

20952/S-011

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N20592



N20592

Zyprexa
(Olanzapine)

REC -

11/29/00

8:49 AM

Lilly

NDA 20-592

SE1-011

VOLUME 1

Action Package

Relapse Prevention

Due: 10/17/00 (10 mos)

Olanzapine Action Package – Table of Contents

20-592 / SE1-011

Efficacy Supplement: Longer-term Use/Maintenance of Response

PDUFA = 10/17/00 (10 months)

One Volume

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 - ~~Draft Insert - Division~~
 - Draft Insert - Sponsor
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- G. Pediatric Page
- H. Debarment Certification
- I. DSI
 - Audit Status - Completed / review included
 - List of Investigators – NA: included in M.O. review
- J. Division Director Memo — *NONE*
- K. Clinical Team Leader Memo
- L. Clinical Review
- M. Statistical Review
- N. Sponsor contact info/background

L O D F S 11/9/00
SH

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-592 SE1 - 011

Drug Zyprexa (olanzapine)

Applicant Lilly

RPM Steven D. Hardeman, R.Ph

Phone 301-594-5525

505(b)(1) This application is a 505(b)(1)

505(b)(2) Reference listed drug

Fast Track

Rolling Review

Review priority: **Standard**

Pivotal IND(s) IND 28,705 ~~28,705~~

Application classifications:

Chem Class 6
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:

Primary 17 OCT 2000
Secondary 17 DEC 2000

Arrange package in the following order:

Indicate N/A (not applicable),
X (completed), or add a
comment.

GENERAL INFORMATION:

- ◆ User Fee Information: User Fee Paid
 User Fee Waiver (attach waiver notification letter)
 User Fee Exemption

◆ Action Letter..... AP AE NA

◆ Labeling & Labels

- FDA revised labeling and reviews..... ✓
- Original proposed labeling (package insert, patient package insert)..... ✓
- Other labeling in class (most recent 3) or class labeling..... NA
- Has DDMAC reviewed the labeling?..... Yes (include review) No
- Immediate container and carton labels..... NA
- Nomenclature review..... NA

◆ Application Integrity Policy (AIP) Applicant is on the AIP. This application is is not on the AIP.

Exception for review (Center Director's memo)..... _____
OC Clearance for approval..... _____

Continued ⇨

- ◆ Status of advertising (if AP action) Reviewed (for Subpart H - attach review) Materials requested in AP letter N/A
- ◆ Post-marketing Commitments None
 - Agency request for Phase 4 Commitments
 - Copy of Applicant's commitments
- ◆ Was Press Office notified of action (for approval action only)? VIA DFS Yes No N/A
 - Copy of Press Release or Talk Paper
- ◆ Patent
 - Information [505(b)(1)] ✓
 - Patent Certification [505(b)(2)] ✓
 - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] ✓
- ◆ Exclusivity Summary NA @ AE ✓ 11/9/00
- ◆ Debarment Statement
- ◆ Financial Disclosure
 - No disclosable information ✓
 - Disclosable information - indicate where review is located
- ◆ Correspondence/Memoranda/Faxes N/A
- ◆ Minutes of Meetings NA
 - Date of EOP2 Meeting _____
 - Date of pre NDA Meeting _____
 - Date of pre-AP Safety Conference _____
- ◆ Advisory Committee Meeting NA
 - Date of Meeting
 - Questions considered by the committee
 - Minutes or 48-hour alert or pertinent section of transcript
- ◆ Federal Register Notices, DESI documents N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ✓
- ◆ Clinical review(s) and memoranda ✓

Continued ⇨

- ◆ Safety Update review(s) NA

- ◆ Pediatric Information
 - Waiver/partial waiver (Indicate location of rationale for waiver) Deferred Pediatric Page..... ✓
 - Pediatric Exclusivity requested? Denied Granted Not Applicable
- ◆ Statistical review(s) and memoranda ✓
- ◆ Biopharmaceutical review(s) and memoranda..... NA
- ◆ Abuse Liability review(s) NA
 Recommendation for scheduling
- ◆ Microbiology (efficacy) review(s) and memoranda NA
- ◆ DSI Audits ✓
 - Clinical studies bioequivalence studies

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda NA
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability
- ◆ DMF review(s)
- ◆ Environmental Assessment review/FONSI/Categorical exemption
- ◆ Micro (validation of sterilization) review(s) and memoranda
- ◆ Facilities Inspection (include EES report)
 Date completed Acceptable Not Acceptable
- ◆ Methods Validation Completed Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda NA
- ◆ Memo from DSI regarding GLP inspection (if any) ✓

Continued ⇨

◆ Statistical review(s) of carcinogenicity studies NA

◆ CAC/ECAC report NA

/s/

Steve Hardeman
11/9/00 01:35:02 PM



NDA 20-592/SE1-011

Lilly Research Laboratories
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Brophy:

Please refer to your supplemental new drug application dated December 15, 1999, received December 17, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) tablets.

We acknowledge receipt of your submission of October 18, 2000, which constituted a complete response to our action letter of October 12, 2000.

This supplemental new drug application provides for the use of Zyprexa (olanzapine) for the maintenance of treatment response.

We have completed the review of this supplemental application, 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 enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-592/SE1-011." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, 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 (63 FR 66632)(21 CFR 314.55 (or 601.27)). FDA is deferring submission of the pediatric assessments of safety and effectiveness that may be required under these regulations until we have had an opportunity to more carefully consider the question of whether or not there may be a health benefit from studies in pediatric patients, and if so, in which populations. FDA will inform you on or before June 1, 2001, whether pediatric studies are required under the rule. If FDA determines at that time that pediatric studies are necessary, FDA will also set a specific time at which you must submit the required assessments.

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 NDA and a copy to the following address:

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

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, call Steven D. Hardeman, R.Ph., Regulatory Project Manager, at (301) 594-5525.

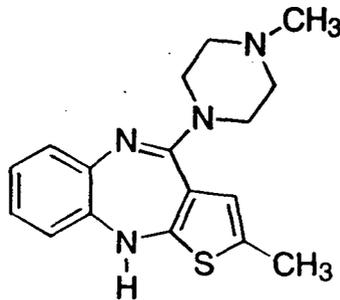
Sincerely,

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

Enclosure

**ZYPREXA®
(Olanzapine) Tablets****ZYPREXA® ZYDIS®
(Olanzapine) Orally Disintegrating Tablets****DESCRIPTION**

ZYPREXA (olanzapine) is a psychotropic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-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 μ mol), 5 mg (16 μ mol), 7.5 mg (24 μ mol), 10 mg (32 μ mol), or 15 mg (48 μ mol). 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.

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

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

CLINICAL PHARMACOLOGY**Pharmacodynamics:**

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin 5HT_{2A/2C} (K_i =4 and 11 nM, respectively), dopamine D₁₋₄ (K_i =11-31 nM), muscarinic M₁₋₅ (K_i =1.9-25 nM), histamine H₁ (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 μ M).

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 (5HT₂) 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 5HT₂ with similar receptor affinities may explain

some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1,5} receptors may explain its anticholinergic effects. Olanzapine's antagonism of histamine H₁ 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. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

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

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

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1 -acid glycoprotein.

Metabolism and Elimination--Following a single oral dose of ¹⁴C 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 (\leq 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 treatment of schizophrenia was established in 2 short-term (6-week) controlled trials of inpatients who met DSM III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in one of the two trials, but this trial did not compare these two drugs on the full range of clinically relevant doses for both.

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

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

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5.0±2.5 mg/day, 10.0±2.5 mg/day, and 15.0±2.5 mg/day) on a once daily schedule, the two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high dose group over the medium dose group.

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

In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open label treatment for at least 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in BPRS

positive symptoms or hospitalization, was planned for 12 months, however, criteria were met for stopping the trial early due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months.

Bipolar 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 treatment of schizophrenia.

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

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

Bipolar 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, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Interference with Cognitive and Motor Performance--Because olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery,

including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

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

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

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

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

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

Phenylketonurics--ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34 and 0.45 mg per 5 and 10 mg tablet, respectively).

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

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

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

Olanzapine may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Olanzapine--Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 (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 C_{max} 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/m² basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily dose on a mg/m² 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/m² 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/m² 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/m² basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥ 2 mg/kg/day and in female rats dosed at ≥ 4 mg/kg/day (0.5 and 2 times the maximum recommended human daily dose on a mg/m² 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/m² 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/m² basis). Diestrus was prolonged and estrus delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily dose on a mg/m² 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/m² 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/m² basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily dose on a mg/m² 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/m² 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 a complete understanding of the safety profile of olanzapine.

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

Incidence of Adverse Events in Short-Term, Placebo-Controlled 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 Trials¹

Body System/Adverse Event	Percentage of Patients Reporting 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

Table 1 (cont.)
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Clinical Trials¹

Percentage of Patients Reporting Event

Body System/Adverse Event	Olanzapine (N=532)	Placebo (N=294)
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

Table 1 (cont.)
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Clinical Trials¹
Percentage of Patients Reporting Event

Body System/Adverse Event	Olanzapine (N=532)	Placebo (N=294)
Nervous System (cont.)		
Hypertonia	3	2
Articulation impairment	2	1
Respiratory System		
Rhinitis	7	6
Cough increased	6	3
Pharyngitis	4	3
Special Senses		
Amblyopia	3	2
Urogenital System		
Urinary incontinence	2	1
Urinary tract infection	2	1

¹ Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion, depression, diarrhea, dysmenorrhea², hallucinations, headache, hostility, hyperkinesia, myalgia, nausea, nervousness, paranoid reaction, personality disorder³, 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 Clinical Trials--The following findings are based on clinical trials.

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

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

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

	Percentage of Patients			
	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.

Adverse Event	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)
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.

In the olanzapine clinical trial database, as of September 30, 1999, 4577 olanzapine-treated patients (representing approximately 2255 patient-years of exposure) and 445 placebo-treated patients who had no history of diabetes mellitus and whose baseline random plasma glucose levels were 140 mg/dL or lower were identified. Persistent random glucose levels ≥ 200 mg/dL (suggestive of possible diabetes) were observed in 0.8% of olanzapine-treated patients (placebo 0.7%). Transient (i.e., resolved while the patients remained on treatment) random glucose levels ≥ 200 mg/dL were found in 0.3% of olanzapine-treated patients (placebo 0.2%). Persistent random glucose levels ≥ 160 mg/dL but < 200 mg/dL (possibly hyperglycemia, not necessarily diabetes) were observed in 1.0% of olanzapine-treated patients (placebo 1.1%). Transient random glucose levels ≥ 160 mg/dL but < 200 mg/dL were found in 1.0% of olanzapine-treated patients (placebo 0.4%).

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 and 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: diabetic coma and priapism.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class--Olanzapine is not a controlled substance.

Physical and Psychological Dependence--In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily dose on a mg/m² 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.

During the first 2 years of marketing, Eli Lilly and Company received reports of 178 cases of possible or definite overdose with olanzapine alone (at doses up to 1500 mg). Symptoms possibly but not necessarily causally attributable to the overdose were reported in 76% of these cases while 24% of reported cases had no symptoms attributable to overdose. In symptomatic patients, symptoms with $\geq 10\%$ incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and one patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, coma, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In one case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

Overdosage Management--The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation,

which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. ~~Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.~~

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

DOSAGE AND ADMINISTRATION

Schizophrenia

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

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

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

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

Bipolar 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).

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

HOW SUPPLIED

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

	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	NDC-0002- 4415-60
Blisters - ID* 100	NDC-0002- 4112-33	NDC-0002- 4115-33	NDC-0002- 4116-33	NDC-0002- 4117-33	NDC-0002- 4415-33
Bottles 1000	NDC-0002- 4112-04	NDC-0002- 4115-04	---	NDC-0002- 4117-04	NDC-0002- 4415-04

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

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

	TABLET STRENGTH	
	5 mg	10 mg
ZYPREXA ZYDIS Tablets*		
Tablet No.	4453	4454

Debossed	5	10
NDC Codes:		
Dose Pack 30	NDC-	NDC-
(Child-Resistant)	0002-	0002-
	4453-85	4454-85

ZYPREXA is a registered trademark of Eli Lilly and Company.

