 0.2 μM (equivalent to 40 ng/mL, the peak concentration observed in patients chronically treated with a 17.5 mg/day dose), the predicted in vivo inhibition by olanzapine on the glucuronidation of valproate was 0.02%. Therefore it is highly unlikely that olanzapine will affect valproate plasma concentrations in patients when both drugs are used concurrently.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

The use of olanzapine in the treatment of patients diagnosed with manic or mixed episode associated with bipolar I disorder has been studied in a double-blind placebo-controlled, multicenter trial (F1D-MC-HGEH) and two single-site open-label trials F1D-UT-HGES and F1D-MC-HGET which were conducted under the US IND for olanzapine (IND 28,705). These were presented in my previous review. This supplement adds a new study HGGW along with open label extension patients from HGEH. Information included in this integrated summary of efficacy had several cut-off dates; 1) HGEH acute phase data as of 28 August 1997, 2) HGEH open-label
data as of 15 October 1998, and 3) HGGW acute phase data as of 24 February 1999.

Please see enumeration tale below.

Patient Enumeration by Database, Study Type, and Study Design

	Treatment Group	
Database/Study Type/Study Design	**Olanzapine**	**Placebo**
Placebo-Controlled Studies	125	129
HGEH Open-Label	113(59)[a]	
Total	179	129

Number in parentheses (59) represents olanzapine-treated patients participating in open-label extension studies, but already counted in the Olanzapine column under Placebo-Controlled

5.1.2 Demographics

The patients were approximately equal in terms of the sexual breakdown and were 75% Caucasian. The mean and median ages were 38-39 in both placebo and study drug groups. Please see the table below.

Patient Characteristics Bipolar Integrated Database Acute Phase

Variable	Placebo (N= 129)	Olz (N= 125)	Total (N= 254)	p- Value
Sex: No. (%)				
No. Patients	129	125	254	.802*
Male	67 (51.9)	62 (49.6)	129 (50.8)	
Female	62 (48.1)	63 (50.4)	125 (49.2)	
Origin: No. (%)				
No. Patients	129	125	254	.424*
Caucasian	100 (77.5)	93 (74.4)	193 (76.0)	
African Descent	22 (17.1)	22 (17.6)	44 (17.3)	
East/ SE Asian	0	3 (2.4)	3 (1.2)	
Hispanic	6 (4.7)	7 (5.6)	13 (5.1)	
Other Origin	1 (0.8)	0	1 (0.4)	
Age: yrs.				
No. Patients	129	125	254	.674**
Mean	38.83	39.40	39.11	
Median	39.41	38.48	38.93	
Standard Dev.	10.21	11.19	10.68	
Minimum	18.68	18.15	18.15	
Maximum	62.58	67.13	67.13	
RMP. F1DP. JCLLIB(ISBSAB2) RMP. F1DP. SASMACRO(SBASEA)				

5.1.3 Extent of Exposure (dose/duration)

A summary of olanzapine exposure across study HGGW and all phases of study HGEH by the modal daily dose is presented in the table below. Modal dose is defined as the dose the patient was prescribed for the most number of days. This table includes 125 patients from placebo-controlled phases of studies HGGW and HGEH as well as 54 patients who first received olanzapine during the open-label phase of study HGEH. Of the 125 patients with olanzapine exposure from the placebo-controlled phases, 59 patients went on to have additional olanzapine exposure during the open-label phase of study HGEH. From the table below, there was a total of 24,137 patient days of exposure to olanzapine across the placebo-controlled and open-label phases of both studies.

Patient Exposure to Olanzapine Therapy
Modal Daily Dose
Combined HGGW and all phases of HGEH

Duration (Days) (%)	Dosage Range <5 mg	5 - <10 mg	10 - <15 mg	15 - <20 mg	>=20 mg	Total
<=7 (10.1%)	1	0	7	3	7	18
7< - 14 (6.1%)	0	0	2	5	4	11
14< - 28 (21.8%)	2	1	3	14	19	39
28< - 56 (16.2%)	0	3	4	9	13	29
56< - 84 (2.8%)	1	0	1	0	3	5
84< - 112 (4.5%)	0	0	2	4	2	8
112< - 140 (3.4%)	0	1	3	1	1	6
140< - 168 (2.2%)	0	0	1	1	2	4
168< - 224 (5.0%)	0	2	3	1	3	9
224< - 280 (2.2%)	0	0	1	2	1	4
280< - 336 (1.7%)	0	0	1	2	0	3
336< - 365 (12.8%)	0	5	4	3	11	23
>365 (11.2%)	0	3	7	8	2	20
Total	4	15	39	53	68	179
(%)	(2.2%)	(8.4%)	(21.8%)	(29.6%)	(38.0%)	

Total patient days of exposure: 24137

5.1.4 Disposition

A statistically significantly greater proportion of patients in the olanzapine group (61.6%) relative to the placebo group (38.0%) completed the acute phase of the studies (p<.001). A statistically significantly greater proportion of patients in the placebo group (43.4%) than in the olanzapine group (28.0%) discontinued during the acute phase for lack of efficacy (p=.013). There was no significant difference in the proportion of patients in the olanzapine group (7.2%) than in the placebo group (7.0%) that discontinued for patient decision. The proportions of patients who discontinued for an adverse event were comparable between groups (olanzapine, 1.6%; placebo, 2.3%).

Patient Disposition

Bipolar Integrated Database Acute Phase

Reason for Discontinuation	Placebo (N=129) n (%)	Olz (N=125) n (%)	Total (N=254) n (%)	p-Value*
Reporting Interval Complete	49 (38.0)	77 (61.6)	126 (49.6)	<.001
Adverse Event	3 (2.3)	2 (1.6)	5 (2.0)	1.00
Lack of Efficacy	56 (43.4)	35 (28.0)	91 (35.8)	.013
Lost to Follow-up	4 (3.1)	1 (0.8)	5 (2.0)	.370
Patient Decision	9 (7.0)	9 (7.2)	18 (7.1)	1.00
Criteria not met / Compliance	1 (0.8)	1 (0.8)	2 (0.8)	1.00
Sponsor Decision	3 (2.3)	0	3 (1.2)	.247
Physician Decision	4 (3.1)	0	4 (1.6)	.122

Patients included in the reasons discontinued, Reporting Interval Complete and Lack of Efficacy, may have continued into the next reporting interval or discontinued from the study.
P-value obtained by using a two-tailed Fisher's Exact test

5.2 Secondary Sources

5.2.1 Non-IND Studies

There are no Non-IND studies with which the sponsor has been associated.

5.2.2 Post-Marketing Experience

There is post-marketing experience with olanzapine used in Bipolar disorders and this is described in section 8.5.1.3 of this review.

5.2.3 Literature

The sponsor compared safety data from completed and ongoing worldwide clinical studies through a cutoff date of 01 May 1997 with safety data initially submitted to the FDA for the indication of psychotic disorders on 22 September 1995 (NDA 20-592). The sponsor feels the additional literature search for olanzapine reflected in the current database reveals no substantial change in the safety profile from that of the original submission. The databases used for this search are: Medline Derwent Drug File SciSearch, Embase PsycINFO Biosis. I did not see any literature reports in the 41 articles in the sponsor's bibliography reviewed by title that would be directly relevant to this review.

5.3 Adequacy of Clinical Experience

The exposure to olanzapine appears to be of an adequate duration and dosage and the clinical experience is otherwise satisfactory.

5.4 Data Quality and Completeness

The data quality appears to be adequate and complete in that the specified scales and tests were appropriate and performed, with results collected and analyzed.

6.0 Summary of Human Pharmacokinetics

There are no changes in this section outside of the two drug interaction studies summarized in section 8.9.3 on drug-drug interactions presented later in this review.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

As of 24 February 1999, the efficacy of olanzapine had been investigated in 2 protocols, F1D-MC-HGEH (N=139) and F1D-MC-HGGW (N=118), for the treatment of mania associated with bipolar I disorder. HGEH was designed with two substudies (Study 1 and 2) and an open-label extension. Information included in this integrated summary of efficacy was from several sources; 1) HGEH acute phase data as of 28 August 1997, 2) HGEH open-label

data as of 15 October 1998, and 3) HGGW acute phase data as of 24 February 1999.

F1D-MC-HGEH- was conducted at 16 study sites in the United States among patients with a DSM-IV diagnosis of bipolar I disorder displaying an acute manic or mixed episode (with or without psychotic features) as determined by the SCID-P. This trial compared olanzapine (5, 10, 15, or 20 mg/day) with placebo, and was divided into 2 studies:

Study 1 included 72 patients from 8 study sites.
Study 2 included 67 patients from 8 study sites.

F1D-MC-HGGW was conducted at 26 study sites in the United States in 115 patients meeting DSM-IV diagnostic criteria for manic or mixed episode (with or without psychotic features) associated with bipolar I disorder according to the SCID-P. This study compared olanzapine (5, 10, 15, or 20 mg/day) with placebo.

7.2 Summary of Studies Pertinent to Efficacy

Study HGEH

This study was previously reviewed with one of the two equal sub-studies supportive of efficacy. The sponsor has now provided the following section indicating an error in their analysis of the positive substudy.

On August 28, 1997 the HGEH study database was locked. This database was the basis of the December 3, 1997 submission. Subsequently, it was found that Patient 001-1007 in Study 2, who was randomized to placebo, had an incorrectly labeled final visit. When the patient came into the site for Visit 3, the site discontinued the patient from the acute phase of the study and started the patient on open-label medication. When the patient came in for the next visit, the study site incorrectly recorded the visit as a Visit 4 (part of the double-blind phase) instead of a Visit 301 (open-label phase). Patient 001-1007 Y-MRS total scores across the visits were 35, 34, 37, and 45 for Visits 1, 2, 3, and 4(301), respectively. Hence in the original analysis of change from baseline to endpoint of the acute phase, the patient's change in the Y-MRS total score was calculated to be an increase of 11 points instead of an increase of 3 points.

On January 28, 1998, this error was identified by Lilly personnel. However, not until our analyses during March of 1999 in preparation for this ISE was it discovered that this database error changes the p-Value of the primary analysis of the Y-MRS total score from p=.046 to p=.054 in Study 2 (see Tables 3.37 and 3.38). However, given 1) the magnitude of the change in p-Values is small, 2) the change from baseline to endpoint of the CGI-BP mania score in Study 2 remains significant, 3) the response rates for Study 2

do not change and remain statistically significant, and 4) all the efficacy results in the combined acute analysis of HGEH do not change in significance, we feel that this error does not affect the overall efficacy conclusions from HGEH.

Study F1D-MC-HGGW

Investigators/Sites

This multicenter study was conducted by 26 investigators, all licensed physicians practicing psychiatry, at 26 study sites. Please see appendix table.

Objectives

The primary objective of this protocol was to assess the efficacy of olanzapine compared with placebo in the treatment of patients diagnosed with manic or mixed episode associated with bipolar I disorder. Improvement in manic symptomatology was measured by reductions from baseline of the Young-Mania Rating Scale (Y-MRS) total score after up to 4 weeks of therapy.

The secondary objectives of the study were as follows:

To assess the efficacy of 5, 10, 15, or 20 mg/day of olanzapine compared with placebo in improving clinical symptomatology in patients diagnosed with manic or mixed episode associated with bipolar I disorder, after up to 4 weeks of therapy. Reductions from baseline on the Positive and Negative Syndrome Scale (PANSS) total, positive, and negative scores; Hamilton Psychiatric Rating Scale for Depression-21 Items (HAMD-21) total score; and the Clinical Global Impressions - Bipolar Version Severity of Illness (CGI-BP Severity - mania, depression, and overall bipolar illness) were used to assess improvement in clinical symptomatology.

To assess the safety of acute treatment with 5, 10, 15, or 20 mg/day of olanzapine compared with placebo. Treatment-emergent adverse events, change in vital signs, laboratory analytes and ECGs, and severity of extrapyramidal symptoms were measured. The Simpson-Angus Scale and the Barnes Akathisia Scale were used to measure extrapyramidal symptoms.

Study Population

The sponsor provided the following criteria for study inclusion shown below.

Patients were included in the study only if they met all of the following criteria:
[1] Male or female patients, 18 to 70 years of age.
[2] Female patients of childbearing potential must have been using a medically accepted means of contraception.
[3] Each patient must have had a level of understanding sufficient to agree to all tests and examinations required by the protocol.
[4] Patients must have been considered reliable.
[5] Each patient (and/or a patient's authorized legal representative) must have understood the nature of the study and must have signed an informed consent document.
[6] Patients must have 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 HGGW.2.) based on clinical assessment and confirmed by structured diagnostic interview SCID-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] History of at least 1 previous manic episode.
[8] Patients must have had an initial score on the Y-MRS total score of at least 20 at both Visits 1 and 2 . .

Study Design

This was a randomized, double-blind, parallel study of patients, initially hospitalized, meeting DSM-IV diagnostic criteria for manic or mixed episode (with or without psychotic features) associated with bipolar I disorder according to the SCID-P. Approximately 240 patients were to have been enrolled in the study. Randomization was performed at a 1:1 ratio into 2 treatment groups: olanzapine (5, 10, 15, or 20 mg/day) or placebo.

Rating Scales

The Y-MRS consists of 11 items. Items 5, 6, 8, and 9 are rated on a scale from 0 (symptom not present) to 8 (symptom extremely severe). The remaining items are rated on a scale from 0 (symptom not present) to 4 (symptom extremely severe). Items 5, 6, 8, and 9 (irritability, speech, content and disruptive-aggressive behavior) are given twice the weight of the remaining 7 in order to compensate for the poor condition of severely ill patients. The Y-MRS total score ranges from 0 to 60 and was the primary efficacy parameter.

The PANSS is a rating scale used to assess the positive symptoms,

negative symptoms, and general psychopathology specifically associated with schizophrenia. The scale consists of 30 items. Each item is rated on a scale from 1 (symptom not present) to 7 (symptoms extremely severe). The sum of the 30 items is defined as the PANSS total score and ranges from 30 to 210. The PANSS positive score and PANSS negative score contain seven items of the 30 PANSS items, and the scores range from 7 to 49. The PANSS general psychopathology score includes 16 of the 30 PANSS items, and the score ranges from 16 to 112.

The Hamilton Psychiatric Rating Scale for Depression used the 21-item version of this scale (HAMD-21) which was administered to assess the severity of depression and its improvement during the course of therapy.

The CGI-BP Severity is a measure of illness severity especially adapted for bipolar illness. It allows rating of mania, depression, and overall illness. CGI-BP Severity is used by the clinician to record the severity of illness at the time of assessment. The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).

Analysis

Primary analyses were done on an intent-to-treat basis. When LOCF mean change from baseline to endpoint was assessed, patients were included in the analysis only if a patient had a baseline and a postbaseline measure. In the bipolar integrated database for randomized patients in HGEH and HGGW, unless otherwise defined, a baseline measure was the Visit 2 observation; if it was missing, then the baseline measure was the Visit 1 observation. For the analyses of olanzapine data from the long-term open-label study, baseline was defined as all of Visits 1 - 5. A patient's endpoint measure was defined as his/her last measure in the appropriate study period. In the categorical analysis of laboratory analytes, subsets of patients were analyzed, and inclusion varied by analyte. All tests of hypotheses were tested at a two-sided a level of 0.05.

Study Outcome

Study F1D-MC-HGGW

Patient Disposition

38.3% of placebo patients dropped out due to lack of efficacy versus 27.2% on study drug. 3.6% of olanzapine patients vs. 1.7% of placebo dropped out due to an adverse event. Please see table below.

F1D-MC-HGGW, Acute Phase

Reason for Discontinuation	Placebo (N=60) n (%)	Olz (N=55) n (%)	Total (N=115) n (%)	p-Value*
Reporting Interval Complete	25 (41.7)	34 (61.8)	59 (51.3)	.040
Adverse Event	1 (1.7)	2 (3.6)	3 (2.6)	.606
Lack of Efficacy	23 (38.3)	15 (27.3)	38 (33.0)	.238
Lost to Follow-up	3 (5.0)	1 (1.8)	4 (3.5)	.620
Patient Decision	5 (8.3)	3 (5.5)	8 (7.0)	.719
Physician Decision	3 (5.0)	0	3 (2.6)	.245

P-value obtained by using a two-tailed Fisher's Exact test

DEMOGRAPHICS

The two study arms are roughly equal in terms of age and sex. The placebo group has fewer members of African descent than study drug, 11.7% vs. 16.4%.

Physical Characteristics

F1D-MC-HGGW, Acute Phase

Variable	Placebo (N=60)	Olz (N=55)	Total (N=115)	p-Value
Sex: No. (%)				
No. Patients	60	55	115	1.00*
Male	30 (50.0)	27 (49.1)	57 (49.6)	
Female	30 (50.0)	28 (50.9)	58 (50.4)	
Origin: No. (%)				
No. Patients	60	55	115	.128*
Caucasian	52 (86.7)	40 (72.7)	92 (80.0)	
African Descent	7 (11.7)	9 (16.4)	16 (13.9)	
East/SE Asian	0	3 (5.5)	3 (2.6)	
Hispanic	1 (1.7)	3 (5.5)	4 (3.5)	
Age:yrs.				
No. Patients	60	55	115	.518**
Mean	38.96	38.30	38.65	
Median	39.18	35.70	37.78	
Standard Dev.	10.13	10.65	10.34	
Minimum	18.68	19.01	18.68	
Maximum	61.60	67.13	67.13	

The following investigators were pooled: (009 011 016 017 019 020 021 025)
RMP.F1DP.JCLLIB(ASBSAGW)
RMP.F1DP.SASMACRO(SBASEA)
* Frequencies are analyzed using a Fisher's exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance

Dosing Information

The majority of patients were dosed in the 15-20mg/day range. See the table below.

