

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-592/S-006

Name: Zyprexa Oral Tablets

Generic Name: olanzapine

Sponsor: Eli Lilly and Company

Approval Date: 03/17/2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-006

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Food and Drug Administration
Rockville MD 20857

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

MAR 17 2000

Dear Dr. Brophy:

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

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

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

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

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 We therefore consider S-008 to be superseded by the approval of S-006; we will not review this application, but it will be retained in our files.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

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

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

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

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

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

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

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

You have been advised that the Pediatric Final Rule (63 FR 66632) requires that all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that your Proposed Pediatric Study Request was submitted to this supplemental NDA on February 25, 2000 and received February 28, 2000. A formal Written Request will be forwarded to you under separate cover.

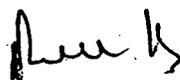
Also, as you know, on February 2, 1999, the financial disclosure rule, published in the Federal Register of February 2, 1998, became effective. Although your supplemental NDA was submitted before this rule was in effect, for any covered clinical studies submitted after February 2, 1999 which relate to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

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

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

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

Sincerely yours,



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

Attachment (agreed-upon package insert text)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-006

APPROVABLE LETTER

NDA 20-592/S-006

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

Dear Dr. Brophy:

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

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

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

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

CLINICAL

Labeling

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

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

Pediatric Studies

Be advised that as of April 1, 1999, all applications for new active ingredients, new dosage forms, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63FR66632). Since it is likely that ZYPREXA will be used in children and adolescents with bipolar disorder, we ask that you commit to conducting, subsequent to approval, studies in these populations as

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

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

Requests for Additional Information for Studies HGEH and HGEW

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

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

FINAL PRINTED LABELING

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

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

PROMOTIONAL MATERIALS

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

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

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Neuropharmacological Drug Products to discuss what further steps need to be taken before the application may be approved. The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely yours,

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

Attachment (draft labeling)

cc:

NDA 20-592/S006: Archival NDA

NDA 20-592/S006: Division File

HFD-002/ORM

HFD-95/DDMS

HFD-101/ADRA(Carter)

HFD-100/Temple

HFD-120/Katz

 /Laughren/Hearst

 /Fitzgerald

 /Seevers

 /Bates

HFD-710/Jin/He

HFD-860/Tammara

HFD-40/DDMAC (with draft labeling)

DISTRICT OFFICE

Drafted by: djb/06OCT99

Revised by: tpl/06OCT99

initialed by: see above

Final:

Doc N:\laughren\zyplab\l\trae1.doc

APPROVABLE (AE)

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

Approvable Letter

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-006

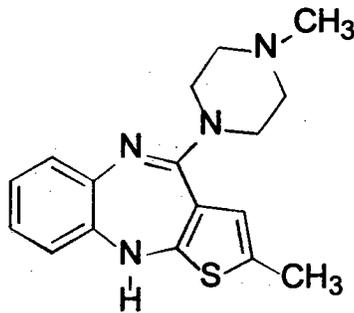
FINAL PRINTED LABELING

FINAL LABELING

ZYPREXA[®] (Olanzapine)

DESCRIPTION

ZYPREXA (olanzapine) is a psychotropic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine. The molecular formula is C₁₇H₂₀N₄S, which corresponds to a molecular weight of 312.44. The chemical structure is:



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

ZYPREXA tablets are intended for oral administration only.

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

CLINICAL PHARMACOLOGY

Pharmacodynamics:

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin 5HT_{2A/2C} (K_i=4 and 11 nM, respectively), dopamine D₁₋₄ (K_i=11-31 nM), muscarinic M₁₋₅ (K_i=1.9-25 nM), histamine H₁ (K_i=7 nM), and adrenergic α₁ receptors (K_i=19 nM). Olanzapine binds weakly to GABA_A, BZD, and β adrenergic receptors (K_i > 10 μM).

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT₂) antagonism. The mechanism of

ZYPREXA® (Olanzapine)
Final Labeling

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 M₁₋₅ 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 α₁ receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics:

Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption.

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

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

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α₁-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

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not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

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

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

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

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

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

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

Clinical Efficacy Data:

Schizophrenia

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

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the

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manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed but less well evaluated scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which is embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

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

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

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

Bipolar Mania

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

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

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

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

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INDICATIONS AND USAGE

Schizophrenia

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

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

The effectiveness of ZYPREXA in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Bipolar Mania

ZYPREXA is indicated for the short-term treatment of acute manic episodes associated with Bipolar I Disorder.