ZYDIS is a registered trademark of R. P. Scherer Corporation.

* ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Scherer DDS Limited, United Kingdom, SN5 8RU.

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

Protect from light and moisture.

ANIMAL TOXICOLOGY

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily dose on a mg/m² 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/m² 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/m² basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily dose on a mg/m² basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

Literature revised **October**, 2000

Eli Lilly and Company
Indianapolis, IN 46285, USA

3.2 PV 3392 AMP

Printed in USA

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/s/

Russell Katz
11/9/00 10:17:14 AM

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46284

OCT 12 2000

Dear Dr. Brophy:

Please refer to your supplemental new drug application dated December 15, 1999, received December 17, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) tablets.

We acknowledge receipt of your submissions of April 6, 2000 and June 30, 2000.

This supplemental new drug application proposes the use of Zyprexa (olanzapine) tablets for the maintenance of treatment response.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as noted in the attachment to this letter.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

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

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw 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.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Steven D. Hardeman, R.Ph., Regulatory Project Manager, at (301) 594-5525

Sincerely,

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

Attachment (labeling)

Attachment

LABELING

We have made revisions to the 3 sections of labeling for which you have proposed language. Our proposed revisions for these 3 sections are as follows:

Under Clinical Efficacy Data, Schizophrenia

[This should be inserted as the last paragraph in this subsection. We do not feel the Kaplan-Meier curve provides any added value. We have indicated that patients were observed for up to 8 months, based on the longest observed olanzapine patient.]

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

Under INDICATIONS AND USAGE, Schizophrenia

[The second paragraph in this subsection should be as follows.]

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

Under DOSAGE AND ADMINISTRATION, Schizophrenia

[This should be the final paragraph under this subsection.]

Maintenance Treatment — there is no body of evidence available

In addition, we ask that you incorporate the following changes to labeling that were requested in our letter of September 25, 2000.

SECTION OF LABELING	LOCATION WITHIN SECTION	CURRENT TEXT	REVISED TEXT
DESCRIPTION	Paragraph 1, Sentence 1	psychotropic	
CLINICAL PHARMACOLOGY, Clinical Efficacy Data-Schizophrenia	Paragraph 1, Sentence 1	management of the manifestations of psychotic disorders	treatment of schizophrenia
CLINICAL PHARMACOLOGY, Clinical Efficacy Data-Schizophrenia	Paragraph 2, Sentence 1	in psychosis	in schizophrenia
INDICATIONS AND USAGE, Schizophrenia	Paragraph 1	management of the manifestations of psychotic disorders	treatment of schizophrenia
DOSAGE AND ADMINISTRATION, Schizophrenia-Usual Dose	Paragraph 2, Sentence 1	Antipsychotic efficacy	Efficacy in schizophrenia
DOSAGE AND ADMINISTRATION, Schizophrenia-Maintenance Treatment	Sentence 1	antipsychotic drugs	

cc:

Archival NDA 20-592

HFD-120/Div. Files

HFD-120/Hardeman

HFD-120/Katz/Laughren/Andreason

HFD-710/Jin/Siddiqui

HFD-002/ORM

HFD-101/ADRA

HFD-42/DDMAC

DISTRICT OFFICE

SI
SI
SI 9/19/2000

final: sdh/September 19, 2000

filename: desktop\zyprexa s-011\Zyprexa S-011 Approvable Letter & Labeling

APPROVABLE (AE)

23 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

Patent Statements (Item 13/Item 14)

ITEM 13: PATENT INFORMATION

Supplemental NDA 20-592

ZYPREXA®

(Olanzapine)

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of olanzapine, as indicated. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act and is the subject of the above-captioned NDA:

Patent Number	Patent Expiry Date	Type of Patent (Drug Substance, Drug Product, or Method of Use)
5,229,382	April 23, 2011	Compound, method of use, formulation
5,605,897	February 25, 2014	Method of use
5,736,541	March 24, 2015	Compound, method of use, formulation
5,919,485	March 24, 2015	Formulation, method of use
5,627,178	April 23, 2011	Method of use
5,817,655	April 23, 2011	Method of use
5,817,656	April 23, 2011	Method of use
5,817,657	April 23, 2011	Method of use

U. S. Patent No. 5,229,382 claims a "method of treating an animal, including a human, suffering from or susceptible to psychosis, acute mania or mild anxiety states...." employing olanzapine as per the indication which is the subject matter of this supplemental NDA.

U. S. Patent No. 5,605,897 claims a method of treating a patient suffering from or susceptible to any of a number of listed conditions, including psychoses, employing olanzapine as per the indication which is the subject matter of this supplemental NDA.

U.S Patent No. 5,736,541 claims an olanzapine polymorph useful for treating any number of listed conditions, including psychoses, employing olanzapine as per the indication which is the subject matter of this supplemental NDA.

U.S. Patent No. 5,919,485 claims a solid oral formulation including tablets and granules of olanzapine useful for treating any number of listed conditions, including psychoses, employing olanzapine as per the indication which is the subject matter of this supplemental NDA.

U.S. Patent No. 5,627,178 claims a method of treating a patient suffering from or susceptible to any of a number of listed conditions, including psychosis, employing olanzapine as per the indication which is the subject matter of this supplemental NDA.

U. S Patent No. 5,817,655 claims a method of treating a patient suffering from or susceptible to any of a number of listed conditions, including psychosis, employing olanzapine as per the indication which is the subject matter of this supplemental NDA.

U.S. Patent 5,817,656 claims a method of treating a patient suffering from any of a number of pathological psychological conditions including mental disorders employing olanzapine as per the indication which is the subject matter of this supplemental NDA.

U.S. Patent 5,817,657 claims a method of treating a patient suffering from any of a number of pathological psychological conditions that relate to the use of psychoactive substances employing olanzapine as per the indication which is the subject matter of this supplemental NDA.

The above patents are either all owned by Eli Lilly and Company, Indianapolis, Indiana and/or its wholly owned subsidiary Lilly Industries, Limited.



Name of authorized official
Director, US Regulatory Affairs

Dec. 7, 1999

Date

ITEM 14: PATENT CERTIFICATION**Supplemental NDA 20-592****ZYPREXA®****(Olanzapine)**

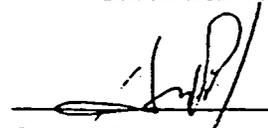
Eli Lilly and Company (Lilly) claims a three year period of exclusivity for the use of Olanzapine in the treatment of Relapse Prevention/Maintenance, as provided by 21 C.F.R. 314.108(b)(5).

Clinical trials conducted which are essential to approval of this supplemental NDA are identified as follows:

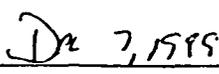
FID-MC-HGGI

As required by 21 C.F.R. 314.50(j)(4), Lilly certifies that to the best of Lilly's knowledge:

1. each of the above clinical investigations included in this supplemental application meets the definition of "new clinical investigation" as set forth in 21 C.F.R. 314.108(a);
2. the above clinical investigations are "essential to approval" of this supplemental application. Lilly, through its employees and others, electronically searched the Scientific literature as of September 16, 1999 via Medline, Derwent Drug File, SciSearch, Embase, PsycINFO, and Biosis and has not discovered any published studies or publicly available reports for which Lilly is seeking approval. In Lilly's opinion and to the best of Lilly's knowledge, there are no published studies or publicly available reports to provide a sufficient basis for the approval of the conditions for which Lilly is seeking approval without reference to the new clinical investigations in this application.
3. the above clinical investigations were each conducted or sponsored by Lilly. Lilly was the sponsor named in the Form FDA-1571 of IND numbers 28,705 under which the new clinical investigation(s) that is essential to the approval of this application was conducted.



Name of authorized official
Director, US Regulatory Affairs



Date

To HoloUAC, Crescenzi
via e-mail
Stlander
11/9/00

EXCLUSIVITY SUMMARY for NDA # 20-592 SUPPL # SE1-011

Trade Name Zyrex Generic Name Olanzapine

Applicant Name Lilly HFD- 120

Approval Date 11/9/00

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/ / NO X /

b) Is it an effectiveness supplement? YES X / NO /

If yes, what type (SE1, SE2, etc.)? SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES X / NO /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

three

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-592 _____

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____
NDA # _____
NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: 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 ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / 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-MK-HGGI

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

Investigation #3 YES / / NO / /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /__ / NO / X /
Investigation #2 YES /__ / NO /__ /
Investigation #3 YES /__ / NO /__ /

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1, Study # FID-MC-HGGI
Investigation # __, Study # _____
Investigation # __, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 28,705 YES / / NO / / Explain: _____

Investigation #2

IND # _____ YES / / NO / / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / / Explain _____ NO / / Explain _____

Investigation #2

YES / / Explain _____ NO / / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are

there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO / X /

If yes, explain: _____

 / SI
Signature of Preparer
Title: Regulatory Project Manager

 / 9/22/00
Date

 / SI
Signature of Office of Division Director

 / 10/12/00
Date

cc:
Archival NDA
HFD-104 / Division File
HFD-104 / RPM / Hardeman
HFD-093 / Mary Ann Holovac
HFD-104 / PEDS / T. Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

/s/

Steve Hardeman
11/9/00 01:07:50 PM

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: 020592 Trade Name: ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
 Supplement Number: 011 Generic Name: OLANZAPINE
 Supplement Type: SE1 Dosage Form:
 Regulatory Action: OP COMIS Indication: MANAGEMENT OF THE MANIFESTATIONS OF PSYCHOTIC DISORDERS
 Action Date: 12/17/99

Indication # 1 Oral Zyprexa has been demonstrated to prevent relapse and maintain response during extended use (up to 6 months).

Label Adequacy: Does Not Apply

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): 9/28/00 Indication language changed to: The effectiveness of oral Zyprexa at maintaining a treatment response in schizophrenic patients who had been stable on Zyprexa for approximately 8 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo controlled trial.

Lower Range
Adult

Upper Range
Adult

Status	Date
Completed	
Deferred	11/9/00

This page was last edited on 9/28/00 ^

Signature -

(S)

9-28-00
Date

/S/

Steve Hardeman
11/9/00 01:47:30 PM

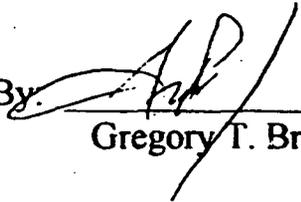
CERTIFICATION

NDA Application No.: 20-592

Drug Name: Zyprexa®

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory T. Brophy, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: 

Gregory T. Brophy, Ph.D.

Title: Director, U.S. Regulatory Affairs

Date: December 15, 1998

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: September 11, 2000

TO: Steve Hardeman, R. Ph., Regulatory Project Manager
Paul Andreason, M.D., Clinical Reviewer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Constance Lewin, M.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-592/SE1-011

APPLICANT: Eli Lilly and Company

DRUG: Zyprexa (olanzapine)

CHEMICAL CLASSIFICATION: 6

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Relapse prevention in the treatment of schizophrenia

CONSULTATION REQUEST DATES: March 6 and June 22, 2000

ACTION GOAL DATE: October 17, 2000

I. BACKGROUND:

Routine clinical inspections were conducted in support of the above-noted application and focused on protocol FID-MC-HGGI(b). Two domestic and two foreign sites were audited, with the foreign sites chosen based upon the relatively large number of subjects each of these sites had enrolled. Goals of these inspections included validation of the primary efficacy endpoint data (select items from the Brief Psychiatric Rating Scale) and safety parameters (adverse event reporting, laboratory test results, and extrapyramidal-symptom rating scales) at the sites, along with an analysis of the adequacy of informed consent.