Modal Drug Dosage
F1D-MC-HGGW, Acute Phase

	Olanzapine
Number of Patients (%)	
5.0 mg	3 (5.5%)
10.0 mg	5 (9.1%)
15.0 mg	21 (38.2%)
20.0 mg	26 (47.3%)
Total	55
Dosage (mg)	
Mean	16.4
Modal	20.0
Median	15.0
Std. Dev.	4.2

Concomitant Medications

Concomitant medications used by at least 10% of the patients are summarized in the table below. There were no statistically significant differences in the categorical use of any concomitant medications during the study. The most frequently used medication was lorazepam, taken by 69.6% of the patients.

Concomitant Medications
Reported by at Least 10% of Patients
F1D-MC-HGGW, Acute Phase

Drug Name	Placebo (N=60) n (%)	Olz (N=55) n (%)	Total (N=115) n (%)	p-Value*
PATIENTS WITH >= 1 DRUG	59 (98.3)	53 (96.4)	112 (97.4)	.606
PATIENTS WITH NO DRUGS	1 (1.7)	2 (3.6)	3 (2.6)	.606
LORAZEPAM	44 (73.3)	36 (65.5)	80 (69.6)	.419
PARACETAMOL	33 (55.0)	31 (56.4)	64 (55.7)	1.00
IBUPROFEN	18 (30.0)	10 (18.2)	28 (24.3)	.192
MAGNESIUM HYDROXIDE	8 (13.3)	6 (10.9)	14 (12.2)	.780

*P-value obtained by using a two-tailed Fisher's Exact test

Analysis

The primary intent of this study was to assess the efficacy of olanzapine compared with placebo in the treatment of overall manic symptomatology as measured by reductions from baseline on the Y-MRS total score after 4 weeks of acute therapy.

Analysis of variance (ANOVA) models were used to evaluate continuous data; the models included the terms for treatment, investigator, and treatment-by-investigator interaction unless there were sparse data. The analyses were performed on the original scale data unless the assumptions of the ANOVA appeared to be violated, in which case, results from the rank-transformed data were reported. Type III sums of squares were used. For analysis of proportions, Fisher's exact test was used. If there were less than 2 patients per treatment group within an investigative site, those data were pooled with data from other small investigative sites. All tests of hypotheses were tested at a two-sided a level of 0.05. Treatment-by-investigator interactions and heterogeneity across investigative sites were tested at a level of 0.10.

Efficacy Results

Please see efficacy tables in appendix.

The following scales were statistically significant for all four weeks of LOCF ratings; Y-MRS, CGI-BP Severity of Mania, CGI-BP Severity of Overall Bipolar Illness, PANSS Total, PANSS Positive.

EFFICACY CONCLUSION FOR HGGW

Study HGGW is a positive study in support of the indication. I spoke with the FDA statistician Kun He Ph.D. and he agrees with this conclusion.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

There was no attempt to find a dose-response relationship since these were dose ranging studies.

The sponsor performed subgroup analyses to examine the consistency of treatment effects over the strata of various demographic populations. The subgroups analyzed were gender, racial origin (Caucasian, other), age (less than 40 years, at least 40 years), bipolar mixed versus bipolar manic, psychotic versus non-psychotic features, presence or absence of a rapid cycling course, concomitant benzodiazapine use, previous episodes of mania in the last 12 months (less than 3, at least 3), previous lithium use, previous valproate use, and previous antipsychotic use. A subgroup was analyzed only if the number of patients in each strata was 10 or more. None of these factors are clear predictors of response.

The question I raised in my previous review about diagnostic validity appears to be largely answered by the additional data from the audit the company provided. The hospital discharge summaries support the companies position that the patients were bipolar but do not explain why the audited group was never treated with any approved antimanic drug in the previous two years.

7.3.2 Size of Treatment Effect

The sponsor has provided the table below indicating the size of the treatment effect.

Treatment Difference in YMRS Total from Baseline to Endpoint 95% Confidence Intervals (Placebo – Olanzapine 5 to 20 mg) Bipolar Acute Overall Integrated Database

Study	Difference Between Means	Lower 95% Confidence Limit	Upper 95% Confidence Limit
F1D-MC-HGEH Study 1	-4.90204	-12.0771	2.27305
F1D-MC-HGEH Study 2	-6.33413	-12.5655	-0.10275
F1D-MC-HGGW	-8.37153	-13.0851	-3.65798
Across all studies	-6.01557	-9.1987	-2.83244

HGEH study 2 demonstrates a treatment effect that is reasonably persuasive even if it just fails to be significant at p=0.54.

7.3.3 Choice of Dose

The modal dose for an individual patient is displayed in the tables below. These tables are consistent with the treatment dose being in the range of 10-20 mg/day. Doses above 20mg/day were not evaluated. No drug concentration information was collected.

Modal Drug Dosage
F1D-MC-HGEH, Acute Phase

Olanzapine
Number of Patients (%)
0.0 mg 2 (2.9%)
5.0 mg 1 (1.4%)
10.0 mg 20 (28.6%)
15.0 mg 20 (28.6%)
20.0 mg 27 (38.6%)
Total 70
Dosage (mg)
Mean 14.9
Median 15.0
Std. Dev. 5.0

Modal Drug Dosage
F1D-MC-HGGW, Acute Phase

	Olanzapine
Number of Patients (%)	
5.0 mg	3 (5.5%)
10.0 mg	5 (9.1%)
15.0 mg	21 (38.2%)
20.0 mg	26 (47.3%)
Total	55
Dosage (mg)	
Mean	16.4
Modal	20.0
Median	15.0
Std. Dev.	4.2

7.3.4 Duration of Treatment

There is insufficient data to support any efficacy claim beyond four weeks of treatment.

7.4 Conclusions Regarding Efficacy Data

HGGW supports the efficacy claim clearly. HGEH-study 2, although barely missing significance at p=0.54 has a treatment effect that is supportive of efficacy. The p value may fall short because the study was not adequately powered. The previous ambiguity regarding the diagnostic status of the patients has been cleared up with additional documentation provided by the sponsor. The sample of patients we audited did seem to be diagnosed bipolar on hospital

admission and discharge summaries. For reasons I don't understand and were not well documented, the attending physicians did not treat them with approved antimanic drugs in the prior two years.

8.0 Safety Findings

8.1 Methods

As of 24 February 1999, olanzapine had been investigated in 3 randomized placebo-controlled clinical trials, F1D-MC-HGEH Study 1 (N=72), F1D-MC-HGEH Study 2 (N=67), and F1D-MC-HGGW (N=115), and 1 long-term open label continuation study, F1D-MC-HGEH (N=113), for the treatment of mania associated with bipolar I disorder. This summary provides a composite of safety data from these trials. The data cutoff date for information included in this integrated summary of safety was 24 February 1999 for HGGW and 16 October 1998 for HGEH. The final acute phase visit for HGGW occurred on 19 February 1999. This integrated safety data base deals only with the 125 Olanzapine patients and 129 placebo patients who participated in the acute trials. The 49 placebo patients rerandomized to Olanzapine in HGEH open phase are dealt with separately by the sponsor and I have included them in section 9.0 of this review.

In the acute phase of these three studies, 125 patients were assigned to receive at least one dose of olanzapine and 129 patients were assigned to receive placebo.

Data from the three double-blind placebo-controlled studies (HGEH Study 1, HGEH Study 2, and HGGW) have been combined to comprise the bipolar integrated safety database. The maximum duration of the acute phases of these studies ranged from 3 weeks (HGEH Study 1 and HGEH Study 2) to 4 weeks (HGGW).

The more commonly encountered adverse experiences were assessed using data from the placebo-controlled trials. Less frequent, but more grave adverse experiences were investigated by examining any death, reasons for premature discontinuation from clinical trials and the sponsor's safety reports of potentially serious adverse events from all patients throughout both the double-blind and open study periods.

8.2 Deaths

There were no deaths during or within 30 days of the patients' participation in the acute phase of these trials. One death by suicide was reported approximately 9 months after the patient completed study HGGW. One death was reported after completion of the one-year open-label phase of HGEH. This patient 003-1112 was found dead by a family member one day after completing the open-label phase of HGEH. The autopsy report concluded the patient died of arteriosclerotic cardiovascular disease with myocardial fibrosis and diabetes mellitus as contributing factors. Patient summaries for these patients were provided and reviewed.

8.3 Assessment of Dropouts

8.3.1 Overall Pattern of Dropouts

A statistically significant number of placebo patients dropped out due to lack of efficacy as compared to study drug. Please see the table below.

Table 2.4. Patient Disposition
Bipolar Integrated Database Acute Phase

Reason for Discontinuation	Placebo (N=129) n (%)	Olz (N=125) n (%)	Total (N=254) n (%)	p-Value*
Reporting Interval Complete	49 (38.0)	77 (61.6)	126 (49.6)	<.001
Adverse Event	3 (2.3)	2 (1.6)	5 (2.0)	1.00
Lack of Efficacy	56 (43.4)	35 (28.0)	91 (35.8)	.013
Lost to Follow-up	4 (3.1)	1 (0.8)	5 (2.0)	.370
Patient Decision	9 (7.0)	9 (7.2)	18 (7.1)	1.00
Criteria not met / Compliance	1 (0.8)	1 (0.8)	2 (0.8)	1.00
Sponsor Decision	3 (2.3)	0	3 (1.2)	.247
Physician Decision	4 (3.1)	0	4 (1.6)	.122

Patients included in the reasons discontinued, Reporting Interval Complete and Lack of Efficacy, may have continued into the next reporting interval or discontinued from the study.
P-value obtained by using a two-tailed Fisher's Exact test

8.3.2 Adverse Events Associated with Dropout

Of the 254 patients included in the bipolar integrated acute database, 5 patients (2 olanzapine-treated and 3 placebo-treated patients) discontinued from the studies because of an adverse event. None of the rates of discontinuation for the reported adverse events showed a statistically significant difference between the olanzapine-treated and the placebo-treated patients. Among the placebo-treated patients, 3 discontinued because of adverse events including 1 report of agitation, 1 report of dystonia and 1 report of convulsion. Among the olanzapine-treated patients, 2 discontinued because of adverse events including 1 report of rash and 1 report of unintended pregnancy. Patient summaries for these patients were provided and reviewed.

Table 2.5. Adverse Events Reported as Reason for Discontinuation Bipolar Integrated Database Acute Phase

Event Classification	Placebo (N=129) n (%)	Olz (N=125) n (%)	p-Value*
PATIENTS DISCONTINUED	3 (2.3)	2 (1.6)	1.00
AGITATION	1 (0.8)	0	1.00
CONVULSION	1 (0.8)	0	1.00
DYSTONIA	1 (0.8)	0	1.00
RASH	0	1 (0.8)	.492
UNINTENDED PREGNANCY	0	1 (0.8)	.492

• Frequencies are analyzed using a Fisher's Exact test.

Of the 113 patients included in the open-label extension, only 7 patients (6.2%) discontinued from the trial because an adverse event. The adverse events reported as the reason for discontinuation by olanzapine-treated patients are summarized in the table below.

Adverse Events Reported as Reason for Discontinuation F1D-MC-HGEH, Open-Label Phase

Event Classification	Olz (N=113) n (%)
PATIENTS DISCONTINUED	7 (6.2)
DEPRESSION	2 (1.8)
ACCIDENTAL INJURY	1 (0.9)
DRUG DEPENDENCE	1 (0.9)
HOSTILITY	1 (0.9)
HYPERGLYCEMIA	1 (0.9)
UNINTENDED PREGNANCY	1 (0.9)

The patient who discontinued for hyperglycemia was an insulin-dependent diabetic with a history of difficulty maintaining proper blood sugar levels.

8.4 Search for Serious Adverse Events

Serious adverse events were defined as any experience that was fatal or life threatening, incapacitating, permanently disabling, required hospitalization, or resulted in a prolongation of hospitalization, or was a congenital anomaly, cancer, or an overdose.

The table below summarizes all serious adverse events in the placebo-controlled phases of studies HGGW and HGEH. There were 5 serious adverse events occurring in 3 olanzapine-treated patients compared to 23 serious adverse events occurring in 11 placebo treated patients. The 5 serious adverse events were 1 anxiety, 1 hostility, 1 libido increased, and 2 paranoid reactions among olanzapine-treated patients. There were no statistically significant differences between treatment groups for any of the serious adverse events. Patient summaries for these patients were provided and reviewed.

Summary of Serious Adverse Events
Bipolar Integrated Database Acute Phase

SERIOUS	Olz-0520			Placebo			Overall
	N	n	%	N	n	%	p-Value
AGITATION	125	0	0.0%	129	3	2.3%	.247
ANXIETY	125	1	0.8%	129	1	0.8%	1.00
CONFUSION	125	0	0.0%	129	2	1.6%	.498
CONVULSION	125	0	0.0%	129	1	0.8%	1.00
DELUSIONS	125	0	0.0%	129	1	0.8%	1.00
DEPRESSION	125	0	0.0%	129	2	1.6%	.498
HALLUCINATIONS	125	0	0.0%	129	1	0.8%	1.00
HOSTILITY	125	1	0.8%	129	0	0.0%	.492
INSOMNIA	125	0	0.0%	129	2	1.6%	.498
INTENTIONAL OVERDOSE	125	0	0.0%	129	1	0.8%	1.00
LIBIDO INCREASED	125	1	0.8%	129	0	0.0%	.492
NERVOUSNESS	125	0	0.0%	129	2	1.6%	.498

PAIN	125	0	0.0%	129	1	0.8%	1.00
PARANOID REACTION	125	2	1.6%	129	1	0.8%	.618
PERSONALITY DISORDER	125	0	0.0%	129	3	2.3%	.247
THINKING ABNORMAL	125	0	0.0%	129	1	0.8%	1.00

The table below summarizes the serious adverse events in the open-label phase of study HGEH. There were 86 serious adverse events occurring among 27 olanzapine-treated patients. Patient summaries for these patients are provided in the patient summaries sections of the integrated summary of safety and were reviewed.

Table Summary of Serious Adverse Events
F1D-MC-HGEH Open Label Final

Serious Events	N	n	%
DEPRESSION	113	9	8.0%
THINKING ABNORMAL	113	8	7.1%
INSOMNIA	113	7	6.2%
AGITATION	113	5	4.4%
HALLUCINATIONS	113	5	4.4%
ANXIETY	113	4	3.5%
MANIC REACTION	113	4	3.5%
NERVOUSNESS	113	4	3.5%
PERSONALITY DISORDER	113	4	3.5%
DELUSIONS	113	3	2.7%
HOSTILITY	113	3	2.7%
PARANOID REACTION	113	3	2.7%
ACCIDENTAL OVERDOSE	113	2	1.8%
CONFUSION	113	2	1.8%
EUPHORIA	113	2	1.8%
LIBIDO INCREASED	113	2	1.8%
PSYCHOSIS	113	2	1.8%
SLEEP DISORDER	113	2	1.8%
ABDOMINAL PAIN	113	1	0.9%
ACCIDENTAL INJURY	113	1	0.9%
ADDICTION	113	1	0.9%
ALCOHOL INTOLERANCE	113	1	0.9%

CHEST PAIN	113	1	0.9%
CHOLECYSTITIS	113	1	0.9%
DRUG DEPENDENCE	113	1	0.9%
EMOTIONAL LABILITY	113	1	0.9%
INCREASED APPETITE	113	1	0.9%
INTENTIONAL INJURY	113	1	0.9%
OVERDOSE	113	1	0.9%
SPEECH DISORDER	113	1	0.9%
SUICIDE ATTEMPT	113	1	0.9%
THIRST	113	1	0.9%
TWITCHING	113	1	0.9%

Dropouts and deaths have been discussed in previous sections. Laboratory abnormalities, overdoses, withdrawal phenomena and pregnancy related events will be discussed in subsequent sections of this review.

8.5 Other Safety Findings

8.5.1 ADR Incidence Tables

8.5.1.1 Appropriateness of Adverse Event Categorization and Preferred Terms

The sponsor has modified the list of COSTART term and provided reasons for the alterations in their modified COSTART list. I have reviewed this list and find the organization to be reasonable. This table lists all COSTART classification terms reflecting a treatment-emergent adverse event in the primary database for olanzapine.

8.5.1.2 Incidence in Controlled Clinical Trials

Somnolence, dry mouth, dizziness, and asthenia were reported statistically significantly more frequently in olanzapine-treated patients than in placebo-treated patients. No treatment-emergent adverse events were reported statistically significantly more frequently in placebo-treated patients than in olanzapine-treated patients. However, the percentage of patients reporting at least one treatment-emergent adverse event was not statistically significantly different between treatment groups. The most commonly reported treatment-emergent adverse events (> 10% incidence) among olanzapine-treated patients were somnolence, dry

mouth, dizziness, headache, asthenia, agitation, constipation, and dyspepsia. Among placebo-treated patients, the most common events were agitation, headache, nervousness, somnolence, anxiety, hostility, and personality disorder.

Among events seen in 5% of the patients, those with 2 times the incidence in study drug vs. placebo include: somnolence, dry mouth, dizziness, asthenia, constipation, dyspepsia, pain, weight gain and increased appetite.

8.5.1.3 Post Marketing Spontaneous Reports

The sponsor had provided an analysis of postmarketing use of olanzapine for bipolar patients. It is reproduced in truncated form in italics below.