II. RESULTS (by protocol/site):

NAME	CITY	STATE or COUNTRY	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Ishaque	Chula Vista	California	April 4, 2000	May 30, 2000	VAI
Remer &					
Pfister	Bismarck	North Dakota	April 4, 2000	July 24, 2000	VAI
Jakovljevic	Zagreb	Croatia	June 27, 2000	Pending	VAI
Folnegovic-Smalc	Zagreb	Croatia	June 27, 2000	Pending	VAI

Protocol F1D-MC-HGGI(b)

1. Site #1 (Saleem Ishaque, M.D. – Chula Vista, California):

Nine (9) subjects were screened at this site, seven (7) of whom enrolled into the study. Two (2) subjects were randomized into the double-blind period of the study. Records for all subjects were reviewed. Although a Form FDA 483 was not issued, inspection revealed that several protocol-required laboratory tests were not conducted (Visit 2 labs for subjects 5601, 5602, and 5603; and termination labs for subject 5607). These omissions are not considered significant deviations.

Data acceptable

2. Site #2 (Elsa Remer, M.D., and Gregory Pfister, Pharm.D. – Bismarck, North Dakota):

Six (6) subjects were enrolled at this site, three (3) of whom were randomized into the double-blind period of the study. Two (2) subjects were discontinued from the study due to lack of efficacy, and two (2) subjects withdrew consent. Two subjects (5404 and 5406) were reported to have completed the protocol, although technically they did not because the study was terminated by the sponsor prior to the protocol's completion. In these two instances, at the sponsor's request the reason for discontinuation was reported as protocol completion.

Although Form FDA 483 was not issued, review of the establishment inspection report (EIR) revealed that subject 5402 had clinically significant abnormalities of total bilirubin, ALT/SGPT, AST/SGOT, urea nitrogen, uric acid, and creatinine kinase at the early-termination visit, but these abnormalities were neither recorded in the subject's case report form (CRF) as adverse events nor reported to the IRB. With the exception of the total bilirubin, all of the foregoing laboratory parameters for this subject were within normal limits at screening. The laboratory abnormalities in question are contained in the sponsor's laboratory data listings but were not recorded as adverse events.

Data acceptable

3. Site #3 (Miro Jakovljevic, M.D. – Zagreb, Croatia):

Fifty (50) subjects were screened at this site, forty-eight (48) of whom enrolled into the study. Twenty-eight (28) subjects were randomized into the double-blind period of the study. Twenty (20) subjects discontinued the study, for varied reasons. Because the sponsor terminated the study following an interim analysis, no subjects completed Study Period IV (the double-blind period).

Records for thirty-two (32) subjects were reviewed, including the records of all randomized subjects. Inspection revealed violations of federal regulations pertaining to adverse event reporting and informed consent. A Form FDA 483 was issued for the following observations: (a) A serious adverse event (SAE) report was not submitted to the

sponsor or IRB for the two-day hospitalization of subject 1027. This subject was hospitalized for work-up of pre-existing amenorrhea; (b) An adverse event (AE) report was not submitted to the sponsor or IRB for a clinically significant creatinine kinase elevation (25,300 U/L) noted for subject 1045 at Visit 2. Of note, the baseline and follow-up results were within normal limits; and (c) The informed consent used at this site was deficient in that it did not contain a statement of whom to contact in the event of a research-related injury to the subject.

The foregoing represents a preliminary summary of the inspectional findings at this site. The EIR has not yet been received. Should additional items of significance be noted upon review of the EIR, you will be notified promptly.

Data acceptable

4. Site #4 (Vera Folnegovic-Smalc, M.D., Sc.D. – Zagreb, Croatia):

Fifty (50) subjects were screened at this site, forty-eight (48) of whom enrolled into the study. Forty-four (44) subjects were randomized into the double-blind period. Seventeen (17) subjects discontinued from the study, for various reasons. Because the sponsor terminated the study following an interim analysis, no subjects completed Study Period IV (the double-blind period).

Records for 25 subjects were reviewed. Inspection revealed several violations of federal regulations pertaining to recordkeeping and informed consent. A Form FDA 483 was issued for the following observations: (a) Inadequate documentation to support several delayed entries on PANSS ratings for subject 1220 at study visits 1, 8, 12, and 14; (b) Lack of documentation for protocol-required physical and/or psychiatric examinations at visit 1 for subjects 1201, 1203, 1205, 1208, and 1214; and (c) Deficient informed consent that did not contain a statement of whom to contact in the event of a research-related injury to the subject.

The foregoing represents a preliminary summary of the inspectional findings at Dr. Folnegovic-Smalc's site. The EIR has not yet been received. Should additional items of significance be noted upon review of the EIR, you will be notified promptly.

5. Erroneous sponsor data listings pertaining to Sites #3 and #4 (Drs. Jakovljevic and Folnegovic-Smalc – Zagreb, Croatia):

At both of these sites, inspection revealed erroneous entries in the sponsor's concomitant-medication data listings, in that the drug timolol was reported as the generic equivalent of Normabel. Various study records showed, and the clinical investigators confirmed, that Normabel used at these sites was actually diazepam. The sponsor's representative explained that the discrepancies in the data listings are due to a deficiency in the WHO database, which currently does not indicate that the tradename Normabel is actually associated with both timolol and diazepam.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

None of the inspection findings appear to affect the reliability of the data submitted by Drs. Ishaque, Remer and Pfister, Jakovljevic and Folnegovic-Smalc in support of NDA 20-592/SE1-011. Accordingly, it is recommended that the data submitted by these clinical investigators may be used in support of the pending application.

As noted above, this clinical inspection summary contains preliminary assessments of the two inspections conducted in Zagreb, Croatia, since the EIRs have not yet been received. Should either of those reports contain any significant findings in addition to those outlined above, you will be so notified.

Key to Classification:

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviation(s) from regulations. Data acceptable

VAI-r = Deviation(s) from regulations, response requested. Data acceptable

OAI = Significant deviations from regulations. Data unreliable

(SI)
Constance Lewin, M.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

(SI)
Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

DISTRIBUTION:

NDA 20-592

Division File

HFD-45/Program Management Staff (electronic copy)

HFD-47/Hajarian/Lewin

HFD-47/GCP II Branch Chief

HFD-47/Kline for GCPB File #####

HFD-47/Reading File

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

DATE: September 18, 2000

FROM: Thomas P. Laughren, M.D. 151
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for Zyprexa (olanzapine)
for the longer-term treatment of schizophrenia

TO: File NDA 20-592/S-011
[Note: This overview should be filed with the 12-15-99
original submission of this supplement.]

1.0 BACKGROUND

Zyprexa (olanzapine) is a 5HT₂/D₂ antagonist that was approved for the "management of the manifestations of psychotic disorders" on 9-30-96. Zyprexa was approved for the treatment of acute manic episodes on 3-17-00. Supplement 011 includes data in support of a claim for Zyprexa "to prevent relapse and maintain response during extended use (up to 6 months)," in patients with schizophrenia. The proposed dose range for this new indication is 10 to 20 mg/day.

We did not meet with the sponsor to discuss the development program for this claim, nor did we have a pre-supplement meeting. The study supporting this supplement was conducted under IND 28,705. I did speak with Dr. Beasley of Lilly on 1-14-98 regarding the plan to have a data monitoring board and formal stopping rule for this study. The protocol was submitted 2-20-98. I again spoke with Dr. Beasley on 4-14-99, and he informed me that the triangular test that was being used to monitor relapse rates triggered the need for an interim analysis. This analysis was done and revealed a significantly shorter time to relapse and higher relapse rate in placebo patients compared to olanzapine patients in the trial. He, therefore, requested FDA endorsement of the termination of the trial. There was a delay of several weeks while this issue was being discussed within the Division of Biometrics, but Dr. Jin subsequently indicated to me (see 5-13-99 memo) that the study could be terminated. We notified Lilly (see 5-19-99 letter) and the study was terminated.

Since the proposal is to use the currently approved Zyprexa formulations for this expanded claim, there was no need for chemistry, pharmacology, or biopharmaceutics reviews of this supplement. ~~The primary review of the clinical efficacy and safety data was done by Paul Andreason, M.D. from the clinical group. Ohidul Siddiqui, Ph.D., from the Division of Biometrics, reviewed the efficacy data for study HGGI, the single long-term trial for which results were submitted in support of this supplement.~~

The original supplement for this expanded indication (S-011) was submitted 12-15-99. There was no safety update.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

As Zyprexa is a marketed product, there were no chemistry issues requiring review for this supplement.

3.0 PHARMACOLOGY

As Zyprexa is a marketed product, there were no pharmacology/toxicology issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

As Zyprexa is a marketed product, there were no biopharmaceutics issues requiring review for this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Summary of Study HGGI

HGGI was a randomized, double-blind, parallel group, multicenter study of the relapse prevention design. There were 19 sites, including only 2 US centers that contributed only a total of n=5 patients. The remaining sites were entirely in Eastern European countries. The study enrolled adult outpatients meeting DSM-IV criteria for either schizophrenia or schizoaffective disorder. Patients who were already stable on olanzapine were entered directly into an 8-week further stabilization phase, and patients not on olanzapine were switched to olanzapine before the 8-week phase. Prior

to randomization, all patients had to be stable on a dose of olanzapine between 10 and 20 mg/day. Patients were then randomized (2:1, olanzapine:placebo) to either continuation on their fixed olanzapine dose or they were switched to placebo, for a 12-month followup period. Assessment instruments included the BPRS and others, however, the primary outcome was time to relapse defined in terms of changes in the BPRS, as follows: (1) increase of any item to > 4 and an increase of that item more than 2 units since randomization; (2) increase of any item to > 4 and an increase of the positive subscale more than 4 units since randomization; or (3) hospitalization for positive psychotic symptoms. Proportion of relapses was one of several secondary outcomes. The primary efficacy analysis was based on the log-rank test of Kaplan-Meier survival curves.

As noted, there was a protocol specified interim analysis plan with a stopping rule in the event of an early strongly positive result. This plan utilized application of the triangular test, and is described in detail in the statistical review. We had reached prior agreement with the sponsor on the acceptability of this plan. Criteria for stopping the study were met, and the study was stopped with 326 randomized patients. At that point, the longest exposed olanzapine patient was 243 days and the longest placebo patient was 188 days. Thus, one way to characterize this trial in terms of length is on the basis of the longest surviving patient, i.e., 243 days or approximately 8 months. It is not reasonable to characterize it as a 12 month trial; the sponsor in their proposed labeling characterized the trial as a 6-month trial, apparently on the basis of the longest surviving patient placebo patient.

Of 583 patients originally screened, 326 completed the stabilization phase and were randomized (n=224 on olanzapine and n=102 on placebo). Patients were roughly half male, all Caucasian, and the mean age was 36 years. 82% of patients met diagnostic criteria for schizophrenia, and the remaining patients met criteria for schizoaffective disorder. Completers (i.e., patients who had not dropped out at the time of study termination) included 47/102 (46%) of placebo patients and 194/224 (87%) of olanzapine patients. Time to relapse was significantly longer for olanzapine treated patients than for placebo treated patients (for log rank test, $p < 0.001$). The Cox proportional hazards analysis revealed a 10-fold greater chance of relapse among placebo patients compared to olanzapine patients. Relapse proportions were 28/102 (27%) in the placebo group and 9/224 (4%) in the olanzapine group. The results were generally consistent across the centers. Thus, even though we have little experience with studies in Eastern Europe, some reassurance can be drawn from the consistency of the findings across centers. Results were also consistent for males vs females and for those < 35 vs those ≥ 35 .

5.1.2 Conclusions Regarding Efficacy Data

Both Drs. Andreason and Siddiqui concluded that study HGGI provides evidence of longer-term maintenance of efficacy in patients who had remained in a stable clinical state during at least 8 weeks of open label treatment with olanzapine, and I agree. Both Drs. Andreason and I agree that this benefit should be characterized as maintenance of efficacy rather than as prevention of relapse, as proposed by the sponsor. First of all, olanzapine did not prevent relapse; rather, it delayed relapse. Second, relapse is an arbitrarily defined event for which there is no general consensus regarding how to define it. What one can conclude from a study of this design is that olanzapine maintenance

treatment provided greater protection from worsening than provided by placebo in stable schizophrenic patients. It's difficult to know how best to characterize the trial in terms of length of protection. The issue the clinician wants addressed is how long to maintain a patient on treatment following improvement during acute treatment. This study does not answer that question. However, it seems to me, it does provide a basis for judging that patients achieving relatively brief periods of stability (roughly 8 weeks) might reasonably be continued for at least another 8 months (the approximate actual duration of the maintenance phase). I have proposed labeling language to characterize this benefit.

5.2 Safety Data

Dr. Andreason has reviewed the relatively small amount of additional safety data for olanzapine in study HGGI in detail. Essentially there were no surprises and no new findings that would change our impressions about the short-term or long-term safety of this drug, and no need to make any changes to labeling based on these additional data. The sponsor has also not proposed any additional labeling language based on any of the safety findings.

5.3 Clinical Sections of Labeling

As noted, we have modified the sponsor's proposed additions to label regarding these new efficacy findings, i.e., changes under Clinical Pharmacology (Clinical Efficacy Data), Indications and Usage, and Dosage and Administration. In addition, I have added to the letter changes that we have requested as part of an antipsychotic relabeling project to focus the claim for these drugs on schizophrenia rather than the currently nonspecific target of _____

_____ I expect this separate letter to have issued to Lilly and most other manufacturers of antipsychotic products at the time an action letter issues for this supplement.

6.0 WORLD LITERATURE

There was no literature to review as part of this supplement.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Zyprexa is not approved for the longer-term treatment of schizophrenia anywhere at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this supplement to the PDAC.

9.0 DSI INSPECTIONS

As noted, study HGGI was overwhelmingly a foreign study, with essentially all patients coming from various Eastern European countries. In fact, about 1/3 of the patients in this study came from 3 sites in Croatia. The 2 US sites (involving only 5 total patients) were inspected, and found to be acceptable. In addition, 2 of the Croatian sites were inspected, and also found to be acceptable.

10.0 APPROVABLE LETTER

An approvable letter acknowledging our decision to proceed with an approval action pending agreement on labeling has been included with the approvable package.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has now submitted sufficient data to support the conclusion that olanzapine is effective in the longer-term treatment of schizophrenia. I recommend that we issue the attached approvable letter with our proposed labeling for this product.

cc:

Orig NDA 20-592/S-011

HFD-120/Division File

HFD-120/TLaughren/RKatz/PAndreason/SHardeman

DOC: MEMZYPLT.AE1

**Review and Evaluation of Clinical Data
NDA #20-592**

Sponsor: Lilly Research Laboratories
Drug: Olanzapine
Material Submitted: SE1-011 Response to Approvable letter

Correspondence Date: October 18, 2000

This review details the sponsor's response to the Agency's approvable action on supplement SE1-011 and provides clinical recommendations to the Team Leader and Division Director supporting a potential approval action for the sponsor's most recent draft labeling proposal.

The sponsor agrees with the Divisions proposed draft labeling with one exception. The sponsor wishes to retain the current word "psychotropic" in favor of the Division's proposed _____ in the DESCRIPTION section.

Conclusions and Recommendations

This retention is appropriate. I recommend an approval action on this supplement based on this version of draft labeling.

Paul J. Andreason, M.D.

cc: IND# 28,705
HFD-120
HFD-120/ P Andreason
S Hardeman
T Laughren

/s/

Paul Andreason
11/6/00 02:44:28 PM
MEDICAL OFFICER

Thomas Laughren
11/7/00 08:00:50 AM
MEDICAL OFFICER

I concur with the recommendation that we can now proceed with an approval action.--TPL

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 20-592
Sponsor: Lilly Research Laboratories

Drug: Zyprexa® (olanzapine)
Indication: Treatment of psychosis
Dates of Submission: December 15, 1999
Materials Reviewed: SNDA SE1-011

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1.0 Material Utilized in Review

1.1 Materials from NDA/IND

The following items were examined during the course of this clinical review:

Table 1.1.1 Documents Utilized in Clinical Review	
DATE	DESCRIPTION
SE1-011	NDA efficacy supplement 20-592-SE1-011

1.2 Related Reviews

Original NDA review 20-592.

2.0 Background

2.1 Indication

Olanzapine is indicated for the treatment of psychosis in schizophrenia and the treatment of acute mania in bipolar disorder.

2.2 Related INDs and NDAs

IND-27, 805 is the commercial IND for olanzapine.

2.3 Administrative History

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

The sponsor submitted a NDA supplement proposing that olanzapine was effective in the treatment of manic symptoms for patients with bipolar type I mania on Dec 3, 1997. A "not approvable" action was sent to the sponsor for this NDA on Oct 2, 1998. This supplement was amended and approved March 17, 2000.

2.4 Directions for Use

The recommended starting dose for olanzapine in the treatment of psychotic symptoms associated with schizophrenia is 10-mg/day in a single dose for patients aged 18-65. Patients aged >65 should be started at 5-mg. The maximum recommended dose of olanzapine is 20-mg/day. The starting dose for the treatment of mania associated with bipolar disorder is 10-15-mg/day with the same maximum dosage and dosage adjustment for age.

3.0 Chemistry

There are no chemistry issues to review in this submission.

4.0 Animal Pharmacology

There are no animal pharmacology/toxicology issues to review in this submission.

5.0 Description of Clinical Data Source

Protocol No	Study Design	Study Drug Dose, Route, Duration	N
F1D-MC-HGGI	R, DB, PC, Parallel group, design measuring time to relapse after randomization to drug and placebo	Olanzapine 10, 15, or 20-mg/day, oral, 12-month (2 groups drug and placebo)	360 240 Olz 120 PBO

5.1 Adequacy of Clinical Experience

The protocol studied the appropriate patient population and the sample size was large enough to adequately power, without overpowering, the study.

5.2 Data Quality and Completeness

The data was complete and consistent throughout the submission.

6.0 Human Pharmacokinetics

There are no human pharmacokinetic issues to review with this submission.

7.0 Review of studies for which efficacy claims are made

There is one study in this submission. Study F1D-MC-HGGI "Olanzapine relapse prevention versus placebo in the treatment of schizophrenia."

7.1.1 Investigators and Sites

The investigators and sites involved in this study may be found in table 7.1.1 in the appendix. There were 20 investigators at 19 sites. There were only two US sites. These US sites contributed only five patients to the study (olanzapine n=3; placebo n=2).

7.1.2 Objectives

The primary objective of this study was to assess the efficacy of olanzapine compared to placebo in the prevention of relapse of positive psychotic symptoms as assessed by a worsening in specific items of the BPRS or hospitalization for positive psychotic symptoms.

7.1.3 Study Population

Patients aged 18-65 years with a diagnosis of schizophrenia or schizoaffective disorder as defined by the DSM-IV were included in the study. Patients had to be stable while taking olanzapine 5-20-mg/day. Stable was defined as a GAF score of 40 or greater; total BPRS (1 to 7-scale) less than 37; BPRS items (1 to 7-scale) conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content of less than equal to 4.

7.1.4 Design

This was a randomized, double blind, parallel study of outpatients meeting diagnostic criteria for schizophrenia and schizoaffective disorder according to the DSM-IV. This was a four period study:

1. Screening –patients were seen and evaluated. If patients met inclusion criteria and were taking olanzapine they moved directly to phase 3. If patients were taking a medication besides olanzapine they proceeded to phase 2.

2. Conversion to olanzapine –patients were switched to olanzapine from their previous antipsychotic medication over a six-week period. This could be accomplished via a 2-week period where patients were simultaneously treated with olanzapine and other antipsychotic drugs. To proceed to the next period, patients had to be on a fixed dose of olanzapine 10-20-mg/day.
3. Stabilization- This was an 8-week period where patients were maintained on the olanzapine dose that was fixed in period II. If patients met interim criteria and remained stable on the olanzapine dose fixed in period II, then they were randomized to either continue on olanzapine at their fixed dose, or placebo. After randomization, patients entered phase IV.
4. Double blind maintenance – This was a 12-month double blind and placebo controlled treatment phase. Patients completed the study by either remaining stable for 12 months, or relapsing.

7.1.5 Assessments

Efficacy variables included the PANSS, BPRS (extracted from the PANSS-items 2-9 and 15-24), the Drug Attitude Inventory, and Heinrichs-Carpenter Quality of Life Scale. The BPRS used in this study was measured on a range of 1-7. Safety assessments included physical and psychiatric exams, vital signs, screening ECG, clinical chemistry, hematology, hepatitis screen, thyroid panel, prolactin, pregnancy testing, and abnormal movement scales (Barnes Akathisia Scale, AIMS, and Simpson Angus Scale).

7.1.6 Analysis Plan

Primary Efficacy Variable

The primary efficacy variable was designated as the Kaplan-Meier analysis of time to relapse after randomization. Relapse was defined as either:

1. An increase on any BPRS positive item to >4 and an absolute increase of ≥ 2 on that item since randomization, or
2. An increase of any BPRS positive item to >4 and an absolute increase of ≥ 4 on the BPRS positive subscale since randomization, or
3. Hospitalization for positive psychotic symptoms. The sponsor included a medically threatening suicide, or a completed suicide as criteria for relapse, but as “secondary criteria”.

Secondary Efficacy Variables

The secondary efficacy variables included proportion of relapses, proportion of relapses meeting secondary relapse criteria, and mean change from baseline of PANSS total, positive, negative, and general psychopathology scores.

Interim Analysis

The protocol called for an interim analysis. The sponsor, to limit the number of potential relapses in the event of a strongly positive study result, performed this analysis. Relapse rates were monitored sequentially throughout the trial using the “triangular test”. Indicators to trigger a possible interim analysis were based on the upper and lower bounds of the triangular test. The triangular test was devised with a Type I error of 0.05

(two-sided) and a power of 83% to detect a 20% difference between relapse rates for placebo (60%) and olanzapine (40%) with a maximum number of 240 patients in the olanzapine group and 120 in the placebo group. This method was discussed in meetings between the sponsor and the Biometrics Division prior to the execution of the protocol.

7.1.7 Patient Disposition

The study investigators screened 583 patients. 543 of these patients received open-label olanzapine. 493 of the 543 were taking antipsychotics other than olanzapine and needed to be converted to open label olanzapine; 50 patients were taking olanzapine and proceeded to the "stabilization phase of the protocol. 408 of the 493 patients needing conversion proceeded to the stabilization phase (this produced 458 patients entering the stabilization phase). 326 patients finished the stabilization phase and entered double blind therapy.

Study HGGI was terminated early by design. The protocol provided for an interim analysis that, if positive, would terminate the protocol to reduce the total number of potential patient relapses. 90 (20%) of the patients entering stabilization did not go on to be randomized to the double blind portion of the protocol because of this early termination.

The disposition of these 326 patients is listed in table 7.1.7.1 below.

Reason	Placebo n= 102(%)	Olanzapine n= 264(%)	p-value Fishers exact
Protocol complete	47 (46)	194 (87)	<0.001
Adverse Events	12 (12)	2 (1)	<0.001
Lack of efficacy	31 (30)	12 (5)	<0.001
Lost to follow-up	1 (1)	0	.31
Patient decision	3 (3)	6 (3)	1.00
Criteria not met	8 (8)	10 (4)	.29

7.1.8 Baseline Demographics/Severity of Illness

There were no differences in age, sex age at onset of illness, or severity of illness in the treatment groups at the beginning of the double blind phase. There was a difference in the number of patients with schizoaffective disorder between treatment groups. There was a disproportionately higher number of patients with schizoaffective disorder in the olanzapine treatment group. 82% of the patients in the study were diagnosed as schizophrenic and 18% were diagnosed as schizoaffective. 34/224 (15%) of the patients in the olanzapine treatment group were diagnosed as schizoaffective bipolar as opposed to 7/102 (7%) of the placebo group. Though this is a statistically significant difference, the actual number of patients that this represents does not appear to be able to effect the outcome of the study even if a systematic diagnostically related treatment response existed.