In order to assess whether spontaneous adverse event reports for olanzapine in the treatment of bipolar disorder contribute information regarding the safety of olanzapine that is new or different from information already known, the [ ] database was searched for spontaneous adverse event reports involving patients who may have been treated with olanzapine for bipolar disorder. This search was conducted electronically by the Lilly Global Safety Monitoring Team (GMT) responsible for the [ ] database. The identification of adverse event reports temporally associated with the use of olanzapine in the treatment of bipolar disorder was performed by Lilly personnel and reviewed by a physician board-certified in psychiatry. All olanzapine entries in the [ ] database through 30 June 1997 were searched.

b(4)

After the electronic search and the reviews were conducted, a list was prepared of all Coding Symbol and Thesaurus for Adverse Reaction Terms (COSTART) that appeared in spontaneous adverse event reports in bipolar patients, along with the number of reports of each event term and the percentage of the total events reported in patients with a bipolar disorder diagnosis.

Based on the detailed clinical review of spontaneous adverse event reports for patients considered to have been treated with olanzapine for bipolar disorder and the comparison of the relative frequencies of COSTART classification terms for bipolar versus nonbipolar patients, it cannot be concluded that bipolar patients are at increased risk for any adverse event or any unique adverse events relative to their nonbipolar counterparts.

Similarly, a review of the spontaneous adverse event reports was conducted to evaluate reports from patients who received mood stabilizers concomitantly with olanzapine. The mood stabilizers included in the search were lithium and valproate as well as the

anticonvulsants, used by clinicians as mood stabilizers, carbamazepine, gabapentin, and lamotrigine. There was no conclusive indication that patients treated concomitantly with mood stabilizers are at increased risk for any adverse event or unique adverse events compared with patients not treated concomitantly with mood stabilizers.

Furthermore, spontaneous events that have been reported by bipolar patients and by patients both treated and not treated concomitantly with mood stabilizers are adequately described in the product labeling for olanzapine.

8.5.2 Laboratory Findings

The following sections will provide proportions of patients in the double-blind placebo-controlled trial who met arbitrarily defined criteria for changes in laboratory variables of possible clinical significance. There will also be comparisons of olanzapine versus placebo regarding mean changes in baseline parameters of laboratory values and a listing of patients who discontinued due to laboratory abnormalities.

8.5.2.1 Clinical Chemistry Findings

The chemistry criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial fell outside the defined criteria for changes and the table of change in mean baseline for this section.

A statistically significantly greater proportion of olanzapine-treated than placebo-treated patients experienced high ALT/SGPT (olanzapine, 19.3%; placebo, 1.8%), high AST/SGOT (olanzapine, 9.9%; placebo, 0%), low non-fasting glucose (olanzapine, 5.2%; placebo, 0%), high inorganic phosphorus (olanzapine, 14.4%; placebo, 4.7%) and abnormal urinary glucose (olanzapine, 6.7%; placebo, 0.9%) values. Twenty-three olanzapine-treated patients had an increase in ALT/SGPT above the upper limit of the Lilly reference range at some time during the acute phase, 6 of them returned to within normal limits during continued treatment with olanzapine, 3 of them had a decreasing trend during continued treatment although their ALT/SGPT values were still above the upper limit at their last visit, and 2 of them had increased ALT/SGPT at their last visit. Eight of 12 olanzapine-treated patients who had an increase in AST/SGOT at some time returned to within normal limits during continued treatment with olanzapine, 1 patient had increased AST/SGPT at the last visit. None of these patients displayed clinical symptoms of hepatic dysfunction. For the 5 patients who remained abnormal in ALT/SGPT at their last visits, the hepatitis serology tests all exhibited negative results. There

were no other statistically significant differences between treatment groups in the proportion of patients with treatment-emergent abnormal, high, or low laboratory values at any time during acute treatment.

A summary of baseline-to-endpoint changes by treatment group is presented for each laboratory analyte in the appendix. Statistically significant differences between the olanzapine and placebo groups were observed for; AST/SGOT (olanzapine, 9.09 U/L; placebo, -0.21 U/L); ALT/SGPT (olanzapine, 21.39 U/L; placebo, 1.09 U/L); creatine phosphokinase (olanzapine, -2.49 U/L; placebo, 66.40 U/L); chloride (olanzapine, 1.37 mmol/L; placebo, 0.17 mmol/L); total protein (olanzapine, -0.58 g/L; placebo, 1.09 g/L); albumin (olanzapine, -1.07 g/L; placebo, 0.74 g/L); uric acid (olanzapine, 26.94 mmol/L; placebo, 2.85 mmol/L); cholesterol (olanzapine, 0.44 mmol/L; placebo, 0.15 mmol/L); bicarbonate, HCO3 (olanzapine, -0.93 mmol/L; placebo, -0.26 mmol/L); and total bilirubin (olanzapine, -0.60mmol/L; placebo, 0.21 mmol/L).

Because the absolute change in these analytes was small and/or the placebo group had a larger absolute change than the olanzapine group, the treatment differences observed were not considered to be clinically significant.

Of the 254 patients included in the bipolar integrated database, no patients discontinued because of an abnormal laboratory value.

8.5.2.2 Hematology Findings

The hematology criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the criteria for changes and the table of change in mean baseline for this section.

Statistically significant differences in mean change from baseline between the olanzapine and placebo groups were observed for hematocrit (olanzapine, -1%; placebo, 0%); hemoglobin (olanzapine, -0.12 mml/L-Fe; placebo, 0.06 mml/L-Fe); mean cell hemoglobin (olanzapine, -0.02 fmol(Fe); placebo, -0.00 fmol(Fe)); eosinophils (olanzapine, 0.02 GI/L; placebo, -0.02 GI/L).

There were no significant differences in proportion of patients who fell outside defined criteria values.

No patients discontinued because of an abnormal laboratory value.

8.5.2.3 Urinalysis

The urinalysis criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the defined criteria for changes and the table of change in mean baseline for this section.

Statistically significant differences between the olanzapine and placebo groups were observed for); urinary PH (olanzapine, -0.38 U; placebo, -0.03 U).

There were no significant differences in proportion of patients who fell outside defined criteria values.

No patients discontinued because of an abnormal laboratory value.

8.5.3 Vital Signs

The vital sign criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the defined criteria for changes and the table of change in mean baseline for this section.

There were no statistically significantly differences between the proportions of olanzapine-treated and placebo-treated patients with potentially clinically significant change in vital signs or weight. A potentially clinically significant change in low supine systolic blood pressure was experienced by 5.8% of placebo-treated patients compared with 0.8% of olanzapine-treated patients. No other potentially clinically significant change was reported in more than 5% of patients in either treatment group.

The mean changes from baseline to endpoint in weight and standing pulse were statistically significantly different between the olanzapine and placebo groups. Olanzapine-treated patients had a baseline-to-endpoint mean weight gain of 1.85 kg compared with a mean weight loss of 0.01 kg in the placebo-treated patients. Olanzapine-treated patients had a baseline-to-endpoint mean increase in standing pulse of 3.79 beats/min compared with a mean decrease of 1.05 beats/min in the placebo-treated patients. These

changes were not considered clinically significant by the sponsor or myself.

Of the 254 patients included in the bipolar integrated database, no patients discontinued because of vital signs or weight.

8.5.4 ECGs

The ECG criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the arbitrarily defined criteria for changes and the table of change in mean baseline for this section.

No statistically significant differences existed between the olanzapine and placebo groups in the proportion of patients with potentially clinically significant change in ECG intervals and heart rate.

There were no statistically significant differences between the olanzapine and placebo groups in the analysis of mean change from baseline to endpoint for ECG intervals or heart rate.

Of the 254 patients included in the bipolar integrated database, no patients discontinued because of a change in ECG or heart rate.

8.5.5 Special Studies

None done.

8.5.6 Withdrawal Phenomena/Abuse Potential

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. There is no significant change from previous data and recommendations in this section.

8.5.7 Human Reproduction Data

There are no adequate and well-controlled trials with olanzapine in pregnant females. There is no significant change from previous data and recommendations in this section.

8.6 Overdose Experience

There is no significant change from previous data and recommendations in this section.

8.7 Summary of Important Events Considered Drug Related

There are no significant new findings here.

8.8 Important Events Considered Not Drug Related

Certain events have been discussed elsewhere in this document and have been excluded from this list (i.e., deaths, overdoses, dropouts and changes in laboratory values).

The rest of the serious adverse events are considered not drug related and they are displayed in the Appendix of serious adverse events and were reviewed.

8.9 Summary of Drug Interactions

8.9.1 Drug-Demographic Interactions

The sponsor feels there were no statistically significant treatment-by-subgroup interactions. Subgroup analyses were performed to examine the consistency of treatment effects over the strata of various demographic populations. The subgroups that were candidates for analysis were gender, racial origin (Caucasian, other), and age (less than 40 years, 40 years or older). A subgroup was analyzed only if the number of patients in each strata was 10 or more. The incidence of treatment-emergent adverse events and treatment-emergent abnormal high or low laboratory values, as well as mean change in vital signs, weight, and ECG heart rate and intervals were examined. A few statistically significant treatment-by-subgroup differences were noted, but none were considered clinically relevant by the sponsor or myself.

8.9.2 Drug-Disease Interactions

There are no new precautions regarding drug-disease interactions. The sponsor continues to urge cautious use 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). 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 by the sponsor in patients with significant hepatic disease

8.9.3 Drug-Drug Interactions

The sponsor describes two drug interaction studies that I listed in my previous review of this supplement. The first study was designed to evaluate the influence of fluoxetine on the pharmacokinetic characteristics of olanzapine. A brief summary provided by the sponsor is presented in italics below.

F1D-MS-HGCI: Pharmacokinetic Interaction of Fluoxetine on Olanzapine

Fifteen healthy, non-smoker volunteers (11 males, 4 females), aged 23 to 40 years, completed an interaction study designed to determine the pharmacokinetics, safety, and potential interaction of a single oral dose of olanzapine 5 mg following a single dose or multiple doses of fluoxetine 60 mg. Plasma concentrations for both drugs, sampled up to 120 hours postdose, were measured by either HPLC/EC (olanzapine) or GC/EC (fluoxetine). Safety was assessed by means of clinical examinations, laboratory tests, and the record of symptoms.

Results: *A small (about 16%) increase in olanzapine C_{max} and a small (about 16%) decrease in olanzapine plasma clearance was observed when olanzapine was given with fluoxetine. This result may reflect the known inhibition of CYP2D6 by fluoxetine, and the small magnitude of change thus reflects the minor role of CYP2D6 in the overall metabolic scheme of olanzapine. There were no serious or unexpected adverse events. The most frequent symptoms were dry mouth (6 reports by 2 subjects) and asthenia (4 reports by 2*

subjects). At each period, there was a statistically significant time effect for blood pressure and pulse (in supine position); mean blood pressure and pulse in supine position 4 hours after the administration of olanzapine was lower in all periods. There were no clinically significant changes in laboratory data obtained 5 days after olanzapine dosing. No clinically significant changes were observed during the study in liver enzymes (AST, ALT, and GGT).

Conclusions: *The small pharmacokinetic changes observed in olanzapine Cmax and plasma clearance were statistically significant, but unlikely to be clinically important, and fluoxetine does not modify the safety of olanzapine.*

The sponsor gives a preliminary report on an on-going 2nd study of valproate and olanzapine which is summarized below in italics.

Low-dose valproate (£ 1000 mg daily) administered alone and together with 10 mg olanzapine was safe in each patient enrolled in the study. The pharmacokinetic profile of olanzapine in this study was similar to that captured in the clinical pharmacology data base. No alterations in the pharmacokinetic profile of olanzapine or in the steady-state concentrations of valproate were apparent. The study is ongoing, and recruitment efforts are continuing.

9.0 Safety Update of Open Label Patients

The safety update consists of the open label patients from HGEH who were not included by the sponsor in the integrated safety database consisting of the acute phases of the two trials HGEH and HGGW. F1D-MC-HGEH Open-Label Extension was conducted at 16 investigative sites in the United States. The study included 113 patients with a DSM-IV diagnosis of bipolar I disorder displaying an acute manic or mixed episode (with or without psychotic features) as determined by the SCID-P. This study assessed the use of olanzapine (5, 10, 15, or 20 mg/day).

A total of 113 patients entered the open-label phase of study F1D-MC-HGEH. The average patient exposure was 192.8 days in this group. The median and mean modal daily doses of olanzapine were 15.0 mg/day and 13.8 mg/day, respectively. A total of 59 patients were previously randomized to the olanzapine arm during the acute phase of the study, and a total of 54 patients were previously randomized to placebo.

One death was reported in the long-term open-label database during or within 30 days of discontinuation from the study. Patient 003-1112 was found dead by a family member one day after completing the

open-label phase of HGEH. The autopsy report concluded the patient died of arteriosclerotic cardiovascular disease with myocardial fibrosis and diabetes mellitus as contributing factors. This death is listed in the section on deaths (8.2) in this review.

7 patients (6.2%) discontinued from the trial because of an adverse event (depression (2), accidental injury, drug dependence, hostility, hyperglycemia, and unintended pregnancy). The patient who discontinued for hyperglycemia was an insulin-dependent diabetic with a history of difficulty maintaining proper blood sugar levels. These patients are listed in the main section listing dropouts due to adverse events (8.3.2).

The most commonly reported (incidence > 10%) treatment-emergent adverse events among olanzapine-treated patients were depression (34.5%), somnolence (31.9%), weight gain (31.9%), increased appetite (19.5%), asthenia (17.7%), rhinitis (17.7%), dry mouth (15.0%), insomnia (15.0%), pain (14.2%), headache (13.3%), agitation (10.6%), and anxiety (10.6%).

Olanzapine-treated patients experienced a statistically significant within-group increase from baseline to endpoint in supine diastolic blood pressure (2.45 mm) and weight (5.81kg). In the analysis of potentially clinically significant changes in vital signs, the most frequent change was weight gain (2.8%). None of these 3 cases resulted in discontinuation. No other vital sign had more than 1 patient with a potentially clinically significant change.

From the analysis of laboratory analytes, olanzapine-treated patients experienced a statistically significant within-group increase from baseline to endpoint in erythrocyte count, mean cell hemoglobin concentration, urinary pH, alkaline phosphatase, creatinine, total protein, uric acid, bicarbonate, and total bilirubin. There was a statistically significant within-group decrease from baseline to endpoint in mean cell hemoglobin (MCH), mean cell volume (MCV), urea nitrogen, inorganic phosphorus, and potasium. None of these results were considered clinically significant by the sponsor or myself.

In the analysis of treatment-emergent abnormal, high, or low laboratory values at any time during the open-label phase, the most frequently occurring treatment-emergent laboratory values were increased ALT/SGPT (17.0%) and abnormal urinary protein (12.0%). The only observed potentially clinically significant changes in the open-label database were increases in erythrocyte count (1) and GGT (1) and a decrease in hemoglobin (1). None of these results were considered clinically significant by the sponsor or myself.

In the analysis of mean change from baseline to endpoint for ECG heart rate and interval times, olanzapine-treated patients

experienced no statistically significant within-group changes. The most frequently observed potentially clinically significant change in olanzapine-treated patients was an increase in the corrected QT interval (10.3%).

No olanzapine-treated patients discontinued because of an adverse event associated with ECGs.

10.0 Labeling Review

I will go through the new labeling section by section with comments about changes.

CLINICAL EFFICACY DATA:

This section has been updated to include the results from the bipolar studies. The negative trial is not mentioned and data has been combined to report two positive studies, i.e. HGGW and HGEH (study1 and study2) combined.

INDICATIONS AND USAGE:

The bipolar indication has been added.

PRECAUTIONS- SUICIDE:

The bipolar indication has been added.

USE IN PATIENTS WITH CONCOMITANT ILLNESS:

Material has been added regarding a study in Alzheimers patients.

THE EFFECT OF OTHER DRUGS ON OLANZAPINE:

The two new drug interaction studies have been appropriately described.

GERIATRIC USE:

Material has been added regarding a study in Alzheimers patients.

ADVERSE REACTIONS:

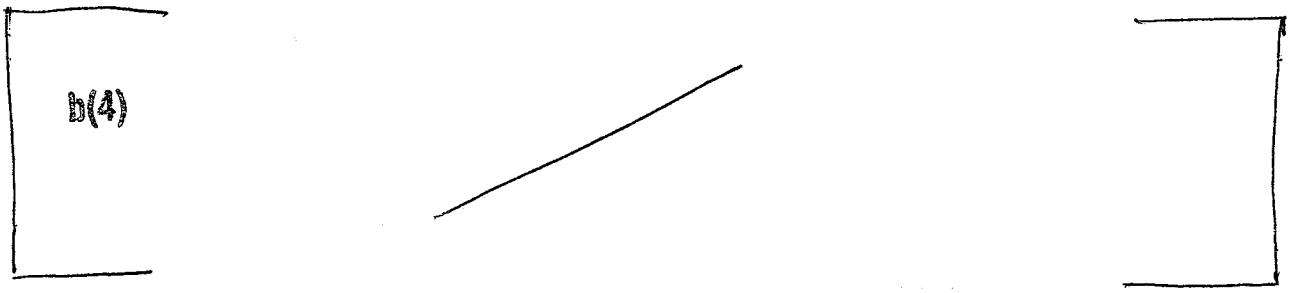
This section is updated for the increased database with certain disclaimers for analyses done only for the psychotic database and believed to be generally applicable to the bipolar patients. Tables have been updated with the bipolar patients added.

ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATIONS:

This section is updated correctly with the bipolar data.

MOST COMMON TREATMENT EMERGENT ADVERSE EVENTS:

This section is updated correctly with the bipolar data.



DOSAGE

The section now has a bipolar mania dosage section. There are disclaimers regarding maintenance therapy.

There are minor corrections of the text in other places which are technical in nature and not of clinical significance.

11.0 Conclusions

Olanzapine is safe when used in patients seen in this database. One of two studies for HGEH is arguable mildly positive while an additional study HGGW is positive.

12.0 Recommendations

I recommend that olanzapine be approved for the acute treatment of bipolar mania or mixed episodes.

Earl D Hearst MD. 8/30/99

Earl D. Hearst, M.D.
Medical Reviewer

file/tlaughren/ehearst/batsed

10-15-99
I agree that this supplement is approvable. See memo to file for detailed comments.
Thomas P. Laughren, MD
TL, PDP

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APPENDIX

Patient Enumeration by Database, Study Type, and Study Design

	Treatment Group	
Database/Study Type/Study Design	**Olanzapine**	**Placebo**
Placebo-Controlled Studies	125	129
HGEH Open-Label	113(59)[a]	
Total	179	129

[a] Number in parentheses (59) represents olanzapine-treated patients participating in open-label extension studies, but already counted in the Olanzapine column under Placebo-Controlled

Table 2.1. Patient Characteristics
Bipolar Integrated Database Acute Phase

Variable	Placebo (N=129)	Olz (N=125)	Total (N=254)	p-Value
Sex: No. (%)				
No. Patients	129	125	254	.802*
Male	67 (51.9)	62 (49.6)	129 (50.8)	
Female	62 (48.1)	63 (50.4)	125 (49.2)	
Origin: No. (%)				
No. Patients	129	125	254	.424*
Caucasian	100 (77.5)	93 (74.4)	193 (76.0)	
African Descent	22 (17.1)	22 (17.6)	44 (17.3)	
East/SE Asian	0	3 (2.4)	3 (1.2)	
Hispanic	6 (4.7)	7 (5.6)	13 (5.1)	
Other Origin	1 (0.8)	0	1 (0.4)	
Age:yrs.				
No. Patients	129	125	254	.674**
Mean	38.83	39.40	39.11	
Median	39.41	38.48	38.93	
Standard Dev.	10.21	11.19	10.68	
Minimum	18.68	18.15	18.15	
Maximum	62.58	67.13	67.13	

RMP.F1DP.JCLLIB(ISBSAB2)
RMP.F1DP.SASMACRO(SBASEA)
* Frequencies are analyzed using a Fisher's exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

Table 2.4. Patient Disposition
Bipolar Integrated Database Acute Phase

Reason for Discontinuation	Placebo (N=129) n (%)	Olz (N=125) n (%)	Total (N=254) n (%)	p-Value*
Reporting Interval Complete	49 (38.0)	77 (61.6)	126 (49.6)	<.001
Adverse Event	3 (2.3)	2 (1.6)	5 (2.0)	1.00
Lack of Efficacy	56 (43.4)	35 (28.0)	91 (35.8)	.013
Lost to Follow-up	4 (3.1)	1 (0.8)	5 (2.0)	.370
Patient Decision	9 (7.0)	9 (7.2)	18 (7.1)	1.00
Criteria not met / Compliance	1 (0.8)	1 (0.8)	2 (0.8)	1.00
Sponsor Decision	3 (2.3)	0	3 (1.2)	.247
Physician Decision	4 (3.1)	0	4 (1.6)	.122

Patients included in the reasons discontinued, Reporting Interval Complete and Lack of Efficacy, may have continued into the next reporting interval or discontinued from the study.
P-value obtained by using a two-tailed Fisher's Exact test
RMP.F1DP.JCLLIB(ISPTDAB2)
RMP.F1DP.SASMACRO(SPATDA)
XRDS0001

HGGW STUDY TABLES

F1D-MC-HGGW Investigators and Other Key Individuals

Site #	Principal Site Investigator	Other Site Investigators
1	**Robert Birnbaum, M.D.** Beth Israel-Deaconess Medical Center, East Campus 330 Brookline Avenue Boston MA 02215	b(4)
2	**K. N. Roy Chengappa, M.D.** Western Psychiatric Institute and Clinic U. of Pittsburgh Medical Center 3811 O'Hara Street Pittsburgh, PA 15213-2593	
3	**Michael Plopper, M.D.** Mesa Vista Hospital 7850 Vista Hill Avenue San Diego, CA 92123	

4	**Leighton Huey, M.D.** Department of Psychiatry University of Connecticut Health Ctr 263 Farmington Avenue Farmington, CT 06030-1410	b(4)

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

Site #	Principal Site Investigator	Other Site Investigators
5	**Susan L. McElroy, M.D.** University of Cincinnati College of Medicine 231 Bethesda Avenue, Suite 7005 Cincinnati, OH 45267	b(4)
6	**Richard Wang, M.D., Ph.D.** 4608 W. Burleigh Street Milwaukee, WI 53210	
7	**Richard H. Weisler, M.D.** 900 Ridgefield Drive, Suite 320 Raleigh, North Carolina 27609	

8	**Scott A. West, M.D.** Psychiatric Institute of Florida, PA 77 West Underwood St., 3rd Floor Orlando, Florida 32806	b(4)

(continued) F1D-MC-HGGW Investigator and Other Key Individuals

Site #	Principal Site Investigator	Other Site Investigators
9	Mohammed Alam, M.D. Elgin Mental Health Center, MB-2 750 South State Street Elgin, IL 60123-7692	b(4)
10	Jambur Ananth, M.D. Harbor - UCLA Medical Center 1000 W. Carson St., Bldg F-9, Box 495 Torrance, CA 90509-2910	
11	**Robert H. Gerner, M.D.** VA at Brentwood Ward 027C Los Angeles, CA 90073	
12	**Philip G. Janicak, M.D.** The Psychiatric Institute UIC Department of Psychiatry 1601 West Taylor Street, M/C 912 Chicago, Illinois 60612-4397	
15	**Louis Fabre, M.D.** Fabre Research Inc. 5503 Crawford Houston, Texas 77004	

(continued) F1D-MC-HGGW Investigator and Other Key Individuals

Site #	Principal Site Investigator	Other Site Investigators
16	**Jeffrey Apter, M.D.** Princeton Biomedical Research Woodland Professional Building 256 Bunn Drive, Suite 6 Princeton, NJ 08540	b(4)
17	**Raj Nakra, M.D.** #1 Barnes Plaza, Suite 16428 St. Louis, MO 63110	
19	**Arifulla Khan, M.D.** Northwest Clinical Research Center 1900 116th NE, Suite 112 Bellevue, WA 98004	
20	**Denis Mee-Lee, M.D.** Hawaii Clinical Research Center 1750 Kalakaua Ave., Suite 2602 Honolulu, HI 96826	

(continued) F1D-MC-HGGW Investigator and Other Key Individuals

Site #	Principal Site Investigator	Other Site Investigators
21	**Joseph McEvoy, M.D.** John Umstead Hospital 1003 12th Street, Building 32-AAU Butner, NC 27509	b(4)
22	**Michael Banov, M.D.** Northwest Behavioral Medicine 108 Margaret Street Marietta, GA 30060	
23	**Jeffrey Simon, M.D.** Northbrook Research Center 4600 W. Schroeder Drive Brown Deer, WI 53223	
24	**Cherian Verghese, M.D.** Albert Einstein Medical Center Tower 7, Inpatient Psychiatry 5501 Old York Road Philadelphia, PA 19141	
25	**Gabor Keitner, M.D.** Rhode Island Hospital Mood Disorders Program Potter Bldg - 3rd floor 593 Eddy Street Providence, RI 02903	

(concluded) F1D-MC-HGGW Investigator and Other Key Individuals

Site #	Principal Site Investigator	Other Site Investigators
26	**Michael DePriest** **Richard Bralliar** 6039 Eldora Suite H Las Vegas, NV 89129	b(4)

* Investigators 13, 14, and 18 never received study medication due to either IRB non-approvals or contract issues.

Table 9.3. Schedule of Events, Protocol F1D-MC-HGGW

Description of Data	V1	V2	V3	V4	V5	V6 or Final	Follow-up (501)
Weeks until next visit	2-4D	1	1	1	1	1	
Informed consent, demographics	X						
Height	X						
Kit number assigned		X					
Weight, temperature, blood pressure, heart rate	X	X	X	X	X	X	
Psychiatric examination - SCID-P	X						
Physical examination	X					X	
Significant Historical Illnesses/Family History	X						
Electrocardiography	X					X	
Previous Drug Therapy	X						
Pre-existing conditions and adverse events	X	X	X	X	X	X	
Study drug dispensed		X	X	X	X		
Concomitant medications	X	X	X	X	X	X	
Visit comments	X	X	X	X	X	X	
Adverse event follow-up, if necessary							X
Patient summary, including comments						X	
Clinical chemistry, electrolyte group	X	X	X[c]	X[c]	X[c]	X[c]	
Hematology, urinalysis	X	X	X[c]	X[c]	X[c]	X[c]	
Thyroid function, hepatitis[a], pregnancy screen[b]	X						
Urine drug screen	X[c]	X[c,d]	X[c]	X[c,d]	X[c,d]	X[c]	
Plasma sample			X			X	
Y-MRS, PANSS, HAM-D, CGI-BP Severity	X	X	X	X	X	X	
Barnes Akathisia, Simpson-Angus	X	X	X	X	X	X	
Inpatient Hospitalization	X	X	X	X	X	X	

Abbreviations: D = days; V = Visit

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

b A serum pregnancy test was performed on all females at Visit 1 and when clinically indicated.

c Labs may have occurred ±1 day relative to the visit.

d Urine Drug Screens were required at Visits 1, 3, and 6, and strongly recommended at Visits 2, 4, and 5.

Table 11.6. Concomitant Medications Reported by at Least 10% of Patients F1D-MC-HGGW, Acute Phase

Drug Name	Placebo (N=60) n (%)	Olz (N=55) n (%)	Total (N=115) n (%)	p-Value*
PATIENTS WITH >= 1 DRUG	59 (98.3)	53 (96.4)	112 (97.4)	.606
PATIENTS WITH NO DRUGS	1 (1.7)	2 (3.6)	3 (2.6)	.606
LORAZEPAM	44 (73.3)	36 (65.5)	80 (69.6)	.419
PARACETAMOL	33 (55.0)	31 (56.4)	64 (55.7)	1.00
IBUPROFEN	18 (30.0)	10 (18.2)	28 (24.3)	.192
MAGNESIUM HYDROXIDE	8 (13.3)	6 (10.9)	14 (12.2)	.780

*P-value obtained by using a two-tailed Fisher's Exact test

Table 11.1. Physical Characteristics
F1D-MC-HGGW, Acute Phase

Variable	Placebo (N=60)	Olz (N=55)	Total (N=115)	p-Value
Sex: No. (%)				
No. Patients	60	55	115	1.00*
Male	30 (50.0)	27 (49.1)	57 (49.6)	
Female	30 (50.0)	28 (50.9)	58 (50.4)	
Origin: No. (%)				
No. Patients	60	55	115	.128*
Caucasian	52 (86.7)	40 (72.7)	92 (80.0)	
African Descent	7 (11.7)	9 (16.4)	16 (13.9)	
East/SE Asian	0	3 (5.5)	3 (2.6)	
Hispanic	1 (1.7)	3 (5.5)	4 (3.5)	
Age:yrs.				
No. Patients	60	55	115	.518**
Mean	38.96	38.30	38.65	
Median	39.18	35.70	37.78	
Standard Dev.	10.13	10.65	10.34	
Minimum	18.68	19.01	18.68	
Maximum	61.60	67.13	67.13	

The following investigators were pooled: (009 011 016 017 019 020 021 025)
RMP.F1DP.JCLLIB(ASBSAGW)
RMP.F1DP.SASMACRO(SBASEA)
* Frequencies are analyzed using a Fisher's exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=investigator, treatment, and interaction.
XDES0001

Table 10.3. Patient Disposition by Visit
F1D-MC-HGGW, Acute Phase

Treatment Group: Placebo
Number of patients in the therapy group: (N=60)

	Visit 3	Visit 4	Visit 5	Visit 6
Reason for Discontinuation	n (%)	n (%)	n (%)	n (%)
Reporting Interval Complete	0	0	0	25 (41.7)
Adverse Event	1 (1.7)	0	0	0
Lack of Efficacy	12 (20.0)	8 (13.3)	3 (5.0)	0
Lost to Follow-up	0	2 (3.3)	1 (1.7)	0
Patient Decision	3 (5.0)	2 (3.3)	0	0
Physician Decision	2 (3.3)	0	1 (1.7)	0
Patients continuing	42 (70.0)	30 (50.0)	25 (41.7)	0

Table 10.3. (concluded) Patient Disposition by Visit
F1D-MC-HGGW, Acute Phase

Treatment Group: Olz
Number of patients in the therapy group: (N=55)

	Visit 3	Visit 4	Visit 5	Visit 6
Reason for Discontinuation	n (%)	n (%)	n (%)	n (%)
Reporting Interval Complete	0	0	0	34 (61.8)
Adverse Event	0	2 (3.6)	0	0
Lack of Efficacy	7 (12.7)	2 (3.6)	5 (9.1)	1 (1.8)
Lost to Follow-up	0	0	1 (1.8)	0
Patient Decision	2 (3.6)	0	1 (1.8)	0
Patients continuing	46 (83.6)	42 (76.4)	35 (63.6)	0

RMP.F1DP.JCLLIB(ASPTDBGW)
RMP.F1DP.SASMACRO(SPATDB)
XRDS0002

Table 10.2. Patient Disposition
F1D-MC-HGGW, Acute Phase

	Placebo (N=60)	Olz (N=55)	Total (N=115)	p-Value*
Reason for Discontinuation	n (%)	n (%)	n (%)	
Reporting Interval Complete	25 (41.7)	34 (61.8)	59 (51.3)	.040
Adverse Event	1 (1.7)	2 (3.6)	3 (2.6)	.606
Lack of Efficacy	23 (38.3)	15 (27.3)	38 (33.0)	.238
Lost to Follow-up	3 (5.0)	1 (1.8)	4 (3.5)	.620
Patient Decision	5 (8.3)	3 (5.5)	8 (7.0)	.719
Physician Decision	3 (5.0)	0	3 (2.6)	.245

P-value obtained by using a two-tailed Fisher's Exact test
RMP.F1DP.JCLLIB(ASPTDAGW)
RMP.F1DP.SASMACRO(SPATDA)
XRDS0001

Table 11.32. Y-MRS Total Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-5.21	8.50	54	-9.57	10.85
4	2	56	-6.91	11.33	54	-12.22	11.59
5	3	56	-6.52	11.69	54	-13.85	12.70
6	4	56	-8.13	12.72	54	-14.78	12.49

p-Values*1

Visit	Week	Overall
3	1	.032
4	2	.004
5	3	<.001
6	4	<.001

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction.

Table 11.33. HAMD-21 Total Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-2.89	5.68	54	-5.80	8.04
4	2	56	-3.95	7.11	54	-6.94	7.49
5	3	56	-4.34	7.25	54	-7.70	8.74
6	4	56	-4.45	6.95	54	-7.83	7.79

p-Values*1

Visit	Week	Overall
3	1	.143
4	2	.091
5	3	.103
6	4	.092

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction.

Table 11.34. CGI-BP Severity of Mania
Visitwise Change from Baseline (LOCF)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-0.45	1.04	54	-1.07	1.03
4	2	56	-0.75	1.40	54	-1.44	1.21
5	3	56	-0.73	1.47	54	-1.69	1.41
6	4	56	-0.88	1.54	54	-1.83	1.45

p-Values*1

Visit	Week	Overall
3	1	.001
4	2	.002
5	3	<.001
6	4	<.001

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction.

Table 11.35. CGI-BP Severity of Depression
Visitwise Change from Baseline (LOCF)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-0.27	0.77	54	-0.57	1.25
4	2	56	-0.50	1.19	54	-0.57	1.06
5	3	56	-0.45	1.23	54	-0.65	1.28
6	4	56	-0.45	1.26	54	-0.74	1.32

p-Values*1

Visit	Week	Overall
3	1	.352
4	2	.800
5	3	.520
6	4	.367

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction.

Table 11.36. CGI-BP Severity of Overall Bipolar Illness
Visitwise Change from Baseline (LOCF)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-0.45	1.08	54	-1.02	1.12
4	2	56	-0.61	1.33	54	-1.46	1.27
5	3	56	-0.59	1.40	54	-1.59	1.35
6	4	56	-0.73	1.43	54	-1.72	1.46

p-Values*1

Visit	Week	Overall
3	1	.003
4	2	<.001
5	3	<.001
6	4	<.001

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction.

Table 11.37. PANSS Total Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-5.61	14.72	54	-12.98	18.05
4	2	56	-7.07	18.24	54	-17.87	18.31
5	3	56	-6.14	18.55	54	-20.11	22.08
6	4	56	-7.43	19.73	54	-21.19	23.73

p-Values*1

Visit	Week	Overall
3	1	.028
4	2	<.001
5	3	<.001
6	4	<.001

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction.

Table 11.38. PANSS Positive Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-2.16	4.85	54	-4.54	6.06
4	2	56	-2.89	6.01	54	-6.17	6.62
5	3	56	-2.61	6.47	54	-7.37	7.59
6	4	56	-2.96	6.61	54	-7.67	7.89

p-Values*1

Visit	Week	Overall
3	1	.017
4	2	.001
5	3	<.001
6	4	<.001

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction.