7.1.9 Concomitant Medications

There were no significant differences in the amount or kind of concomitant medications taken by patients during the double blind treatment phase. Diazepam was the most used

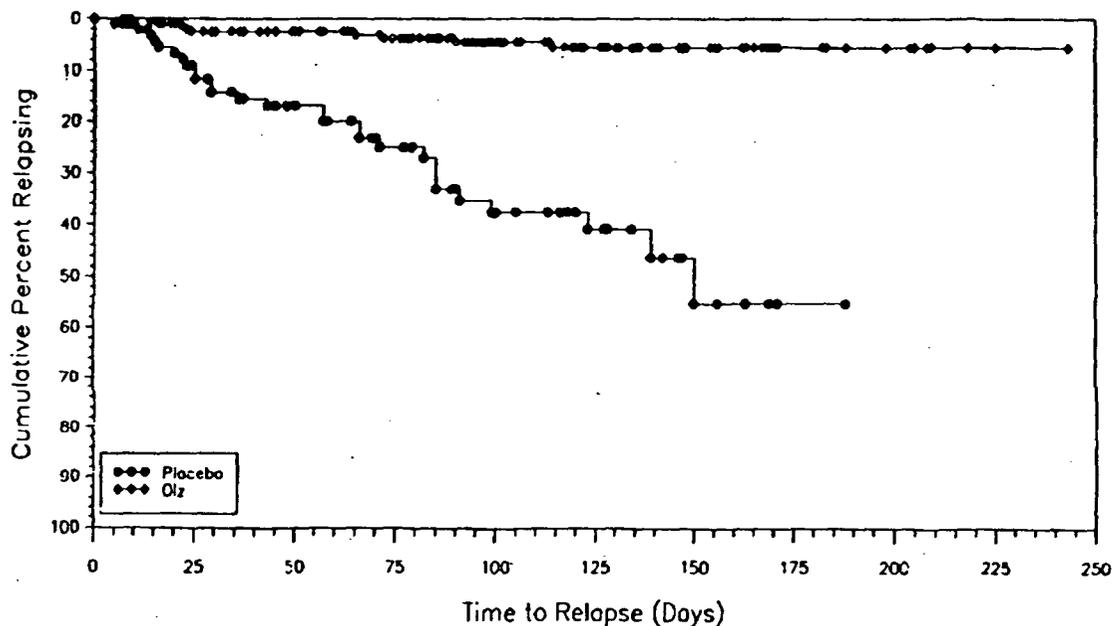
concomitant medication used by 16% of patients. 21% of placebo patients and 13% of olanzapine patients used diazepam ($p=0.103$).

7.1.10 Efficacy Results

Half (50.2%) of the patients who entered the stabilization phase took 10-mg/day. Only one of olanzapine treated patients took 5-mg (0.4%). The other 49% took 15 or 20-mg/day.

The differences between treatment groups with respect to time-to-relapse using Kaplan-Meier product limit analyses are illustrated in figure 7.1.10.1 below.

Figure 7.1.10.1 Time to Relapse Study HGGI Double Blind Treatment Phase



Time to relapse was significantly longer for olanzapine treated patients as a group than compared with placebo treated patients (log rank $p<0.001$). The study was terminated at the time of the interim analysis. At termination the longest olanzapine treated patient had been in the study 243 days as opposed to the longest placebo patient at 188 days. Patients in the placebo group were 9.9 times more likely to relapse than olanzapine treated patients by the Cox proportional hazards model.

Relapse incidence was also greater in the placebo group than in the olanzapine group. 28/102 patient in the placebo group relapsed as opposed to 9/224 of the olanzapine treated patients ($p<0.001$ Cochran-Mantel-Haenszel).

Relapse incidence was generally consistent among olanzapine treated patients when examined by country but varied in the placebo group. This variability was most likely due to smaller sample sizes. For example, there were only 5 patients recruited to sites in the USA. Two patients were randomized to the placebo group and one relapsed (50%). The other three were randomized to olanzapine but none relapsed.

Time to relapse was significantly different in Croatia ($p < 0.001$), Yugoslavia ($p = 0.04$), and the Russian Federation ($p = 0.04$). Table 7.1.10.2 enumerates the numbers of patients in each country who relapsed by group along with significance testing by Fisher's Exact Test.

Country	Therapy	N	N	%	p-Value
Croatia	Placebo	50	18	36	<0.001*
	Olanzapine	105	4	4	
Poland	Placebo	1	0		
	Olanzapine	10	0		
Romania	Placebo	16	3	19	0.16
	Olanzapine	37	2	5	
Russian Federation	Placebo	22	4	18	0.2
	Olanzapine	48	3	6	
United States	Placebo	2	1	50	0.4
	Olanzapine	3	0		
Yugoslavia	Placebo	11	2	18	0.11
	Olanzapine	21	0		

* Fisher's Exact Test

The data is thus relatively consistent across countries by visual inspection.

7.1.11 Conclusions

This study supports a claim of extended efficacy for patients with schizophrenia and schizoaffective disorder who have responded to olanzapine. Patients were maintained for the duration of the study on the dose that they took in the acute open-label treatment phase. Thus this study could not address continued efficacy after lowering the dose of olanzapine after acute treatment.

8.0 Safety

This safety review focuses on the double blind placebo controlled treatment period. Well-controlled acute treatment safety data was generated by the short-term treatment protocols submitted under the original NDA. Long-term uncontrolled data is available in numbers much greater than those provided by this study. Though study HGGI has a design that could examine some long-term safety aspects of olanzapine use, it is too small to provide information about events that might occur less than 3% of the time.

There were no serious unexpected adverse events in the open-label conversion or stabilization phases of this protocol.

8.1.1 Deaths in Study

There were no deaths during the double blind placebo controlled period.

8.1.2 Serious Adverse Events

During double blind treatment 6-olanzapine treated patients experienced 9-serious adverse events. 15-placebo treated patients experienced 22 serious adverse events. Schizophrenic reaction was the most common serious adverse events (n=10 placebo; n=2 olanzapine).

Of the nine serious adverse events in the olanzapine treated patients, patient 600-6006 (vomiting, gastritis, and duodenal ulcer) experienced three; this was unlikely to be related to olanzapine treatment. Patient 140-1443 experienced an infection for which he was hospitalized (salmonella); this was not likely to be olanzapine related. Patient 720-7216 experienced synovitis from a past trauma and underwent surgery; this was not likely to be related to olanzapine treatment.

Other serious adverse events were related to the disease of schizophrenia (schizophrenic reaction=2, thinking abnormal=1, paranoid reaction=1).

There were no unexpected drug-related serious adverse events during the double blind treatment phase.

8.1.3 Dropouts due to Adverse Events

Two olanzapine-treated patients and 12 placebo treated patients dropped out during the double blind treatment phase due to adverse events. All of the placebo dropouts were due to events that were associated with the disease of schizophrenia; one was a suicide attempt.

One olanzapine patient dropped out due to euphoria and the other due to delusions.

Patient 700-7006 (olanzapine treatment group) dropped out due to euphoria on March 4, 1999. The patient was reported to have experienced blunted affect, anxiety, and difficulty with abstract thinking the next day. Euphoria was first reported on February 16, 1999 on day 154 of therapy. It is unlikely that this event was related to olanzapine treatment.

Patient 700-7012 (olanzapine treatment group) dropped out due to delusions. This was unlikely to be related to olanzapine treatment.

There was a statistically significant number of adverse dropouts between the groups. (Olanzapine =2; placebo =12; $p < 0.001$). This reflects a difference in efficacy rather than drug related adverse experiences. All of the adverse experiences that were reported as reasons for discontinuation were likely to be related to treatment efficacy as opposed to drug related events that were not related to the disease process.

8.1.4 Specific Search Strategies

None

8.1.5 Adverse Events

Weight gain was the only common drug related adverse event in the double blind treatment phase of the study (i.e. 5% or greater and at least twice placebo). Weight loss was reported by 7% of placebo patients as an adverse event after stopping olanzapine as opposed to 1% of olanzapine patients in the double blind phase. The paucity of common and drug related adverse events in the double blind treatment phase is probably due to patient selection. Patients only progressed to the double blind phase because they tolerated and responded to olanzapine and adverse events represented changes from the point of randomization.

8.1.6 Laboratory Findings

8.1.6.1 Analysis of Central Tendency

Olanzapine treated patients had significantly greater mean increases from baseline for uric acid and mean red cell volume. Placebo treated patients had significant increases in WBC, segmented neutrophils, BUN, and inorganic phosphorus when compared to olanzapine treated patients. Table 8.1.6.1.1 in the appendix enumerates these changes.

The increases in WBC and segmented neutrophils in the placebo group are consistent with past reports of the usually mild and reversible WBC suppression seen in olanzapine treated patients in the short-term olanzapine clinical development program. The changes in BUN and uric acid are without clinical significance.

8.1.6.2 Analysis of Outliers

Potentially clinically significant changes in laboratory analyte during the double blind treatment phase were rare. Increased CPK was observed in 4 placebo treated patients and no olanzapine treated patients and AST (SGOT) was elevated in 3 placebo patients and no olanzapine treated patients. Both of these laboratory changes were <0.05 by two-tailed Fisher's Exact Test. There was no clinical significance attached to these events.

8.1.7 Vital Signs

8.1.7.1 Analysis of Central Tendency

The only significant mean change in vital signs during the double blind treatment phase was a significant weight loss of 1.97-kg in the placebo group vs. 0.2-kg weight gain in the olanzapine treated group.

8.1.7.2 Analysis of Outliers

There were no discontinuations due to weight or vital signs during the double blind phase. Three PCS changes in vital signs were reported and all of these were in olanzapine treated patients. One patient had a PCS low standing systolic BP, one patient had a PCS high standing BP, and one patient had a PCS low standing pulse. There were no other PCS changes during this phase of treatment.

PCS high systolic BP was defined as ≥ 180 -mmHg and an increase of ≥ 20 -mmHg. PCS low standing BP was defined as ≤ 90 and a decrease of ≥ 20 -mmHg. PCS low standing pulse was defined as ≤ 50 -bpm and a decrease of ≥ 15 -bpm.

8.1.8 ECG Findings

There were no systematically performed ECGs during the double blind treatment phase.

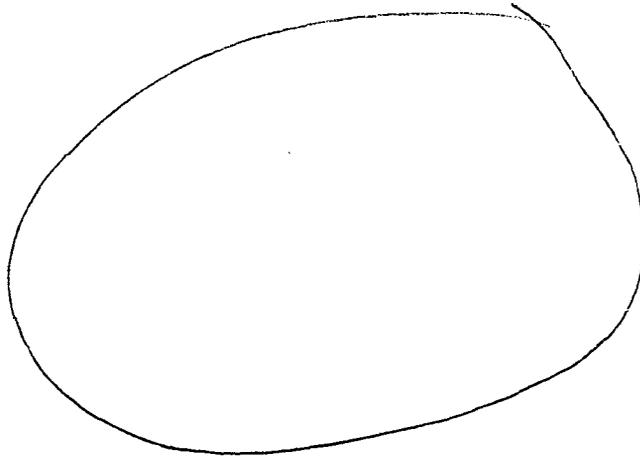
9.0 Labeling Review

The sponsor submits draft labeling that proposes a claim for relapse prevention. Though the primary efficacy measure was "time to relapse" the study tested olanzapine's long-term efficacy. Patients were acutely psychotic at the beginning of the study, treated with olanzapine, and those who responded were randomized after a period of that response to either olanzapine or placebo. "Preventing relapse" implies an initial state of health followed by treatment that is responsible for preventing future episodes of illness. The labeling changes should therefore reflect maintenance of treatment response but not relapse-prevention.

I suggest the following draft labeling:

Under *Clinical Efficacy Data*

The efficacy of olanzapine in the _____
schizophrenia was established in two short-term (6-week) _____



Under **INDICATIONS AND USAGE**

The effectiveness of oral ZYPREXA at maintaining treatment response _____) (see CLINICAL PHARMACOLOGY).

Under **DOSAGE AND ADMINISTRATION**

Maintenance Treatment—While there is no body of evidence available to answer the question of how long the patient treated with olanzapine should remain on it, the effectiveness of oral olanzapine, 10 mg/day to 20 mg/day in maintaining treatment response: _____ has been demonstrated in a _____
_____ see CLINICAL PHARMACOLOGY). Patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

10.0 Conclusions

Study HGGI supported the sponsor's additional claim for maintenance of treatment response but not for relapse prevention (see Section 9.0 Labeling Review).

11.0 Recommendations

Supplement SE1-011 is approvable with the above draft labeling modifications.

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Paul L. Andreason, M.D.
Medical Review Officer, DNDP

cc: NDA 20-592
HFD-120
HFD-120/ P Andreason
S Hardeman
R Katz
T Laughren

9-10-00

I agree that this supplement is approvable. See memo to file for more detailed comments.

151
TL, PDP

Appendix

Table 7.1.1 Investigators and Sites in Study	
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Mandic Nikola, MD, PhD Site #180 Klinicka Bolnica Osijek Psihijatrijska Klinicka Huttlerova 4 31000 Osijek Croatia	Elsa M. Remer, MD Site #540 St. Alexius Medical Center 900 East Broadway Bismarck, ND 59501
Saleem Ishaque, MD Site #560 Synergy Clinical research 450 Fourth Avenue, Suite 409 Chula Vista, CA 91910	Grozkancko Grbesa Site #600 Klinicki Centar Nis Zavod Za Mentalno, Zdravlje Brace Taskovica 48 18000 Nis, Yugoslavia
Miloje Preradovic Site #620 Vojnomedicinska Akademija Klinika za Psihijariju Crootravska 17 1100 Beograd, Yugoslavia	Margarita Morozova Site #700 Russian Mental Health Research Centre Kashirskoye Shosse, 34 115522, Moscow, Russia
Vladimir Totchilov Site #720 St. Petersburg State Medical Academy Department of Psychiatry Piskarevskiy prosp., 47 195067 St. Petersburg, Russia	Dan Prelipceanu Site #800 Spitalul Clinic de Psihiatrie "Prof. Dr. Alexandru Obregia" Soseaua Berceni nr. 10, Sector 4 75622 Bucuresti Romania

Table 7.1.1 Investigators and Sites in Study	
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Andrzej Michorzewski Site #910 Regional Hospital for Nervous & Psychiatric Diseases PL 09-500 Gostynin-Zalesie 1	Artur D. Koscianski Site #920 Szpital Neuropsychicznych 20-442 Lublin, ul. Abramowicka 2
Weodzimiedz Chrzanowski Site #930 Klinika Chorob Psychiczych Pl. Brodowicza 1 16-070 Choroszcz Poland	Taroseaw Tachkowski Site #940 Wojewodzki Osrodek Leznictwa Psychiatryczengo Uj Mickiewicza 24/26 87-100 Torun, Poland

Table 8.1.6.1.1 Mean changes in laboratory analytes during the double blind treatment phase in study HGGI						
Laboratory value	Olanzapine			Placebo		
	Baseline	Change	SD	Baseline	Change	SD
WBC	6.50	0.01	1.55	6.56	0.31	1.72
Neutrophil (seg)	3.82	0.10	1.33	3.88	0.38	1.54
BUN (mmol/L)	4.29	-0.20	1.19	4.32	0.14	2.22
Phosphorus(mmol/L)	1.17	-0.04	0.19	1.11	0.03	0.22
Uric acid (umol/L)	295	9	54	310	-1	80

Statistical Review and Evaluation

SJA 8/22/00

NDA# 20-592 Supplemental SEI-011

AUG 21 2000

Date of Submission: Jan 24, 2000
Due Date: Oct. 17, 2000

Sponsor: Eli Lilly and Company

Name of Drug: Zyprexa (Olanzapine)

Indication: Treatment of Schizophrenia

Documents Reviewed The findings from the statistical analyses

Introduction:

Results of one placebo-controlled, double-blind clinical study (Study F1-D-MC-HGGI) were submitted to demonstrate the efficacy of olanzapine, as compared to placebo in the prevention of relapse of positive psychotic symptoms as assessed by a worsening in specific items of the Brief Psychiatric Rating Scale (BPRS) or hospitalization for positive psychotic symptom psychopathology. The study was conducted in 19 centers. Among the 19 centers, 2 centers are located in U.S (North Dakota, California). The remaining centers are located in Croatia (5 centers), Romania (3 centers), Poland (3 centers), Yugoslavia (2 centers), Russia (2 centers), Gostynin-Zalesie 1 (1 center), and Ul. Abramowicka 2 (1 center).

The study was divided into four phases: a 4- to 9- day screening phase, a 6-week conversion phase where stable outpatients not taking olanzapine switched from their current antipsychotic therapy to olanzapine, an 8-week stabilization phase where patients were observed for continued stabilization at a fixed olanzapine dose, and a 12-month double-blind maintenance phase to compare olanzapine 10, 15, or 20 mg/day to placebo. Randomization was performed at a 2:1 ratio into 2 treatment groups: olanzapine (10, 15, or 20 mg/day) or placebo. Up to 360 patients were supposed to be randomized into the double-blind maintenance phase. The study was stopped early (approximately after 8 months) based on a planned interim analysis with 326 patients (224 in olanzapine, and 102 in placebo) in the double-blind maintenance phase.

Figures 1 and 2 list the study design and patient disposition of the study. The study participants were outpatients of age 18 to 65 years who met diagnostic criteria for schizophrenia or schizoaffective disorder as defined by DSM-IV. Stabilization must have been present at visit 1. Stabilization was defined as outpatient status; Global Assessment of Functioning (GAF) scale score (current) greater than or equal to 40; total Brief Psychiatric Rating Scale (BPRS) (1 to 7 scale) less than or equal to 36; BPRS items (1 to 7 scale) conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content of less than or equal to 4.

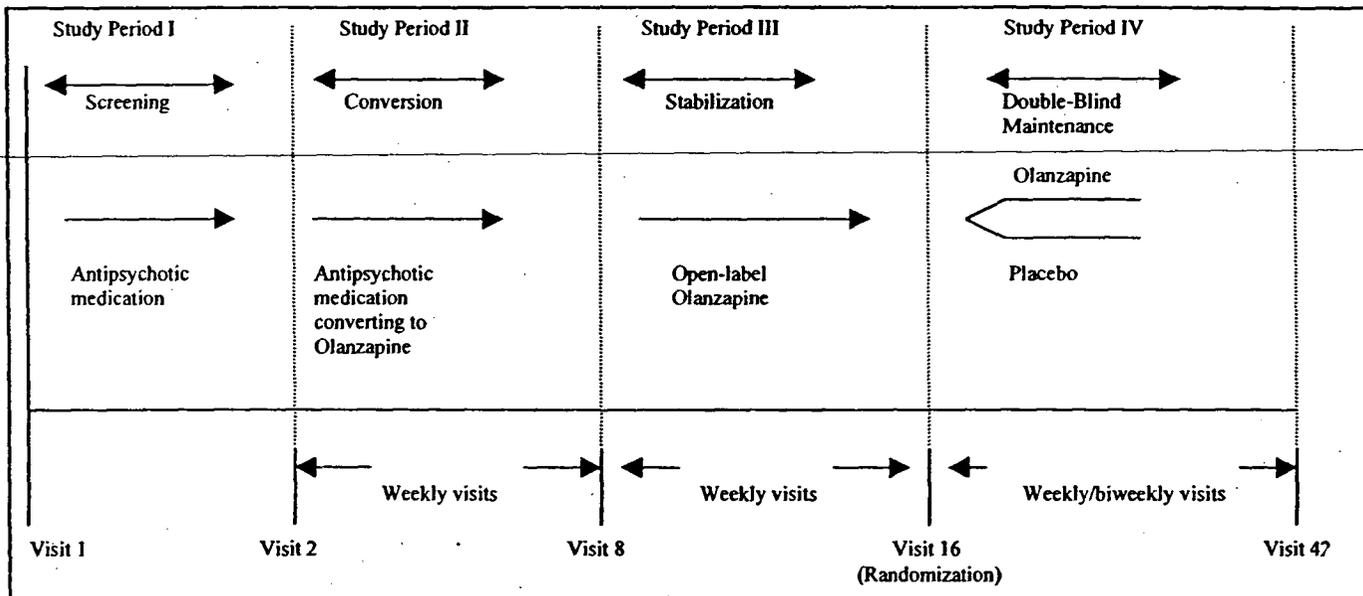


Figure 1. Study Design

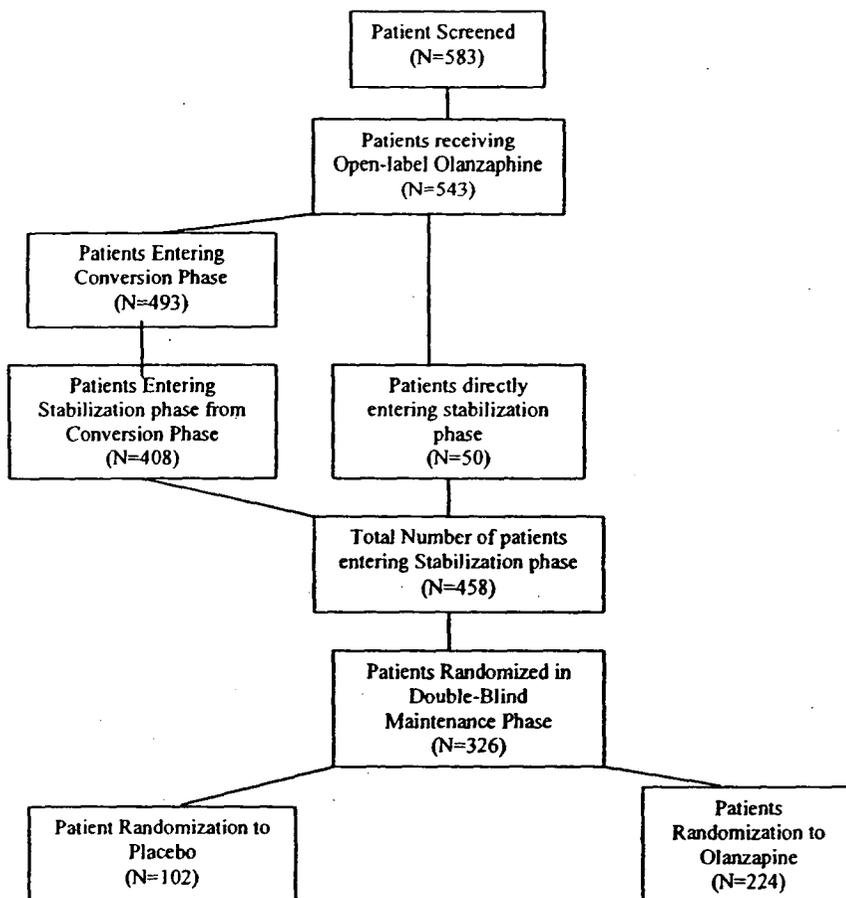


Figure 2. Summary of Patient Disposition

The primary objective of this study was to evaluate the efficacy of olanzapine, as compared to placebo in preventing relapse of psychotic symptoms as assessed by a worsening in specific items of Brief Psychiatric Rating Scale (BPRS) or hospitalization for positive psychotic symptom psychopathology. The secondary objectives were to determine the safety and efficacy of olanzapine, as compared to placebo with respect to some other scales.

Time to relapse, based on the change from baseline in specific items of the BPRS or hospitalization for positive psychotic symptom psychopathology, was defined as the primary efficacy measure of this study. The definition of relapse was:

1. An increase on any BPRS positive item (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to >4 and an absolute increase of ≥ 2 on that specific item since randomization at visit 16 (i.e., Period IV),
OR
2. An increase of any BPRS positive item to >4 and an absolute increase of ≥ 4 on the BPRS positive subscale (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) since randomization at visit 16,
OR
3. Hospitalization for positive psychotic symptom psychopathology.