Table 11.39. PANSS Negative Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-0.80	3.31	54	-1.80	4.44
4	2	56	-0.79	3.89	54	-2.43	4.68
5	3	56	-0.54	3.98	54	-2.31	5.42
6	4	56	-0.63	4.41	54	-2.78	6.50

p-Values*1

Visit	Week	Overall
3	1	.618
4	2	.073
5	3	.094
6	4	.077

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW2)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator, treatment and interaction.

Table 11.24. Y-MRS Total Score
Visitwise Change from Baseline (OC)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-5.21	8.50	54	-9.57	10.85
4	2	40	-9.73	11.46	44	-15.02	9.74
5	3	29	-12.38	10.59	40	-17.63	10.76
6	4	25	-17.96	8.07	35	-20.97	8.56

p-Values*1

Visit	Week	Overall
3	1	.039
4	2	.042
5	3	.034
6	4	.196

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table 11.25. HAMD-21 Total Score
Visitwise Change from Baseline (OC)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-2.89	5.68	54	-5.80	8.04
4	2	39	-5.26	7.75	44	-8.20	7.67
5	3	29	-8.38	7.43	40	-9.23	9.17
6	4	25	-9.64	6.60	35	-10.66	7.25

p-Values*1

Visit	Week	Overall
3	1	.034
4	2	.082
5	3	.505
6	4	.286

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table 11.26. CGI-BP Severity of Mania
Visitwise Change from Baseline (OC)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-0.45	1.04	54	-1.07	1.03
4	2	40	-1.15	1.25	44	-1.75	1.08
5	3	29	-1.38	1.24	40	-2.15	1.25
6	4	25	-1.88	0.97	35	-2.60	1.06

p-Values*1

Visit	Week	Overall
3	1	.004
4	2	.043
5	3	.011
6	4	.015

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table 11.27. CGI-BP Severity of Depression
Visitwise Change from Baseline (OC)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-0.27	0.77	54	-0.57	1.25
4	2	40	-0.58	1.32	44	-0.73	1.06
5	3	29	-0.62	1.27	40	-0.78	1.31
6	4	25	-0.72	1.40	35	-1.03	1.32

p-Values*1

Visit	Week	Overall
3	1	.193
4	2	.512
5	3	.446
6	4	.196

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table 11.28. CGI-BP Severity of Overall Bipolar Illness
Visitwise Change from Baseline (OC)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-0.45	1.08	54	-1.02	1.12
4	2	40	-0.93	1.23	44	-1.80	1.11
5	3	29	-1.17	1.28	40	-2.03	1.19
6	4	25	-1.76	0.97	35	-2.43	1.17

p-Values*1

Visit	Week	Overall
3	1	.011
4	2	.003
5	3	.005
6	4	.045

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table 11.29. PANSS Total Score
Visitwise Change from Baseline (OC)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-5.61	14.72	54	-12.98	18.05
4	2	40	-11.38	18.31	44	-22.68	16.25
5	3	29	-15.76	17.58	40	-26.05	21.40
6	4	25	-21.12	17.49	35	-30.54	22.94

p-Values*1

Visit	Week	Overall
3	1	.022
4	2	.002
5	3	.008
6	4	.050

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table 11.30. PANSS Positive Score
Visitwise Change from Baseline (OC)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-2.16	4.85	54	-4.54	6.06
4	2	40	-4.23	5.63	44	-7.75	6.08
5	3	29	-5.31	6.48	40	-9.70	7.02
6	4	25	-6.84	5.93	35	-11.11	7.09

p-Values*1

Visit	Week	Overall
3	1	.031
4	2	.006
5	3	.004
6	4	.012

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

Table 11.31. PANSS Negative Score
Visitwise Change from Baseline (OC)
F1D-MC-HGGW, Acute Phase

		Placebo (1)			Olz (2)		
Visit	Week	n	Mean	SD	n	Mean	SD
3	1	56	-0.80	3.31	54	-1.80	4.44
4	2	40	-1.10	4.15	44	-3.23	4.59
5	3	29	-1.93	4.05	40	-3.00	5.75
6	4	25	-2.24	5.07	35	-4.20	7.32

p-Values*1

Visit	Week	Overall
3	1	.233
4	2	.033
5	3	.317
6	4	.185

The following investigators were pooled: (009 011 016 017 019 020 021 025)
Mean change is tested with Student's t-test
RMP.F1DP.JCLLIB(ASEFBGW3)
RMP.F1DP.SASMACRO(SEFCYB)
*1 Type III Sums of Squares from an analysis of variance (ANOVA):
PROC GLM model=investigator and treatment.

SAFETY TABLES

Table 2.5. Adverse Events Reported as Reason for Discontinuation
Bipolar Integrated Database Acute Phase

Event Classification	Placebo (N=129) n	(%)	Olz (N=125) n	(%)	p-Value*
PATIENTS DISCONTINUED	3	(2.3)	2	(1.6)	1.00
AGITATION	1	(0.8)	0		1.00
CONVULSION	1	(0.8)	0		1.00
DYSTONIA	1	(0.8)	0		1.00
RASH	0		1	(0.8)	.492
UNINTENDED PREGNANCY	0		1	(0.8)	.492

* Frequencies are analyzed using a Fisher's Exact test.
XAES0003

Table 2.14. Laboratory Analytes
Mean Change from Baseline to Endpoint
Bipolar Integrated Database Acute Phase

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy (Int*1)
HCT	1	Placebo	113	0.43	0.04	0.00	0.03	.050
		Olz	119	0.43	0.04	-0.01	0.03	(.840)
HGB	mml/L-Fe	Placebo	115	8.84	0.88	0.06	0.45	.003
		Olz	120	8.78	0.83	-0.12	0.46	(.556)
RBC	TI/L	Placebo	115	4.66	0.46	0.03	0.26	.129
		Olz	120	4.63	0.47	-0.02	0.26	(.425)
MCHC	mml/L-Fe	Placebo	113	20.64	0.93	0.05	0.99	.495
		Olz	119	20.47	0.95	-0.05	0.92	(.071)
MCH	fmol(Fe)	Placebo	115	1.90	0.11	-0.00	0.05	.029
		Olz	120	1.91	0.12	-0.02	0.06	(.063)
WBC	GI/L	Placebo	115	7.66	2.36	-0.18	1.84	.477
		Olz	120	7.98	1.96	-0.33	1.94	(.259)
POLYS	GI/L	Placebo	115	4.62	1.78	-0.08	1.51	.737
		Olz	120	5.01	1.55	-0.13	1.68	(.403)
LYMPHS	GI/L	Placebo	115	2.31	0.84	-0.05	0.65	.057
		Olz	120	2.24	0.74	-0.20	0.63	(.494)
MONOS	GI/L	Placebo	115	0.51	0.18	-0.02	0.20	.664
		Olz	120	0.52	0.17	-0.01	0.18	(.355)
EOSN	GI/L	Placebo	115	0.17	0.16	-0.02	0.09	.027
		Olz	120	0.15	0.12	0.02	0.13	(.187)
BASO	GI/L	Placebo	115	0.06	0.04	-0.01	0.04	.262
		Olz	120	0.06	0.03	-0.00	0.04	(.961)
MCV	fL	Placebo	113	92.50	5.31	-0.41	3.44	.198
		Olz	119	93.18	6.37	-1.04	3.82	(.769)
PLTCT	GI/L	Placebo	115	256.23	62.58	6.17	37.53	.051
		Olz	120	265.43	84.52	-4.74	48.35	(.562)

Table 2.14. (continued) Laboratory Analytes
Mean Change from Baseline to Endpoint
Bipolar Integrated Database Acute Phase

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)
U-SPGR	NO UNITS	Placebo	115	1.02	0.01	0.00	0.01	.661
		Olz	121	1.02	0.01	-0.00	0.01	(.730)
U-PH	U	Placebo	115	5.65	0.77	-0.03	1.03	.008
		Olz	121	5.78	0.83	-0.38	0.96	(.607)
AST	U/L	Placebo	117	26.20	18.18	-0.21	15.21	.001
		Olz	123	22.47	9.60	9.09	26.36	(.743)
ALT	U/L	Placebo	117	32.36	29.48	1.09	18.53	<.001
		Olz	123	27.03	21.16	21.39	56.09	(.927)
CPK	U/L	Placebo	116	134.42	142.54	66.40	270.69	.013
		Olz	123	135.33	133.56	-2.49	134.63	(.528)
ALKPH	U/L	Placebo	117	70.26	20.76	0.84	10.93	.168
		Olz	123	68.10	16.95	2.50	11.11	(.080)
GGT	U/L	Placebo	118	40.45	80.70	-1.48	57.29	.188
		Olz	123	32.88	50.73	5.62	29.15	(.236)
BUN	mmol/L	Placebo	117	4.58	1.26	-0.05	1.22	.160
		Olz	123	4.39	1.22	0.17	1.33	(.550)
CREAT	umol/L	Placebo	117	97.62	15.80	1.21	9.91	.140
		Olz	123	95.87	13.82	-1.01	9.88	(.013)
CALC	mmol/L	Placebo	117	2.34	0.11	0.01	0.11	.051
		Olz	123	2.34	0.11	-0.02	0.11	(.741)
PHOS	mmol/L	Placebo	116	1.25	0.24	-0.02	0.21	.059
		Olz	123	1.23	0.20	0.04	0.25	(.599)
SODIUM	mmol/L	Placebo	117	139.51	2.86	0.27	3.45	.505
		Olz	122	138.89	2.55	0.56	2.78	(.812)
POTAS	mmol/L	Placebo	116	4.29	0.39	-0.08	0.39	.910
		Olz	122	4.30	0.39	-0.07	0.41	(.074)

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Table 2.14. (continued) Laboratory Analytes
Mean Change from Baseline to Endpoint
Bipolar Integrated Database Acute Phase

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)
CHLOR	mmol/L	Placebo	117	103.59	3.11	0.17	3.76	.010
		Olz	122	103.04	3.06	1.37	3.12	(.353)
TPROT	g/L	Placebo	117	70.91	5.04	1.09	5.04	.017
		Olz	123	71.36	4.81	-0.58	5.30	(.502)
ALBUM	g/L	Placebo	116	40.82	3.37	0.74	2.99	<.001
		Olz	123	40.93	3.58	-1.07	2.98	(.607)
NFGLU	mmol/L	Placebo	116	5.72	1.65	-0.14	1.54	.074
		Olz	123	5.79	1.66	0.23	1.75	(.516)
UR AC	umol/L	Placebo	117	302.94	81.22	2.85	53.64	<.001
		Olz	123	300.01	77.91	26.94	59.47	(.247)
CHOL	mmol/L	Placebo	117	4.88	1.06	0.15	0.87	.011
		Olz	123	4.74	1.02	0.44	0.91	(.462)
BICARB	mmol/L	Placebo	116	25.92	2.31	-0.26	2.23	.034
		Olz	122	25.51	2.55	-0.93	2.68	(.511)
T.BILI	umol/L	Placebo	116	8.82	3.75	0.21	3.10	.049
		Olz	120	8.17	3.22	-0.60	3.32	(.422)

Reporting SI units
The interaction variable for this run is STUDYC instead of investigator.
RMP.F1DP.JCLLIB(ISSE8B2)
RMP.F1DP.SASMACRO(SSAFEE8)
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=protocol, treatment, and interaction.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
Note: Each protocol has at least one patient in each treatment group.
XLAS0006

Table 2.14. (concluded) Laboratory Analytes
Mean Change from Baseline to Endpoint
Bipolar Integrated Database Acute Phase

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

Table 2.9. Vital Signs and Weight
Mean Change from Baseline to Endpoint
Bipolar Integrated Database Acute Phase

Research Project Code: F1D

			-----Baseline------		Change to -----Endpoint-----		p-Values
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)
WEIGHTKG	Placebo	117	84.08	19.71	-0.01	2.36	<.001
	Olz	124	81.91	17.27	1.85	2.67	(.503)
PULSE_ST	Placebo	117	84.28	10.97	-1.05	14.82	.028
	Olz	123	82.32	11.28	3.79	16.09	(.027)
TEMPCPO	Placebo	120	36.63	0.50	0.07	0.57	.130
	Olz	123	36.71	0.52	-0.04	0.60	(.791)
SYSBP_OR	Placebo	118	1.08	9.86	-0.29	14.45	.351
	Olz	120	-1.53	9.38	1.28	14.89	(.212)
PULSE_OR	Placebo	117	6.15	8.53	-0.08	10.72	.114
	Olz	120	4.61	9.21	2.73	14.32	(.148)
SYSBP_SU	Placebo	120	122.97	14.88	-0.76	17.39	.060
	Olz	122	120.61	15.40	2.82	15.47	(.021)
DIABP_SU	Placebo	120	75.82	10.65	1.08	11.77	.630
	Olz	122	75.58	10.92	0.06	13.48	(.118)
PULSE_SU	Placebo	120	78.54	10.28	-1.26	12.94	.340
	Olz	122	78.21	11.45	0.76	14.47	(.092)
SYSBP_ST	Placebo	118	121.72	14.88	-0.56	16.11	.281
	Olz	123	122.07	15.11	1.26	14.64	(.099)
DIABP_ST	Placebo	118	77.07	9.83	2.24	12.32	.096
	Olz	123	79.46	11.29	-0.59	12.89	(.553)

Table 2.9. (concluded) Vital Signs and Weight
Mean Change from Baseline to Endpoint
Bipolar Integrated Database Acute Phase

RMP.F1DP.JCLLIB(ISSFD6B2)
RMP.F1DP.SASMACRO(SSAFEC1)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.
XLAS0006

Note: Models:

FULL2 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=protocol, treatment, and interaction.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
Note: Each protocol has at least one patient in each treatment group.

XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
DIABP_ST	Diastolic Blood Pressure - Standing
DIABP_SU	Diastolic Blood Pressure - Supine
PULSE_OR	Pulse - Ortho
PULSE_ST	Pulse - Standing
PULSE_SU	Pulse - Supine
SYSBP_OR	Systolic Blood Pressure - Ortho
SYSBP_ST	Systolic Blood Pressure - Standing
SYSBP_SU	Systolic Blood Pressure - Supine
TEMPCPO	Temp in Centigrade Standardized to PO
WEIGHTKG	Weight in kg.

Table 2.17. ECG Intervals and Heart Rate
Mean Change from Baseline to Endpoint
Bipolar Integrated Database Acute Phase

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)
ECGHR	Placebo	100	74.11	12.71	1.40	14.24	.181
	Olz	113	74.55	13.22	4.26	15.01	(.405)
INTPRSEC	Placebo	100	0.15	0.02	0.00	0.03	.200
	Olz	113	0.15	0.02	-0.00	0.02	(.973)
INTQRSEC	Placebo	100	0.08	0.01	0.00	0.01	.458
	Olz	113	0.08	0.03	-0.00	0.03	(.315)
INTQTC	Placebo	100	409.82	26.63	-2.67	29.27	.138
	Olz	113	405.00	28.30	2.66	23.53	(.585)
INTQTMSC	Placebo	100	370.82	29.96	-5.14	32.83	.474
	Olz	113	366.14	30.51	-8.81	30.54	(.110)
INTRRSEC	Placebo	100	0.83	0.14	-0.01	0.17	.097
	Olz	113	0.83	0.16	-0.05	0.17	(.300)

RMP.F1DP.JCLLIB(ISHBTB2)
RMP.F1DP.SASMACRO(SSAFEC1)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL5 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=protocol, treatment, and interaction.
Note: Pairwise p-Values are not reported.
Note: At least one protocol does not have patients in every treatment group.

XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
ECGHR	Heart Rate Per Minute
INTPRSEC	Intervals PR / Second
INTQRSEC	Intervals QRS / Second
INTQTC	Intervals QT Corrected
INTQTMSC	Intervals QT / Msec
INTRRSEC	Intervals RR / Second

Table 2.16. Incidence of Potentially Clinically Significant Change in ECG Intervals and Heart Rate
Bipolar Integrated Database Acute Phase

ECG Interval	Direction	No.	Therapy	N	n	(%)	- p-Values - Overall
ECG Heart Rate	High	1)	Placebo	100	0	0.0%	
		2)	Olz	113	0	0.0%	
	Low	1)	Placebo	100	0	0.0%	
		2)	Olz	113	0	0.0%	
ECG PR Interval	High	1)	Placebo	98	3	3.1%	.103
		2)	Olz	110	0	0.0%	
ECG QRS Interval	High	1)	Placebo	88	9	10.2%	1.00
		2)	Olz	103	10	9.7%	
ECG QT corrected	High	1)	Placebo	77	7	9.1%	.247
		2)	Olz	90	14	15.6%	
ECG QT Interval	High	1)	Placebo	98	1	1.0%	.464
		2)	Olz	113	0	0.0%	

Frequencies analyzed using two-tailed Fisher's Exact Test

Table 2.12. Incidence of Potentially Clinically Significant Changes in Laboratory Analytes Bipolar Integrated Database Acute Phase

Analyte	Direction	No.	Therapy	N	n	(%)	- p-Values - Overall
ALBUMIN	Low	1)	Placebo	116	0	0.0%	
		2)	Olz	123	0	0.0%	
ALKALINE PHOSPHATASE	High	1)	Placebo	117	0	0.0%	
		2)	Olz	123	0	0.0%	
ALT/SGPT	High	1)	Placebo	115	0	0.0%	.123
		2)	Olz	123	4	3.3%	
AST/SGOT	High	1)	Placebo	116	0	0.0%	.498
		2)	Olz	123	2	1.6%	
BILIRUBIN, TOTAL	High	1)	Placebo	116	0	0.0%	
		2)	Olz	120	0	0.0%	
CALCIUM	High	1)	Placebo	117	0	0.0%	
		2)	Olz	123	0	0.0%	
	Low	1)	Placebo	117	0	0.0%	
		2)	Olz	123	0	0.0%	
CHOLESTEROL	High	1)	Placebo	117	0	0.0%	
		2)	Olz	123	0	0.0%	

Frequencies analyzed using two-tailed Fisher's Exact Test

Table 2.12. (continued) Incidence of Potentially Clinically Significant Changes in Laboratory Analytes Bipolar Integrated Database Acute Phase

Analyte	Direction	No.	Therapy	N	n	(%)	- p-Values - Overall
CREATINE PHOSPHOKINASE	High	1)	Placebo	111	4	3.6%	.436
		2)	Olz	117	2	1.7%	
CREATININE	High	1)	Placebo	117	0	0.0%	
		2)	Olz	123	0	0.0%	
EOSINOPHILS	High	1)	Placebo	114	0	0.0%	
		2)	Olz	119	0	0.0%	
ERYTHROCYTE COUNT	High	1)	Placebo	115	0	0.0%	
		2)	Olz	120	0	0.0%	
	Low	1)	Placebo	115	0	0.0%	
		2)	Olz	120	0	0.0%	
GGT (GGPT/SGGT/YGGT)	High	1)	Placebo	116	2	1.7%	.616
		2)	Olz	121	1	0.8%	

GLUCOSE, NON-FASTING	High	1) Placebo	115	1	0.9%	1.00
		2) Olz	123	2	1.6%	
	Low	1) Placebo	114	0	0.0%	
		2) Olz	123	0	0.0%	

Frequencies analyzed using two-tailed Fisher's Exact Test

Table 2.12. (continued) Incidence of Potentially Clinically Significant Changes in Laboratory Analytes
Bipolar Integrated Database Acute Phase

Analyte	Direction	No.	Therapy	N	n	(%)	- p-Values - Overall
HEMATOCRIT	High	1)	Placebo	111	0	0.0%	
		2)	Olz	118	0	0.0%	
	Low	1)	Placebo	113	0	0.0%	
		2)	Olz	116	0	0.0%	
HEMOGLOBIN	High	1)	Placebo	114	0	0.0%	
		2)	Olz	120	0	0.0%	
	Low	1)	Placebo	115	0	0.0%	
		2)	Olz	119	0	0.0%	
INORGANIC PHOSPHORUS	High	1)	Placebo	112	1	0.9%	.477
		2)	Olz	123	0	0.0%	
	Low	1)	Placebo	116	0	0.0%	
		2)	Olz	123	0	0.0%	
LEUKOCYTE COUNT	High	1)	Placebo	115	0	0.0%	
		2)	Olz	120	0	0.0%	
	Low	1)	Placebo	114	2	1.8%	.236
		2)	Olz	120	0	0.0%	
NEUTROPHILS, SEGMENTED	Low	1)	Placebo	115	0	0.0%	

Frequencies analyzed using two-tailed Fisher's Exact Test

Table 2.12. (continued) Incidence of Potentially Clinically Significant Changes in Laboratory Analytes
Bipolar Integrated Database Acute Phase

Analyte	Direction	No.	Therapy	N	n	(%)	- p-Values - Overall
NEUTROPHILS, SEGMENTED	Low	2)	Olz	120	0	0.0%	
PLATELET COUNT	High	1)	Placebo	115	0	0.0%	
		2)	Olz	119	0	0.0%	
	Low	1)	Placebo	115	0	0.0%	
		2)	Olz	120	0	0.0%	
SODIUM	High	1)	Placebo	117	0	0.0%	
		2)	Olz	122	0	0.0%	

	Low	1) Placebo	117	1	0.9%	.492
		2) Olz	121	0	0.0%	
TOTAL PROTEIN	Low	1) Placebo	117	0	0.0%	
		2) Olz	123	0	0.0%	
UA-CASTS, GRANULAR	Increase>=2	1) Placebo	115	0	0.0%	
		2) Olz	121	0	0.0%	
UA-CASTS, HYALINE	Increase>=2	1) Placebo	115	0	0.0%	
		2) Olz	121	0	0.0%	

Frequencies analyzed using two-tailed Fisher's Exact Test
RMP.F1DP.JCLLIB(ISSFTLB2)
RMP.F1DP.SASMACRO(SSUMTAB)

Table 2.12. (continued) Incidence of Potentially Clinically Significant Changes in Laboratory Analytes
Bipolar Integrated Database Acute Phase

Analyte	Direction	No.	Therapy	N	n	(%)	- p-Values - Overall
UA-GLUCOSE	Increase>=2	1)	Placebo	114	0	0.0%	1.00
		2)	Olz	121	1	0.8%	
UA-KETONES	Increase>=2	1)	Placebo	115	0	0.0%	
		2)	Olz	121	0	0.0%	
UA-PH	High	1)	Placebo	115	0	0.0%	
		2)	Olz	121	0	0.0%	
	Low	1)	Placebo	115	0	0.0%	
		2)	Olz	121	0	0.0%	
UA-PROTEIN	Increase>=2	1)	Placebo	115	1	0.9%	.487
		2)	Olz	121	0	0.0%	
UA-RBC	Increase>=2	1)	Placebo	112	0	0.0%	.498
		2)	Olz	120	2	1.7%	
UA-SPECIFIC GRAVITY	High	1)	Placebo	114	0	0.0%	
		2)	Olz	121	0	0.0%	
	Low	1)	Placebo	115	0	0.0%	
		2)	Olz	121	0	0.0%	

Frequencies analyzed using two-tailed Fisher's Exact Test
RMP.F1DP.JCLLIB(ISSFTLB2)
RMP.F1DP.SASMACRO(SSUMTAB)

Table 2.12. (concluded) Incidence of Potentially Clinically Significant Changes in Laboratory Analytes
Bipolar Integrated Database Acute Phase

Analyte	Direction	No.	Therapy	N	n	(%)	- p-Values - Overall
UA-WBC	Increase>=2	1)	Placebo	114	1	0.9%	.485
		2)	Olz	121	0	0.0%	
UREA NITROGEN	High	1)	Placebo	117	0	0.0%	
		2)	Olz	123	0	0.0%	
URIC ACID	High	1)	Placebo	117	1	0.9%	1.00
		2)	Olz	121	1	0.8%	

Frequencies analyzed using two-tailed Fisher's Exact Test
RMP.F1DP.JCLLIB(ISSFTLB2)
RMP.F1DP.SASMACRO(SSUMTAB)

Table 2.8. Incidence of Potentially Clinically Significant Changes in Vital Signs and Weight
Bipolar Integrated Database Acute Phase

Vital	Direction	No.	Therapy	N	n	(%)	- p-Values - Overall
Orthostatic Sys BP	Decrease	1)	Placebo	118	2	1.7%	1.00
		2)	Olz	120	3	2.5%	
Standing Diastolic BP	High	1)	Placebo	117	2	1.7%	1.00
		2)	Olz	120	2	1.7%	
	Low	1)	Placebo	118	0	0.0%	1.00
		2)	Olz	123	1	0.8%	
Standing Pulse	High	1)	Placebo	117	1	0.9%	1.00
		2)	Olz	123	2	1.6%	
	Low	1)	Placebo	117	1	0.9%	1.00
		2)	Olz	123	2	1.6%	
Standing Systolic BP	High	1)	Placebo	118	0	0.0%	1.00
		2)	Olz	123	1	0.8%	
	Low	1)	Placebo	116	4	3.4%	.715
		2)	Olz	123	3	2.4%	
Supine Diastolic BP	High	1)	Placebo	120	2	1.7%	.622
		2)	Olz	121	1	0.8%	

Frequencies analyzed using two-tailed Fisher's Exact Test

Criteria for Identifying Patients with Potentially Clinically Significant Change in Urinary Analytes

Analyte	Low	High	
UA- Specific Gravity	1.001	1.035	
UA- pH	4. 6	8.0	
UA- RBC	increase ›2	and score	›3
UA- WBC	Increase ›2	and score	›3
UA- Casts	increase ›2	and score	›3
UA- Protein	increase ›2	and score	›3
UA- Ketones	increase ›2	and score	›3
UA- Glucose	increase ›2	and score	›3

Abbreviations: UA = urinary analytes; RBC = red blood cells (erythrocytes); WBC = white blood cells

Criteria for Identifying Patients with Potentially Clinically Significant Change in Vital Signs and Weight

Parameter	Low		High		
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) a	--		›	101° F and increase	› 2
Weight (kg)	decrease › 10%		increase	› 10%	
Orthostatic hypotension (mm Hg)	› 30 mm Hg decrease in systolic BP (supine to standing)		--		

Abbreviations: BP = blood pressure; mm Hg = millimeters of mercury; bpm = beats per minute; F = Fahrenheit; kg = kilograms

a Converted to Celsius for analysis.

Criteria for Identifying Patients with Potentially Clinically Significant Change in ECG Intervals and Heart Rate Bipolar Integrated Database Acute Phase

Interval	Low	High
PR	--	200 msec
QRS	--	100 msec
QT	--	450 msec
QTc	--	430 msec
Heart rate	40 bpm	120 bpm

Review and Evaluation of Clinical Data
NDA #20-592

Sponsor:	Lilly Research Laboratories
Drug:	Olanzapine
Material Submitted:	Briefing document for meeting with the sponsor
Correspondence Date:	November 23, 1999

I. 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. There were 2500 subjects exposed to olanzapine in the development program upon which the safety evaluation was made.

On November 12, 1999 a teleconference was held with the Division and the sponsor to discuss case summaries of patients who died in study HGEU. This submission is a written report of case summary revisions and adverse event tables for study HGEU. The sponsor submitted a supplement to NDA 20-592 (SE1-006) with the goal of claiming an indication for the treatment of acute mania in bipolar affective disorder. Concomitantly, the sponsor submitted supplement [ ]. Supplement 006 was declared approvable [ ] it contained safety data that shall appear in Zyprexa®. The sponsor makes several appeals for changes in draft labeling that the Division is considering based on the review of study HGEU from the sponsor's NDA supplement [ ].

II. Data Reviewed-:

- Revised case summaries for patients who died during or with 30-days of terminating treatment in study HGEU
- Revised adverse event tables

Revised case summaries-
Study HGEU in supplement [ ] reports 5 deaths in patients during or within 30-days of treatment. The supplement reports that there were 3 patient-deaths in the 15-mg group, and 1 each in the 5 and 10-mg groups. On further review of the cases, the sponsor reports that these patients were not actually exposed to the dose levels that their dose groups indicated. Two of the 15-mg group deaths actually only received up to 10-mg. Patients in the 15-mg treatment group in study HGEU received 5-mg/day for 1-week then 10-mg/week for the second week before reaching a dose of 15-mg/day in the third week.

Patients 006-601 and 023-2312 though assigned to the 15-mg dose group only reached the 10-mg level. The death rate that originally appeared dose dependent was not related to the actual dose that the patient received.

The sponsor also proposed revised adverse event tables that were discussed and shall be submitted in draft labeling as a part of their response to the Division letter to the sponsor that was dated October 28,1999. One patient (015-1525) was inadvertently assigned to the 15-mg group due to a transcription error but was truly in the placebo group. This does not substantially change the adverse event table.

III. Conclusions and Recommendations

Given that two of the patients who died actually received 10-mg in lieu of 15-mg, the [ ] description of the deaths in the PRECAUTION section when the sponsor submits their next version of draft labeling. This is an appropriate change, and shall be considered along with other changes in draft labeling in the sponsors complete response to the letter of October 28, 1999.

2/23/00

Paul J. Andreason, M.D.

cc: IND# 28,705
HFD-120
HFD-120/ P Andreason
E Hearst
S Hardeman
T Laughren

2-25-00

Lilly's clarification that there is no dose dependent mortality, along with the fact that there was no unifying mechanism for death in these patients, led us to agree that there is insufficient data at present to support a conclusion of drug-related mortality. Alternatively, we have agreed to strengthening labeling with findings suggesting a different tolerability profile in patients with Alzheimer's Disease (see my 2-25-00 memo to file).

Thomas P. Laughren, MD
TL, PDP

MEMORANDUM

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

DATE: February 25, 2000

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Zyprexa (olanzapine) for the treatment of manic or mixed episodes in bipolar disorder

TO: File NDA 20-592/S-006
[**Note:** This memo should be filed with the 12-22-99 response to our approvable letter.]

1.0 BACKGROUND

In our 10-28-99 approvable letter, we requested a phase 4 commitment to conduct additional studies in pediatric patients with bipolar disorder. We also requested additional information regarding studies HGEH and HGEW, i.e., a breakdown of the number of patients enrolled by each episode type (manic or mixed), and a table listing patients and visits for which total YMRS scores were treated as missing. Finally, we attached our proposal for labeling.

Lilly responded to our approvable letter with a 12-22-99 submission, including an alternative labeling proposal and responses to the other questions and requests in our letter.
-Regarding pediatric studies, Lilly agreed to submit a pediatric development plan within 120 days of the approvable letter.
-Regarding the breakdown of episode types for the 2 positive studies, these were as follows:

-HGEH 2	Manic 19%	Mixed 81%
-HGGW	Manic 43%	Mixed 57%

-Regarding missing data, there were no instances in which it was necessary to exercise the rule and exclude YMRS data.

The review team, up to the level of Team Leader, interacted with the sponsor over a period of several weeks, including an exchanges of draft labeling and a teleconference in order to resolve the differences in labeling. On 2-15-00, we faxed version AP1ZYPLB.DOC to Lilly, and they responded

with a 2-18-00 counterproposal. In a 2-22-00 telcon, we reached final agreement on labeling on all issues except whether or not to change the psychosis indication to schizophrenia. Dr. Katz and I discussed that issue on 2-23-00, and decided to retain the current labeling language for now, as requested by Lilly. The mutually agreed upon final labeling [AP2ZYPLB.DOC] is included with the approval letter.

The following were the 2 major labeling issues that were discussed and negotiated:

-Inclusion of safety findings from study HGEU, a study of olanzapine in patients with psychiatric/behavioral symptoms in association with Alzheimer's Disease:

-In our labeling proposal included with the 10-28-99 approvable letter, we had added a [redacted] Upon reexamination of doses actually received, Lilly clarified that there was not dose dependent mortality. That clarification, along with the fact that there was no unifying mechanism for death in these patients, i.e., there were several different causes of death, all common conditions in this very sick and elderly population, led us to agree that the [redacted] In fact, there is insufficient data at present to support a conclusion of drug-related mortality. Alternatively, we have agreed to strengthening the already existent "Dysphagia" statement under Precautions and the addition under "Use in Patients with Concomitant Illness" the adverse event findings from study HGEU. These findings suggestive of a different tolerability profile in patients with Alzheimer's Disease are also now noted in the "Geriatric Use" subsection under Precautions.

-Changing the psychosis indication to focus exclusively on schizophrenia:

-We had considered changing the psychosis indication from "management of the manifestations of psychotic disorders" to simply the "treatment of schizophrenia," as part of a policy shift on psychotropic indications. However, Lilly expressed great concern that competitiors, formulary committees, and others might misuse this labeling difference for their product relative to other antipsychotics. Alternatively, we have decided to attempt to effect this change as a class labeling action.

I believe that Lilly has submitted sufficient data to support the conclusion that Zyprexa is effective and acceptably safe in the short-term treatment of acute manic and mixed episodes associated with Bipolar I Disorder. I recommend that we issue the attached approval letter with the version of labeling for which we were able to reach mutual agreement with the sponsor.

cc:
Orig NDA 20-592/S-006
HFD-120
HFD-120/TLaughren/RKatz/PAndreason/EHearst/DBates

DOC: MEMZYPMN.AP1

6 page(s) of draft labeling has been removed from this portion of the review.

Medical Review #2 (2/25/00)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-006

ADMINISTRATIVE and CORRESPONDENCE

Exclusivity Checklist

NDA: 20-592/S-006				
Trade Name: ZYPREXA				
Generic Name: OLANZAPINE				
Applicant Name: ELI LILLY & COMPANY				
Division: DNDP, HFD-120				
Project Manager: DORIS J. BATES, PH.D.				
Approval Date:				
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	
c. If yes, what type? (SE1, SE2, etc.) SE1				
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.				
Explanation:				
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:				
Explanation:				
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 (3)			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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?	Yes		No	X
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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 (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.	Yes	X	No	
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)		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product OLANZAPINE (IN PSYCHOSIS)				
NDA # 20-592 (ORIGINAL)				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	
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).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
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)		No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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)		No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**				
Basis for conclusion:				
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)		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)	
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)	
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 #:	FID-MC-HGEH			
Investigation #2, Study #:	FID-MC-HGGW			
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 HGEH	Yes		No	X
Investigation #2 HGGW	Yes		No	X
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:

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

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 HGEH	Yes		No	X
Investigation #2 HGGW	Yes		No	X
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:

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

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	HGEH
Investigation #2	HGGW
Investigation #3	

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 HGEH	Yes	X	No	
IND#: 28,705				
Explain:				
Investigation #2 HGGW	Yes	X	No	
IND#: 28,705				
Explain:				

Investigation #3 | Yes | | No |
IND#:
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?

Investigation #1 | Yes | | No |
IND#:
Explain:

Investigation #2 | Yes | | No |
IND#:
Explain:

Investigation #3 | Yes | | No |
IND#:
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:

BACK TO TOP

Signature of PM/CSO Brian T. Botta, Ph.D
Date: 17 September 1999 and 25 February 2000

Signature of Division Director
Date: 2/16/00

cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20592	**Trade Name:**	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
Supplement Number:	6	**Generic Name:**	OLANZAPINE
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	AP	**Proposed Indication:**	mania associated with bipolar disorder

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

initial entry 01-SEP-98 NA action 02-OCT-98 resubmission S-006 12-APR-99 updated comments 15-SEP-99 AE action 28-OCT-99 resubmission 22-DEC-99 updated comments 25-FEB-00

there is a pediatric commitment for the initial indication (antipsychotic) but not for the pending indication (mania). The resubmission includes a commitment to submit a proposed pediatric development plan within 120 days of the AE letter (February 26, 2000)

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DORIS BATES

Signature

25 Feb 00

Date

ZYPREXA® (OLANZAPINE)
BIPOLAR MANIA EFFICACY SUPPLEMENT
CSO ADMINISTRATIVE AND LABELING REVIEW

SUBMISSION: NDA 20-592 / SE1-006: Approved March 17, 2000
DATES: April 26, 2000 (FPL submitted); June 14, 2000 (WORD file of FPL provided as review aid)
APPLICANT: Eli Lilly and Company
DOSAGE FORM AND STRENGTH: Tablets, 2.5, 5.0, 7.5, 10.0, 15.0, 20.0 mg (20 mg not marketed)
INDICATION: treatment of acute manic or mixed episodes in bipolar disorder.

SCOPE OF REVIEW: This labeling review compares the Final Printed Labeling (FPL), submitted pursuant to the approval of S-006 on March 17, 2000, to the agreed-upon labeling text that accompanied the approval letter. [An earlier CSO review addressed changes in labeling that developed during review of S-006, comparing the agreed-upon labeling at approval to the prior FDA labeling text, issued when the approvable action was taken.]

MATERIAL REVIEWED:
1. Agreed-upon labeling text (FDA) as attached to March 17, 2000 AP letter (filename AP3ZYPLB.DOC)
2. FPL WORD file as submitted June 14, 2000 (pamphlet code DV 3555 DVP)
3. FPL as submitted April 26, 2000 (PI hardcopy; same pamphlet code as WORD file; checked vs. WORD file)

LIST OF ATTACHMENTS:
1. Agreed-upon labeling text from AP letter (Attachment 1)
2. Printout of WORD file as submitted by firm (pamphlet code DV 3555 DVP) (Attachment 2)
3. Printout of "Track Changes" WORD file comparing the DV 3555 DVP WORD file with the agreed-upon labeling text AP3ZYPLB.DOC (Attachment 3)
4. Review Jacket: submitted FPL hardcopy, DV 3555 DVP

ADMINISTRATIVE HISTORY:
The FPL reviewed here is already superseded by two later submissions:

- NDA 21-086: submitted 05MAY2000 [Ack/retain review ongoing]: addition of information on the approved new dosage form Zyprexa Zydis® to the Zyprexa package insert (pamphlet code is DV 3556 DVP).
- NDA 20-592 / SLR-012: submitted 09MAY2000 [review ongoing]: Changes Being Effected according to 314.70(c) (pamphlet code is PV 3390 AMP): includes
  - Changes to the WARNINGS section (added information on Neuroleptic Malignant Syndrome)
  - Changes to the ADVERSE REACTIONS subsections:
    - *Additional Findings Observed in Clinical Trials* (added information on [redacted])
    - *Postintroduction Reports* (added diabetic coma to events reported since market introduction).
  - this PI revision also includes the Zydis® dosage form information as submitted 4 days earlier to NDA 21-086.

These two submissions are not addressed in this review. This review focuses only on comparison of the submitted FPL to the agreed-upon labeling at the time of approval of S-006.

CSO LABELING REVIEW:

1. The submitted FPL (hard copy version, review jacket) was carefully compared to the WORD file for the same labeling by the CSO and found to match.
2. A line by line comparison of the current label DV 3555 DVP (WORD file. Attachment 2) to the agreed-upon labeling (AP3ZYPLB.DOC, Attachment 1) was performed using the subroutine "track changes" in MS WORD. This comparison (Attachment 3) indicated the following minor changes (all described with reference to AP3ZYPLB.DOC):
   - DOCUMENT HEADER: "Final Labeling" deleted on all pages, pamphlet code added to p.1.
   - DESCRIPTION: Line spacing changes.
   - CLINICAL PHARMACOLOGY: Minor changes related to formatting (line spacing, font changes from italic to normal to preserve uniform appearance of headings/subheadings).
   - INDICATIONS AND USAGE: Line spacing changes.
   - CONTRAINDICATIONS: Line spacing changes.
   - WARNINGS: Line spacing changes.
   - PRECAUTIONS: Line spacing changes; Use in Patients With Concomitant Illnesses changed to Use in Patients With Concomitant Illness.
   - ADVERSE REACTIONS:
     - Overall: Line spacing changes;
     - insertion of the word "a" into the last sentence, fifth paragraph, to read "... to gain a complete understanding...".
     - One apparent spurious change: replacement of the word "studied" in last sentence, sixth paragraph, by itself (possible spacing error).
     - Tables: formatting / layout changes, no content change.
     - *Other Adverse Events* section: minor changes in font, spacing for consistent appearance.
   - DRUG ABUSE AND DEPENDENCE: Line spacing changes.
   - OVERDOSAGE: Line spacing changes.
   - DOSAGE AND ADMINISTRATION: Line spacing changes, spurious changes related to possible spacing errors (apparent replacements of a word or term by the identical word or term).
   - HOW SUPPLIED: Line spacing changes, spurious changes related to possible spacing errors (apparent replacement of a word or term by the identical word or term).
   - ANIMAL TOXICOLOGY: Line spacing changes.
   - DOCUMENT END: addition of text revision date, change FDA filename code to Lilly pamphlet code, line spacing changes

Recommendation: It is recommended that the submitted FPL be acknowledged and retained as identical to the agreed-upon labeling provided with the approval letter of March 17, 2000.

Reviewer: Doris J. Bates, Ph.D., RPM _____

Concurrence: John S. Purvis, Chief, Project Management Staff _____

attachments (for copy to original NDA file after review concurrence):

1. Agreed-upon labeling text from AP letter
2. Printout of WORD file as submitted by firm (pamphlet code DV 3555 DVP)
3. Printout of "Track Changes" WORD file comparing the DV 3555 DVP WORD file with the agreed-upon labeling text
4. Review Jacket: submitted FPL hardcopy, DV 3555 DVP

CC:
Orig NDA (with attachments as above) SE1--006, SLR-008
HFD-120 Division File
HFD-120/Purvis/Bates/Hardeman
HFD-120/20-592/s-006 action package, labeling subsection

d:...\supps\20592\s006\ackretn.doc

ZYPREXA® (OLANZAPINE)
BIPOLAR MANIA EFFICACY SUPPLEMENT
CSO ADMINISTRATIVE AND LABELING REVIEW

SUBMISSION: NDA 20-592 / SE1-006, SLR-008
DATES: **S-006**: December 3, 1997 (original submission), April 12, 1999 (response to NA letter), December 22, 1999 (response to AE letter).
S-008: August 26, 1998.
APPLICANT: Eli Lilly and Company
DOSAGE FORM AND STRENGTH: Tablets, 2.5, 5.0, 7.5, 10.0, 15.0, 20.0 mg (20 mg not marketed)
INDICATION(S): original indication: antipsychotic. S-006 provides for use of olanzapine in the treatment of acute manic or mixed episodes in bipolar disorder.
SCOPE OF REVIEW: This labeling review addresses:

- changes in the ***approved*** package insert since submission of SE1-006; see ADMINISTRATIVE HISTORY and CSO Labeling Review..
- changes between the most recent ***approved*** package insert, cited above, and the ***agreed-upon labeling*** negotiated between DNDP and the applicant; see ADMINISTRATIVE HISTORY and CSO Labeling Review.

This review has also surveyed the following supplements, submitted and / or approved in the same interval, to validate that they ***did not*** have or require associated labeling changes. They are not described in the ADMINISTRATIVE HISTORY.

- S-005, manufacturing supplement for changes in contract manufacture of the drug substance, submitted 24SEP97 and approved 04DEC97. There are no related labeling disclosures required for this change.
- S-007, manufacturing supplement for addition of a new bulk packaging site for the drug product, submitted 19DEC97 and approved 23MAR98. The requirement for disclosure of the name and place of business of the manufacturer, packer, ***or*** distributor of the drug product, per 21 CFR 201.10, does not apply to bulk packaging.

NOTE: Final Printed Labeling will be submitted following approval of this supplement and must be identical to the agreed-upon labeling enclosed with the approval letter. A separate CSO review (Acknowledge and Retain) will compare the FPL to the agreed-upon labeling when received.

MATERIAL REVIEWED / SUPERSEDED:

1. (reviewed): APPROVED package insert PV 2965 AMP (revision of November 19, 1998 to correct a misspelling of the trademark) (text provided by S. Hardeman, CSO)
2. (reviewed) APPROVED package insert PV 3330 AMP (revision of June 29,1999) (text provided by S. Hardeman, CSO, and by Lilly). This insert includes the 15 mg tablet (S-004) and was approved after PV 2965 AMP was implemented; these two approved inserts were compared to identify any unapproved changes.
3. (superseded) DRAFT Package insert PV 2963-F AMP (first draft of proposed bipolar text, submitted December 3, 1997) **This draft is superseded by draft insert PV 3330-A AMP.**
4. (superseded) DRAFT package insert PV 3330-A AMP (second draft of proposed bipolar text, December 22, 1999, based on PV3330AMP and including geriatric safety and use text based on data provided in [ ] (see Administrative History)). **This text is superseded by the agreed upon labeling text as confirmed in writing by Lilly on February 29, 2000.**
5. (superseded) DRAFT proposed changes to text in Geriatric Use section (S-008, August 26, 1998, S. Hardeman, CSO; See Administrative History). **This text is superseded by the draft insert PV 3330-A AMP and the agreed upon labeling text as confirmed by Lilly on**

- WARNINGS: No observed changes.
- PRECAUTIONS: No observed changes.
- ADVERSE REACTIONS: No observed changes.
- DRUG ABUSE AND DEPENDENCE: No observed changes.
- OVERDOSAGE: No observed changes.
- DOSAGE AND ADMINISTRATION: No observed changes.
- HOW SUPPLIED: Changes in PV3330 in agreement with the addition of the 15 mg tablet:
  - blue film coating
  - bottles of 30 (15 mg only) added
  - 15 mg tablet description added to master table
- ANIMAL TOXICOLOGY: No observed changes.

Agreed upon labeling vs. approved insert PV 3330 AMP, with changes superseding S-008 and including data from [ ]

Draft insert PV 2963 F-AMP was based on approved insert PV 2965. It is superseded by PV 3330-A AMP, which is based on approved insert PV 3330 AMP. Therefore, the changes listed above between the two approved versions of FPL are also reflected in the two successive drafts and have been carried through to the agreed upon labeling for S-006.

Labeling supplement S-008 (see Administrative History) proposed revised language for the Geriatric Use subsection of the package insert. There are also changes to the Geriatric Use subsection and the ADVERSE REACTIONS section of PV 3330-A AMP which were recommended by the Division in connection with [ ] but the patient data generated in connection with it remain relevant to product labeling. In a February 28, 2000 teleconference with John Roth, regulatory project manager at Lilly, it was confirmed that the geriatric language proposed in supplement S-008, is addressed, and therefore may be superseded, by the agreed upon labeling for S-006. See also FAX, February 29, 2000. (attachment 2)

A line by line comparison of the agreed upon labeling for S-006 to prior approved FPL PV 3330 AMP indicates that no additional changes in wording have been made other than those relevant to the following areas, as indicated (underlining) in the marked-up version of agreed upon labeling (attachment 3):

- the proposed indication bipolar mania affects:
  - Description (first line)
  - Clinical Pharmacology (*Pharmacodynamics*)
  - Clinical Efficacy (new subsection Bipolar Mania, with text)
  - Indications and Usage (new subsection Bipolar Mania, with text)
  - Precautions (General – text added to the existing section for Suicide and *Drug Interactions*)
  - Adverse Reactions (new text in introductory paragraphs, new tables and modifications to contents of existing tables, new information in *Incidence of Adverse Events in Short-Term, Placebo-Controlled Trials* subsection, new information in *Other Adverse Events Observed During the Clinical Trial Evaluation* section, revisions to reported frequency,

February 29, 2000. The S-008 proposed text is Attachment 1 to this review; Lilly's FAX is Attachment 2.

6. (reviewed) FDA / Lilly Agreed Upon Labeling Text (agreement confirmed in writing by Lilly, FAX, February 29, 2000). **This text is Attachment 3 to this review.**
7. (reviewed) Tabular Summary of Labeling Changes (Approved Package Insert), provided by Lilly, March 3, 2000. **This text is Attachment 4 to this review.**

ADMINISTRATIVE HISTORY:

- **Changes to prior approved labeling** made during the review of S-006 include the following other supplements / annual reports which have been approved or accepted:
  - S-004, manufacturing supplement for the 15 mg tablet, submitted 14APR97 and approved 09SEP97; labeling revised 29JUN99 (PV 3330 AMP). This insert declares the 15 mg dosage strength, provides its description and inactive ingredients, and lists bottles of 30 tablets for this strength per CMC supplement SCM-004, approved 09SEP97. (NOTE: the delay in revision of FPL is attributed to delay in market introduction of 15 mg tablets by the applicant. Note also that the 20 mg tablets are not currently marketed.)
  - S-010, CBE labeling supplement for the addition of priapism to a new "Postintroduction Reports" subsection in ADVERSE REACTIONS, submitted 13OCT98 and approved 11JAN99 (PV 2964 AMP).
  - Y-003 (Annual Report) includes Insert PV 2965 AMP which corrects misspelling of the trademark ZYPREXA in PV 2964 AMP, effective 05NOV99.
- **Changes to the current agreed upon labeling** for S-006 also include information related to the following two supplements which have been superseded or withdrawn:
  - S-008, labeling supplement for revision of the Geriatric Use subsection in conformance with the Geriatric Labeling Final Rule, submitted 26AUG98. The revisions proposed in S-008 are addressed and **superseded** by the inclusion of language relevant to [ ] (see below) in the agreed upon labeling text for the current action (S-006). See CSO Labeling Review and Action Letter.
  - • [
    [ ]
    [ ] the supplement provided additional safety and efficacy data which have been incorporated into the agreed-upon final labeling for S-006.
- As noted above, inserts PV 2963-F AMP and 3330-A AMP are draft inserts only and include the applicant's proposed / revised proposed language for the bipolar indication.

CSO LABELING REVIEW:

Approved inserts: PV 2965 AMP vs. PV 3330 AMP.

A line by line comparison of the prior approved label PV 2965 AMP and the current label PV 3330 AMP indicated the following changes (all are described with reference to PV 3330):

- DESCRIPTION: 15 mg strength added; "color mixture white" deleted from list of inactives; titanium dioxide listed; FD&C Blue No. 2 Aluminum Lake listed as colorant in tablet coating (15 mg) and printing ink (all other strengths).
- CLINICAL PHARMACOLOGY: No observed changes.
- INDICATIONS AND USAGE: No observed changes.
- CONTRAINDICATIONS: No observed changes.

severity of AEs by body system within this section)
- Dosage and Administration (Bipolar Mania subsection)

- superseded supplement S-008 affects:
  - Precautions (*Geriatric Use* text))
- [ ]
  - Precautions (*General* – Dysphagia, Use in Patients with Concomitant Illness, *Geriatric Use*)
  - Adverse Reactions (including tables, *Other Adverse Events Observed During the Clinical Trial Evaluation* section, revisions to reported frequency, severity of AEs by body system)

Some additional text rearrangements have been incorporated for clarity. See clinical reviews for more detail on the basis of the revisions.

Recommendation: It is recommended that the agreed-upon labeling text be implemented as it stands in the approval letter for NDA 20-592/SE1-006. Implementation of the package insert revisions for S-006 supersedes the Geriatric Labeling text revisions proposed by the applicant in S-008 and includes information relevant to the use of the drug in Alzheimer's dementia, as presented in [ ].

Reviewer: Doris J. Bates, Ph.D., RMO

Concurrence: John S. Purvis, Chief, Project Management Staff John S. Purvis 3/15/00

attachments (for copy to original NDA file after review concurrence):
1. S-008 Cover Letter
2. FAX from applicant, 29FEB2000
3. Agreed-upon labeling (printout)
4. Labeling change summary from applicant, March 3, 2000

CC:
Orig NDA (with attachments as above) SE1–006, SLR-008
HFD-120 Division File
HFD-120/Purvis/Bates
HFD-120/20-592/s-006 action package, labeling subsection

d:...\supps\20592\s006\pirevue2.doc

FACSIMILE TRANSMISSION

Eli Lilly and Company
Lilly Research Laboratories
U.S. Regulatory Affairs
Phone No. (317) 276-5185
FAX (317) 276-1652

CONFIDENTIAL CONFIDENTIAL

TO: Dr. Doris Bates
COMPANY: FDA
FAX #: 1-301-594-2859
Number of Pages: 3
(Including cover sheet)

FROM: John Roth
PHONE #: 317-433-3523
DATE: 3-3-00

Message: Doris - As we discussed, I'm faxing the labeling summary for versions PV2963AMP and later. Please let me know if this is the information you need. Thanks for your help and enjoy your weekend.

2 page(s) of draft labeling has been removed from this portion of the review.