Secondary efficacy measures included relapse incidence and positive and Negative Syndrome Scale (PANSS) total and subscale scores. Severity of adverse events, severity of extrapyramidal symptoms, vital signs, and laboratory analytes were measures. The Simpson-Angus Scale, the Barnes Akathisia Scale, Abnormal Involuntary Movement Scale (AIMS) were used to measure extrapyramidal symptoms.

The primary efficacy analysis was based on log-rank test of Kaplan-Meier survival curves. This analysis used a two-sided α level of 0.014 (adjusted to account for the interim analysis); the same level (i.e., 0.014) that was used in the interim analysis. The primary analysis was performed on an intent-to-treat population. Analysis of variance (ANOVA) models were used to analyze the secondary continuous efficacy measures. To analyze the proportions, Fisher's exact test was used. All secondary efficacy hypotheses comparing the difference between and within treatments were tested at a two-sided α level of 0.05.

Interim analyses:

Relapse rates were monitored sequentially throughout the trial using the triangular test to protect against continuing a treatment that was not efficacious. Indicators to initiate a possible interim analysis were based on the upper and lower bounds of the triangular test (Whitehead 1997¹). An interim analysis had been performed during the trial based on the observed test statistics of the triangular test that fell in the rejection region of the null

¹ Whitehead J. 1997. The triangle test. In: The design and analysis of sequential clinical trials. 2nd ed. New York: John Wiley & Sons Ltd. p 76-87.

hypothesis. Interim data analysis was done on the time to relapse data using log-rank test of Kaplan-Meier survival curves. Statistical significance between the time to relapse for olanzapine-treated and placebo-treated patients was observed, and hence the study was stopped prematurely for final analysis of all efficacy and safety data. In the interim analysis, an adjustment for multiple comparisons of the primary efficacy analyses (time to relapse) was made based on the spending function approach with an O'Brien-Fleming type boundary such that an overall two-sided alpha level of 0.05 was maintained. The Lan-Demets methodology was chosen since the number of interim analyses did not need to be predetermined. The significance level for an interim analysis was determined only by the alpha spending function and by past and current interim analysis times.

Sponsor's Results:

The results reported here are based on the 326 randomized patients at the double-blind maintenance phase. There were 53.1% males among the 326 patients. All of the patients were Caucasians. The mean age of the patients was 35.86 (range from 18-66 years) years. No statistically significant differences between the two treatment groups in age, gender, and origin were observed. Among the patients who entered the double-blind maintenance phase, based on DSM-IV criteria, 81.6% were diagnosed (at screening phase) as schizophrenic and 18.5% were diagnosed as schizoaffective. The treatment groups were comparable at baseline (last of Visit 1 to 16) with respect to all illness characteristics except principal diagnosis. There was a significant difference in diagnoses between treatment groups, primarily due to a higher number of schizoaffective-bipolar patients in the olanzapine group as compared with the placebo group. This difference was not large enough to substantially alter comparisons of efficacy between treatment groups.

Baseline PANSS scores were similar between treatment groups. The mean PANSS total score was 42.46, and the range was 30 to 74. The mean baseline PANSS positive score was 8.84, and the range was 7 (totally asymptomatic) to 19 (mildly ill). All patients randomized into the double-blind maintenance phase met the inclusion criteria. The inclusion criteria for the study specified that patients must have a score of 4 (moderate) or less on all BPRS positive items at baseline (visit 16).

The study was stopped after a planned interim analysis with 326 patients in the double-blind maintenance phase. The interim analysis was done after eight months (approximately) of the original twelve months of the double-blind maintenance period. The study had demonstrated a statistically significant maintenance effect with olanzapine, as compared to placebo. Before stopping the trial, the sponsor discussed the interim analysis results with Dr. Laughren (FDA) in a telephone conversation.

The primary efficacy analysis during the double blind maintenance phase was time to relapse (using the priori protocol specified primary definition of relapse). Time to relapse was significantly longer for olanzapine-treated patients compared with the placebo-treated patients (log-rank $p < .001$). Figure 3 illustrated the Kaplan-Meier survival curves of the two treatment groups. At the time the study was terminated, the longest double-blind exposure of an olanzapine-treated patient was 243 days; the longest

double-blind exposure of a placebo-treated patient was 188 days. In the Cox proportional hazards model analysis, the placebo-treated patients were 9.92 times more likely to relapse as compared to the olanzapine-treated patients. The 95% confidence interval for the risk of relapse ratio for patients taking placebo compared to patients taking olanzapine was (4.65, 21.16). At each time point during the double-blind maintenance phase, the estimated probability of an olanzapine-treated patient relapsing was less than of a placebo-treated patient. The 95% confidence interval for the percentage of relapse at six months for olanzapine-treated patients was 1.9% to 9.2%, as compared to 34.5% to 75.9% for placebo-treated patients.

The olanzapine-treated patients had a longer time until relapse than the placebo-treated patients in each country. The difference between treatment groups was statistically significant in Croatia ($P < .001$), the Russian Federation ($p = .044$), and Yugoslavia ($p = .042$).

The percentage of olanzapine-treated patients that met the primary² relapse definition at any point during the double-blind maintenance phase was significantly less than that of placebo-treated patients (4.0% versus 27.5%, $p < .001$). No additional patients in the study met the secondary³ relapse definition. More placebo-treated patients were relapsed as compared to the rate for the olanzapine-treated patients within each country. The difference was significant in Croatia ($p < .001$).

The secondary efficacy analyses included the mean change from baseline (last of visits 1 to 16) to LOCF endpoint (last of visits 17 to 33) in PANSS total, negative, and general psychopathology scores. The difference between treatment groups in mean change from baseline to LOCF endpoint in PANSS total score was significant ($p = .002$). Olanzapine-treated patients had relatively stable PANSS total scores (mean change = 1.78) compared with a mean worsening of PANSS total score for placebo-treated patients (mean change = 17.69). Similar results were observed for all PANSS subscales; however, the difference in mean change for PANSS negative only approached statistically significant ($p = .064$).

For Heinrichs-Carpenter Quality of Life Scale (QLS) total score and all subscores, the mean changes for olanzapine-treated patient indicated improvement and mean changes for placebo-treated patients indicated worsening. The difference between treatment groups in mean change was significant for total score ($p = .001$), intrapsychic foundations subscore ($p = .001$), and instrumental role category subscore ($p < .001$).

² An increase on any BPRS positive item (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to >4 and an absolute increase of ≥ 2 on that specific item since randomization at visit 16 (i.e., Period IV), OR an increase of any BPRS positive item to >4 and an absolute increase of ≥ 4 on the BPRS positive subscale (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) since randomization at visit 16, OR hospitalization for positive psychotic symptom psychopathology.

³ The above criteria, or a completed suicide, or a medically life-threatening suicide attempt.

Relapse incidence and time to relapse were analyzed across demographic subpopulations of age (<35 and >=35) and gender. The findings were similar for males and females as well as in both age groups. As all of patients were Caucasians, no analyses were performed based on patient's ethnicity.

Adverse Events:

Table 1 lists percentages of patients discontinued at the double-blind maintenance period. Patients who were ongoing at the time the study was terminated were classified as protocol complete. A greater percentage of olanzapine-treated patients were classified as protocol complete compared with the placebo-treated patients. Discontinuations due to lack of efficacy were based on patient perception, physician perception, or both and do not necessarily indicate a priori criteria defining a clinical relapse. Fewer olanzapine-treated patients discontinued due to lack of efficacy, and adverse event, as compared with placebo-treated patients. Schizophrenic reaction was the most common adverse event. The percentages of discontinuation due to patient decision, lost-to follow-up, and criteria not met/ not compliance were small and comparable between the two groups.

Table 1: Percentages of patients discontinued at double-blind maintenance phase due to specific reasons.

Reason for discontinuation	Placebo (N=127)	Olanzapine (N=224)
Protocol Complete ¹	47 (46.1%)	194 (86.6%)
Adverse Event	12 (11.8%)	2 (0.9%)
Lack of efficacy	31 (30.4%)	12 (5.4%)
Lost to Follow-up	1 (1.0%)	0
Patient Decision	3 (2.9%)	6 (2.7%)
Criteria not met /not compliance	8 (7.8%)	10 (4.5%)

¹ Only patients who were ongoing at the time the study was terminated were classified as protocol complete.

No deaths occurred during the double-blind maintenance phase. Six olanzapine-treated patients experienced a total of 9 serious adverse events. Fifteen placebo-treated patients experienced a total of 22 serious adverse events. No treatment-emergent adverse events had an incidence >=10% in olanzapine-treated patients. Most treatment-emergent adverse events were of mild or moderate severity. The overall incidence of adverse events rated as severe was greater in placebo-treated patients (21.6%) than in olanzapine-treated patients (3.6%).

Treatment groups were also compared with respect to discontinuation from the double-blind maintenance phase of the study due to adverse events, lack of efficacy, and for any reason using Kaplan-Meier estimated time-to-discontinuation curves. The discontinuation curves were significantly different between treatment groups (log-rank $p<.001$), with olanzapine-treated patients having longer time to discontinuation compared to placebo-treated patients.

Sponsor’s Final Conclusion:

Based on the Kaplan-Meier curves, the difference between olanzapine and placebo in time to relapse was noticeable shortly after randomization. Placebo-treated patients were almost 10 times as likely to relapse over period of observation of up to 6 months compared to olanzapine-treated patients. These results suggest that olanzapine has a broad maintenance efficacy profile, and at a dose of 10, 15, or 20 mg/day, is an effective agent for the prevention of relapse in the maintenance treatment of schizophrenia.

Reviewer’s Analysis and comments:

Table 2 lists the distribution of the patients by treatment group and country of origin. Only 5 (1.53%) patients from US were randomized into the trial. Majority of the patients (47.55%) belong to Croatia.

Table 2: Patients disposition by treatment group and country of origin.

Treatment group	Country						Total
	US	Croatia	Poland	Romania	Russia	Yugoslavia	
Olanzapine	3	105	10	37	48	21	224
Placebo	2	50	1	16	22	11	102
Total	5 (1.53%)	155 (47.55%)	11 (3.37%)	53 (16.26%)	70 (21.47%)	32 (9.82%)	326 (100%)

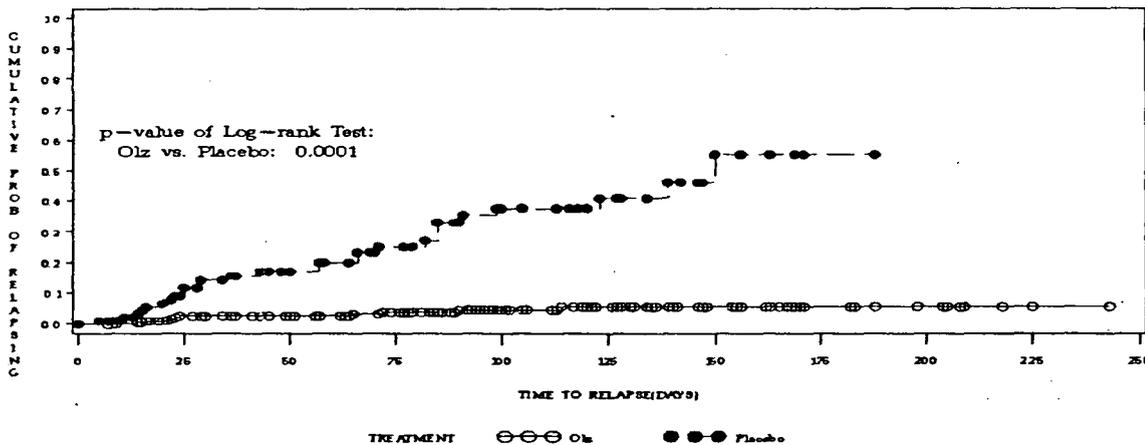


FIGURE 2: KAPLAN-MEIER CURVES OF TIME TO RELAPSE IN BLIND MAINTENANCE PHASE

This reviewer reanalyzed the data set according to the statistical analysis plan specified in the protocol. The findings were consistent with the sponsor’s reported findings. This was true for the both primary and secondary outcome measures. Figure 3 lists the Kaplan-Meier curves of time to relapse in the blind maintenance phase. The p-value of the log-rank test for comparing olanzapine vs. placebo was .0001. The Kaplan-Meier curves and the p-values indicate that olanzapine-treated patients had a significantly longer time until relapse than the placebo-treated patients. The subgroup analyses by age (<35 years, >=35 years) and gender also demonstrated the efficacy of olanzapine, as compared to placebo.