Correspondence: Fax re: Labeling (3/3/00)

NDA 20-592/S006

FACSIMILE TRANSMISSION

Eli Lilly and Company
Lilly Research Laboratories
U.S. Regulatory Affairs
FAX (317) 276-1652

CONFIDENTIAL **CONFIDENTIAL**

To: Doris Bates, Ph.D., FDA
FAX #: 301-594-2859
Date: February 29, 2000
From: Greg Brophy, Ph.D, Eli Lilly & Co.
Phone #: 317-277-3799
Re: NDA 20-592 – Zyprexa® (olanzapine) – Supplement 006 (Bipolar Mania)
Agreement with FDA's Labeling Edits Faxed to Lilly on February 28, 2000
Agreement with FDA's Proposal to Supercede S008 with S006

This fax is in response to:

- The Division's February 28, 2000 fax of revised labeling for the subject supplemental NDA incorporating the suggested editorial corrections suggested in our February 28, 2000 fax.
- The proposal made by Dr. Doris Bates of the Division to supercede the *Geriatric Use* subsection labeling changes proposed in Lilly's previously submitted Geriatric Labeling Supplement (S008 to NDA 20-592; submitted August 26, 1998) with the currently agreed upon *Geriatric Use* subsection labeling in the subject supplemental NDA.

We have reviewed the Division's faxed labeling incorporating our suggested editorial corrections and are in total agreement with this version.

We have also considered the Division's proposal to supercede S008 with the currently agreed upon *Geriatric Use* subsection labeling in the subject supplemental NDA. The primary reason for submitting S008 was to comply with the geriatric final rule (Federal Register Notice, August 27, 1997, Docket No. 89N-0474). It is our understanding from the Division's proposal that you consider the currently agreed upon labeling in the subject supplemental NDA to be in compliance with the geriatric final rule. Accordingly, we are in full agreement with your proposal to supercede S008 with the currently agreed upon labeling in the subject supplemental NDA.

We thank you very much for your continued cooperation during the review of this application. Please call Dr. John Roth at (317) 433-3523 or me at (317) 277-3799 if there are any questions.

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

PHASE 4 COMMITMENT
FDA Response Requested

February 25, 2000

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

Re: NDA 20-592, ZYPREXA® (olanzapine) – S006 (Bipolar Mania)

We are enclosing our plan to address the Phase 4 commitment requested in your October 28, 1999 approvable letter for the referenced supplemental NDA. The enclosed Note to Reviewers provides a brief overview of our plan, and the enclosed Attachment provides a more detailed summary. We are requesting the Division's review and response regarding the acceptability of our proposed plan for its intended purpose.

We thank you for your continued cooperation and assistance and ask that you please call Dr. John Roth at (317) 433-3523 or me at (317) 277-3799 if there are any questions. We look forward to working with you on this important matter.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U. S. Regulatory Affairs

Enclosure

Redacted 21 page(s)

of trade secret and/or

confidential commercial

information from

Administrative + Correspondence: Phase 4 Commitment (2/25/00)

Meeting Minutes, Discussion of Response to AE Letter
NDA 20-592/SE1-006
Zyprexa (olanzapine) in Treatment of Bipolar I Disorder
Eli Lilly & Co.

Date/Time/Site: 5 January 2000, 10:00 a.m., WOC II 4037
Participants: R. Katz, T. Laughren, P. Andreason, J. Ware (meeting recorder).
Draft: 25 February 2000, by D. Bates
Final:

Background: An approvable letter, with draft labeling, was issued for this supplement on October 28, 1999. Lilly notified the Division of their intent to amend the supplement in a letter dated October 26, 1999. Additional information on safety of the drug in the Alzheimer's Dementia population was provided by Lilly on November 24, 1999 and the response to the approvable letter was received December 23, 1999. The response package includes the complete revised labeling proposals from the applicant, and was distributed to Drs. Katz, Laughren, Hearst, Andreason, Mosholder, and Burkhart for further reference.

Discussion: It was agreed by all participants that the December 1999 submission constituted a complete response to the approvable letter.

Decisions/Action Items: The final proposed labeling will be drafted and FAXed to Lilly, with revisions as agreed upon in the December 15, 1999 meeting on the safety package. per Division policy, negative study results will be included in the clinical trials section of the labeling, and secondary outcome measures will not be discussed. A change in the indication from antipsychotic to antischizophrenic will be proposed as part of the final labeling.

Doris J. Bates, PhD, RPM
for the attendees

2-25-00
Thomas P. Laughren, MD
Team Leader, Psychiatric Drugs Group

Post meeting note: A teleconference was held on February 22, 2000 between representatives of Lilly and the FDA clinical review team. On February 23, 2000, following a face to face meeting on another olanzapine indication, it was further discussed, and agreed, that the indication would not be revised to antischizophrenic at this time.

CC:
HFD-120/Original NDA Efficacy Supplement
HFD-120/Division File
/Katz
/Laughren/Hearst/Andreason/Mosholder
/Burkhart
/Bates DJB 25FEB2000

E L E C T R O N I C M A I L M E S S A G E

Date: 12-Jan-2000 12:45pm EST
From: Doris Bates
BATESD
Dept: HFD-120 WOC2 4034
Tel No: 301-594-5536 FAX 301-594-2859

TO: Thomas Laughren (LAUGHREN)
TO: Earl Hearst (HEARSTE)
TO: Paul Andreason (ANDREASONP)

CC: Andrew Mosholder (MOSHOLDERA)
CC: Greg Burkhart (BURKHARTG)

Subject: Zyprexa Information FYI and Feedback

NDA 20-592/S-006: Telecon, 12JAN00, 12:30 p.m.
D. Bates to J. Roth, 317.433.3523

This email documents that I have spoken with John Roth of Lilly, re the Zyprexa resubmission of 22DEC99. He is aware that we have accepted this submission as a complete response and are engaged in review.

He informed me that Lilly had strong hopes of resolving further issues very quickly and that the launch date had been tentatively set for the end Feb 2000. He asked if this date was realistic and I noted that, having been out, I could not answer this off the cuff but that I was under the impression there were other related review issues (DDMAC) which would also need to be addressed.

If acceptable, I will follow up to inform him that our time frame for the labeling review is likely to be later then end February.

Please let me know if a telecon or meeting should be needed to address any labeling review issues with the firm.

58.1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN -6 2000

NDA 20-592/S-006

Eli Lilly and Company, Inc.
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

We acknowledge receipt on December 23, 1999 of your December 22, 1999 resubmission to your supplemental new drug application for ZYPREXA (olanzapine) Tablets, 2.5, 5, 7.5, and 10mg.

This resubmission contains additional clinical information submitted in response to our October 28, 1999 action letter.

With this amendment, we have received a complete response to our October 28, 1999 action letter.

If you have any questions, call Doris J. Bates, Ph.D., Project Manager, at (301) 594-5536.

Sincerely,

1/6/00

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 20-592
HFD-120/Div. Files
HFD-120/D.Bates
HFD-120/Laughren/Andreason/Hearst

1-6-00

DISTRICT OFFICE

Drafted by: jhw/January 5, 2000
Initialed by:
final:
filename: ZYS6AZAC.LTR

RESUBMISSION ACKNOWLEDGEMENT (AC)

Meeting Minutes, Labeling Discussion
NDA 20-592/SE1-006
Zyprexa (olanzapine) in Treatment of Bipolar I Disorder
Eli Lilly & Co.

Date/Time/Site: 15 December 1999, 2:00 p.m., WOC II 4037
Participants: R. Katz, T. Laughren, P. Andreason, A. Mosholder, E. Hearst, D. Bates (meeting recorder). Absent: G. Burkhart
Draft: 29 December 1999
Final:

Background: The efficacy supplement provides for the use of olanzapine in the treatment of bipolar 1 disorder. An approvable letter, with draft labeling, was issued for this supplement on October 28, 1999. Lilly notified the Division of their intent to amend the supplement in a letter dated October 26, 1999.

On November 12, 1999, Dr. C. Beasley and A. Breier of Lilly participated in a teleconference with Dr. T. Laughren in order to discuss the proposed draft labeling as specifically related to safety in patients with dementia of the Alzheimer's type (study HGEU). In the course of this discussion, Lilly proposed deferral of implementation for these labeling revisions and agreed to provide additional information pertinent to their request. This additional information was received November 24, 1999; it includes

- case reviews of all deaths associated with or occurring within 30 days of the acute double-blind phase of Study HGEU
- a revised comprehensive table of treatment-emergent adverse events in study HGEU. Note that the applicant cites errors in the relevant database for this study as the basis for revision of this table.
- revised tables of treatment-emergent adverse events for study HGEU re:
    1. events with two or more occurrences and more occurrences than placebo
    2. dose-dependent AEs
    3. most frequent AEs in all groups (at least 2x incidence on placebo)
    4. AE incidence in combined groups (at least 2x incidence on placebo)
- case summary data, including CRF safety information, ClinTrace summaries, and MEDWATCH forms, for all patients who died during the acute double-blind portion of the study

The November 24 submission was not intended to be a response to the Division's approvable letter, and was clearly marked as such. That response was received December 23, 1999, includes the complete revised labeling proposals from the applicant, and has been distributed to Drs. Katz, Laughren, Hearst, Andreason, Mosholder, and Burkhart for further reference.

Discussion: It was noted that the geriatric dementia population is highly vulnerable to aspiration pneumonia. Although the applicant presents detailed case histories for all five deaths associated with the acute double-blind phase of the study, and argues that these deaths follow markedly different clinical courses, the Division observed that [ ] dysphagia are [ ] which increase the risk of aspiration in precisely this population. Also, it was noted that, although the five deaths occurred at markedly different times during or within 30 days of the acute double-blind phase of the study, all five patients who died had been

receiving drug during this phase; there were deaths in all dose groups (5, 10, 15 mg) with a slight excess in the mid-dose group (3 deaths as opposed to one each in the low and high-dose groups).

Decisions/Action Items: It was agreed that, based on the data provided by the applicant, the Division can make the following changes to the proposed olanzapine labeling:

- [redacted]
- [redacted]
- strengthen the language related to dysphagia [redacted] in the Precautions section of labeling
- [redacted]

[redacted]

In addition, it was agreed that we would request Lilly to evaluate the five deaths from the standpoint of total exposure time, ranked by dose. Finally, it was noted that risperidone use appears to carry similar risks for the geriatric dementia population; the Division will therefore address the risperidone labeling at this time.

A letter will be drafted conveying the new proposals for labeling revisions and our request for further evaluation of the five deaths, as discussed above.

Doris J. Bates, PhD, RPM
for the attendees

Thomas P. Laughren, MD
Team Leader, Psychiatric Drugs Group

2-3-00

Post meeting note: Because the applicant's complete response to the Division's approvable letter has now also been received by the Division, action on both submissions may be combined if appropriate. There is no official classification of response types for efficacy supplements; an internal review timetable of six months or less generally applies.

CC:
HFD-120/Original NDA Efficacy Supplement
HFD-120/Division File
/Katz
/Laughren/Hearst/Andreason/Mosholder
/Burkhart
/Bates
HFD-710/Jin/He

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

December 22, 1999

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

RESPONSE TO APPROVABLE LETTER

Re: NDA 20-592, Zyprexa® (olanzapine) – S006 (Bipolar Mania)

We are providing the following complete response to your October 28, 1999 approvable letter for the referenced supplemental NDA. Please note our October 29, 1999 submission to the referenced NDA notifying you of our intent to amend the referenced supplement.

Attachment 1 provides our response to your proposal for the revised labeling of Zyprexa. Included is our revised labeling proposal, as well as a detailed explanation of our suggested revisions to your proposal. An electronic copy of our revised labeling proposal is also being provided for convenience on the enclosed computer diskette (WORD 6.0 format).

Attachment 2 provides our response to your request related to pediatric studies.

Attachment 3 provides our response to your request for additional information for Studies HGEH and HGGW.

In light of our ongoing labeling discussions with the Division, draft copies of introductory promotional materials are not yet available. However, final materials will be submitted with Form 2253 at the time of first use pursuant to regulatory requirements.

We respectfully request a meeting or conference call with Division representatives to discuss any disagreements concerning our draft labeling response or to clarify any other issues prior to the approval of the referenced supplemental NDA.

Eli Lilly and Company
Pharmaceutical Division

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

November 23, 1999

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

Re: NDA 20-592, Zyprexa® (Olanapine) – Supplement 006 (Bipolar Mania) – General Correspondence

Please refer to your October 28, 1999 approvable letter for the referenced supplemental NDA. Please refer also to the November 12, 1999 telephone conversation between Dr. Tom Laughren (FDA) and our Drs. Charles Beasley and Alan Breier. In this conversation certain aspects of the draft labeling accompanying your October 28 letter were discussed. It was agreed that Lilly would promptly submit information pertinent to this discussion.

This submission is not a response to the October 28 approvable letter for bipolar mania. In the future a complete response to that approvable letter will be submitted.

The attached document provides the information we committed to provide in the November 12 conference call.

Your prompt review of the information provided herein would be appreciated.

Please call Dr. Al Webber at (317) 276-4255 or me at (317) 277-3799 if there are any questions. Thanks you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

cc: Dr. Doris Bates (six sets of two volumes, shrink-wrapped)

FACSIMILE TRANSMISSION

Eli Lilly and Company
Lilly Research Laboratories
U.S. Regulatory Affairs
FAX (317) 276-1652

CONFIDENTIAL **CONFIDENTIAL**

To: Doris Bates, Ph.D., FDA
FAX #: 301-594-2859
Date: 23 August 1999
From: Greg Brophy, Ph.D, Eli Lilly & Co.
Phone #: 317-277-3799
Re: NDA 20-592 – Zyprexa® (olanzapine) – Supplement 006 (Bipolar Mania)
Labeling teleconference scheduled for 10:30 AM, Tuesday, February 22, 2000

This is regarding the teleconference scheduled for Tuesday, February 22, 2000, to discuss Lilly's response to the Division's labeling proposal for the subject supplemental NDA, which was faxed to Lilly on Tuesday, February 15, 2000. We are providing a list of the anticipated participants and a summary of the points we plan to discuss during this teleconference. It is our understanding that the Division will telephone Lilly to initiate the teleconference. The telephone number for the meeting room we will be using at Lilly is 317-276-6682.

Teleconference Participants

FDA
Paul Andreason, M.D.; Doris Bates, Ph.D.; Earl Hearst, M.D.; Tom Laughren, M.D.

Lilly
Robert Baker, M.D.; Alan Breier, M.D.; Charles Beasley, M.D.; Greg Brophy, Ph.D.; John Hayes, M.D.; Jack Jordan; John Roth, Ph.D.; Todd Sanger, Ph.D; Mauricio Tohen, M.D.

Discussion Topics

We have carefully reviewed the Division's proposed labeling text and appreciate the Division's timely and thorough review. We agree for the most part with the Division's proposed labeling. However, as summarized below, there are a few proposed revisions we wish to discuss further during the teleconference. Our labeling proposals pertaining to each of the discussion topics are provided as attachments. In our labeling proposals, all text previously agreed to by the Division is shown in normal font. Changes from the revised labeling in the Division's February 15, 2000 fax are shown as strike-through font for deletions and as double-underlined font for additions.

1.

8 page(s) of draft labeling has been removed from this portion of the review.

Administrative + Correspondence: Labeling Teleconference (8/23/99)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

April 12, 1999

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

RE: NDA 20-592, Zyprexa® (olanzapine) – Amendment to Supplement 006

Enclosed is an amendment to Supplement 006 (for the referenced NDA), submitted December 3, 1997. Supplement 006 received a not-approvable letter dated October 2, 1998.

The enclosed provides the results from study HGGW. It also provides a complete response to the October 2, 1998 not-approvable letter.

This amendment is formatted and organized according to 21 CFR §314.50 and follows the "Guideline for the Format and Content of the Clinical and Statistical Section of New Drug Applications" and the "Guidelines on Formatting, Assembly, and Submitting New Drug and Antibiotic Applications." Cross-referencing to NDA 20-592 supports the enclosed amendment. Items 11 and 12 of the application, the Case Report Tabulations and the Case Report Forms, are provided as an electronic-only archival copy in accordance with the "FDA Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs".

The electronic archival copy of Items 11 and 12 is contained on one CDROM. This CD-ROM is being sent to the Center for Drug Evaluation and Research Central Document Room in accordance with the "FDA Guidance for Industry Providing Regulatory Submissions in Electronic Format – General Considerations". The CD-ROM has been checked and verified to be free of known viruses. This virus checking software was McAfee VirusScan 3.2.0 using Virus Definitions 3.0.3202 created on 15-Feb-1999.

Reference is made to the agreement reached April 2, 1999, between Dr. Doris Bates, FDA, and Steve Ward, Lilly, to not submit an electronic copy of the complete NDA in Adobe Acrobat format as a review aid as was previously planned. If at a subsequent time the reviewers desire such an electronic review aid and feel it is appropriate within FDA to request one, Lilly will promptly submit these electronic files as a review aid under separate cover to Dr. Bates.

To coordinate our activities with yours, we suggest that any written communications concerning this file, regardless of subject be directed to:

Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Any calls dealing with general issues, clinical reports, labels, or literature should be made to:

J. Alan Webber, Ph.D.
(317) 276-4255
[ ] (home)

(Please address all facsimile (fax) transmission to Dr. Al Webber at (317) 276-1652, or, in his absence, to:

Gregory T. Brophy, Ph.D.
(317) 277-3799
[ ] (home)

Any questions about the electronic submission should be directed to:

Steven T. Ward
(317) 276-2952
[ ] (pager)

On holidays, Saturdays, or Sundays, call Dr. Webber or Dr. Brophy at home using the telephone numbers indicated.

Close liaison between the Lilly personnel listed above will result in any messages, no matter how received, being brought to the attention of all concerned.

Please call Dr. Al Webber at (317) 276-4255 or me at (317) 277-3799 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

cc: Dr. Doris Bates – one vol. 1, one vol. containing ISE and ISS

Enclosures