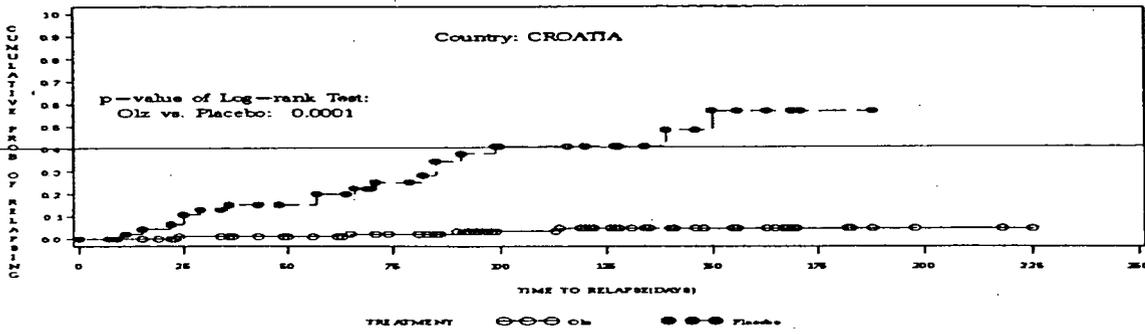


FIGURE 4A: KAPLAN-MEIER CURVES OF TIME TO RELAPSE IN BLIND MAINTENANCE PHASE

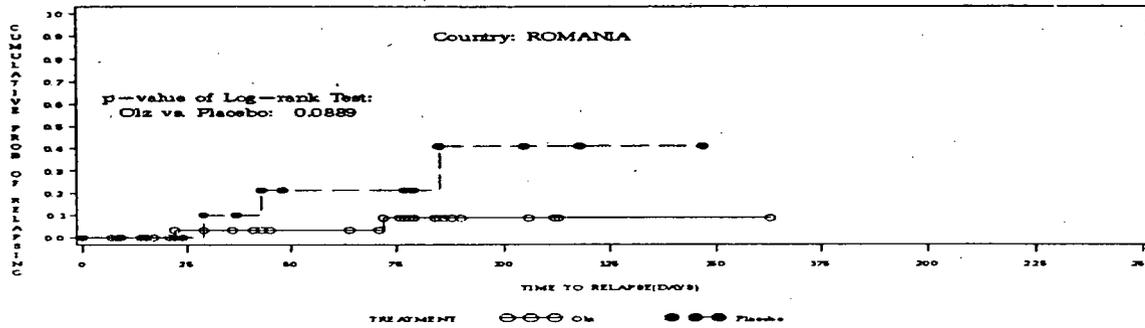


FIGURE 4B: KAPLAN-MEIER CURVES OF TIME TO RELAPSE IN BLIND MAINTENANCE PHASE

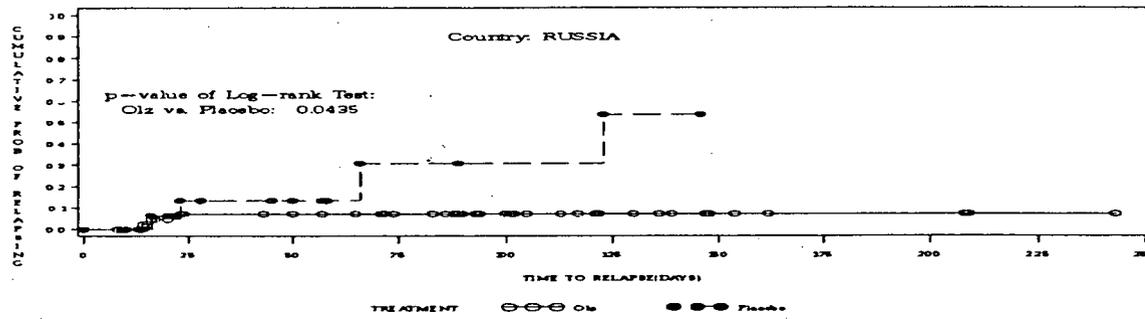


FIGURE 4C: KAPLAN-MEIER CURVES OF TIME TO RELAPSE IN BLIND MAINTENANCE PHASE

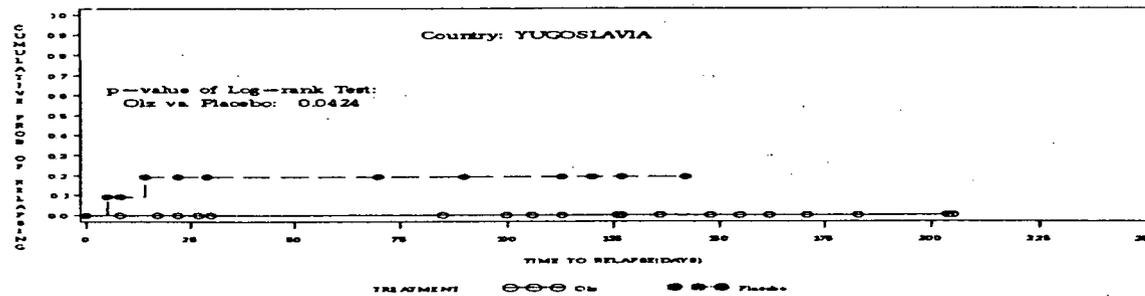


FIGURE 4D: KAPLAN-MEIER CURVES OF TIME TO RELAPSE IN BLIND MAINTENANCE PHASE

Figures 4A-4D list the Kaplan-Meier curves by country. At each of the four countries, olanzapine-treated patients had a longer time until relapse, as compared to the placebo-treated patients.

Reviewer's Overall Conclusion:

In this supplemental new drug application, the sponsor designed the trial and analyzed the dataset appropriately to assess the efficacy of olanzapine, as compared to placebo in the prevention of relapse of positive psychotic symptoms as assessed by a worsening in specific items of the Brief Psychiatric Rating Scale (BPRS) or hospitalization for positive psychotic symptom psychopathology. Due to overwhelming efficacy observed in the prospectively planned interim analysis, and the ethical considerations following from this efficacy, the study was stopped early. The interim analysis was done after eight months (approximately) of the original twelve months of the double-blind maintenance period. The maximum potential patient exposure was approximately 11 months for the first randomized patient. The total exposure to olanzapine and placebo was 21,826 patient-days and 6,602 patient-days, respectively. Out of 326 patients, there were only five patients from US centers, therefore this study was essentially a foreign study.

The study results demonstrated the maintenance of the efficacy of olanzapine, as compared to placebo over long-period of time. This reviewer found sufficient evidence from the statistical analyses of this clinical trial data set to support the claim of this supplemental new drug application.

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Ohidul Siddiqui, Ph.D
Mathematical Statistician

Concur: Dr. Kun Jin

Dr. George Chi

CC:

Arch NDA # 20-592
HFD-120/Dr. Katz
HFD-120/Dr. Laughren
HFD-120/Dr. Andreason
HFD-120/Mr. Hardeman
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Siddiqui
HFD-710/Chron

This application contains the following items: (Check all that apply)		
<input checked="" type="checkbox"/>	1. Index	
<input checked="" type="checkbox"/>	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
	3. Summary (21 CFR 314.50 (c))	
	4. Chemistry section (Cross reference)	
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2), 21 CFR 601.2)	
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2) (Cross reference)	
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2) (Cross reference)	
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))	
<input checked="" type="checkbox"/>	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)	
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (v) (b), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C 335 (b) or (c))	
<input checked="" type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 335 (b) (2) or (j) (2) (A))	
	15. Establishment description (21 CFR Part 600, if applicable)	
<input checked="" type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k) (1))	
<input checked="" type="checkbox"/>	17. Field copy certification (21 CFR 314.5 (k) (3))	
<input checked="" type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input checked="" type="checkbox"/>	19. OTHER (Specify) Financial Disclosure	
CERTIFICATION		
<p>I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including but not limited to the following:</p> <ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202. 5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on reports in 21 CFR 314.80, 314.91, 600.80 and 600.81. 7. Local, state and Federal environmental impact laws. <p>If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.</p> <p>The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.</p> <p>Warning: a willfully false statement is a criminal offense. U.S. Code, title 18, section 1001.</p>		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Gregory T. Brophy, Ph.D. Director, U.S. Regulatory Affairs	12/15/99
ADDRESS (Street, City, State, and ZIP Code)	Telephone Number	
Lilly Corporate Center Indianapolis, IN 46285	(317) 277-3799	
<p>Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p>DHHS, Reports Clearance Officer Paperwork Reduction Project (0910-0338) Hubert H. Humphrey Building, Room 531-H 200 Independence Avenue, S.W.</p> <p>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</p>		
Please DO NOT RETURN this form to this address.		
FORM FDA 366h (4/97)		



NDA 20-592/S-011

Food and Drug Administration
Rockville MD 20857

DEC 21 1999

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Gregory T. Brophy, Ph.D.
U.S. Regulatory Affairs

Dear Mr. Brophy:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Zyprexa (olanzapine)

NDA Number: 20-592

Supplement Number: 011

Date of Supplement: 15-Dec-99

Date of Receipt: 17-Dec-99

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on 15-Feb-2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

10. *(S)*
John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA 20-592/011

Page 2

cc:

Original NDA 20-592/011

HFD-120/Div. Files

HFD-120/CSO/Hardeman

filename:

SUPPLEMENT ACKNOWLEDGEMENT

**Lilly Research Laboratories**
A Division of Eli Lilly and CompanyLilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

December 15, 1999

NDA NO. 20-592 REF NO. SEI-011
NDA SUPPL FOR Labeling

DUPLICATE

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 20857-1706CENTER FOR DRUG EVALUATION
AND RESEARCH

DEC 17 1999

RECEIVED HFD-120

RE: NDA 20-592, Zyprexa® (olanzapine)

This supplement provides the results of study F1D-MC-HGGI entitled "Olanzapine Relapse Prevention Versus Placebo in the Treatment of Schizophrenia," as the basis to change the labeling of the referenced drug. This submission consists of one set of volumes in blue binders (archived copy) and one set of volumes in "rainbow" binders (review copy).

This application is formatted and organized as a supplement according to 21 CFR §314.50 and follows the "Guideline for the Format and Content of the Clinical and Statistical Section of New Drug Application" and the "Guidelines on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications." Items 11 and 12 of the application, the Case Report Tabulations and Case Report Forms, are submitted as an electronic-only archival copy in accordance with the "Guidance to Industry: Archiving Submissions in Electronic Format - NDAs."

The electronic archival copy of Items 11 and 12 is contained on one CDROM and is approximately 182 megabytes. The CDROM is included in the blue binder labeled "ELECTRONIC REGULATORY SUBMISSION FOR ARCHIVE".

All electronic media have been checked and verified to be free of known viruses. The virus checking software was McAfee VirusScan 4.0.2 using virus definitions 4.0.4043 created on September 15, 1999.

To coordinate our activities with yours, we suggest that any written communication concerning this submission, regardless of subject, be directed to me:

Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285-2643

Any calls dealing with administrative issues, questions, clinical reports, or labeling should be directed to:

Michele L. Sharp, PharmD.
(317) 277-8382

Please address all facsimile (fax) transmissions to Dr. Michele Sharp at (317) 276-1652; or, in her absence to me:

Gregory T. Brophy, Ph.D.
(317) 277-2799

On holidays and weekends, call Dr. Sharp or me at home using the telephone numbers provided.

Close liaison between Lilly personnel listed above will result in any message, no matter how received, being brought to the attention of all concerned.

Please call Dr. Michele Sharp at (317) 277-8382 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

Enclosures