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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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

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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 D₂ 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

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patients compared to 15% in placebo patients. This adverse event was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Olanzapine may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Olanzapine--Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 (e.g., fluvoxamine) could potentially inhibit olanzapine elimination. Because olanzapine is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease olanzapine clearance.

Charcoal--The administration of activated charcoal (1 g) reduced the 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

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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.

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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

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used with caution in elderly patients with dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient (*see* PRECAUTIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for olanzapine consisting of 4189 patients with approximately 2665 patient-years of exposure. This database includes: (1) 2500 patients who participated in multiple-dose premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in premarketing bipolar mania trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in a trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; and (4) 1316 patients from 43 additional clinical trials as of May 1, 1997.

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

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

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

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

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide

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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

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

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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.

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Table 1
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)
Body as a Whole		
Accidental injury	12	8
Asthenia	10	9
Fever	6	2
Back pain	5	2
Chest pain	3	1
Cardiovascular System		
Postural hypotension	3	1
Tachycardia	3	1
Hypertension	2	1
Digestive System		
Dry mouth	9	5
Constipation	9	4
Dyspepsia	7	5
Vomiting	4	3
Increased appetite	3	2
Hemic and Lymphatic System		
Ecchymosis	5	3
Metabolic and Nutritional Disorders		
Weight gain	5	3
Peripheral edema	3	1
Musculoskeletal System		
Extremity pain (other than joint)	5	3
Joint pain	5	3
Nervous System		
Somnolence	29	13
Insomnia	12	11
Dizziness	11	4
Abnormal gait	6	1
Tremor	4	3
Akathisia	3	2
Hypertonia	3	2
Articulation impairment	2	1
Respiratory System		
Rhinitis	7	6
Cough increased	6	3

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

Body System/Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=532)	Placebo (N=294)
Respiratory System		
Pharyngitis	4	3
Special Senses		
Amblyopia	3	2
Urogenital System		
Urinary incontinence	2	1
Urinary tract infection	2	1

¹ Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion, depression, diarrhea, 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 Premarketing Clinical Trials --The following findings are based on premarketing clinical trials in schizophrenia.

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

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

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

	Percentage of Patients			
	Placebo	Olanzapine 5 ± 2.5 mg/day	Olanzapine 10 ± 2.5 mg/day	Olanzapine 15 ± 2.5 mg/day
Parkinsonism ¹	15	14	12	14
Akathisia ²	23	16	19	27

* No statistically significant differences.

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

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

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

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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).

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

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

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

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

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

Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with olanzapine (at multiple doses > 1 mg/day) in clinical trials (4189 patients, 2665 patient-years of exposure). This listing does not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening

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

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

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

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

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

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

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

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

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

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

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

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

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

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Final Labeling

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

*Adjusted for gender.

Postintroduction Reports--Adverse events reported since market introduction which were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: priapism.

DRUG ABUSE AND DEPENDENCE

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

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

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

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen

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hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Schizophrenia

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

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

Dosing in Special Populations--The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients \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 maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on olanzapine, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Bipolar Mania

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

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

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

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

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

HOW SUPPLIED

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

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

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

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

Protect from light and moisture.

**ZYPREXA® (Olanzapine)
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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.

[Will carry actual revision date]

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

PRINTED IN USA

DOC AP3AZYPLB.DOC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-592/S-006

MEDICAL REVIEW(S)

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

Sponsor: Lilly Research Laboratories
Drug: Olanzapine
Material Submitted: Briefing document for meeting with the sponsor
Correspondence Date: November 23, 1999

I. Background

Olanzapine is an "atypical" neuroleptic that was approved September 30, 1996; the approval was based on two adequate and well controlled studies showing olanzapine to be superior to placebo in the treatment of psychosis in patients with schizophrenia. There were 2500 subjects exposed to olanzapine in the development program upon which the safety evaluation was made.

On November 12, 1999 a teleconference was held with the Division and the sponsor to discuss case summaries of patients who died in study HGEU. This submission is a written report of case summary revisions and adverse event tables for study HGEU. The sponsor submitted a supplement to NDA 20-592 (SE1-006) with the goal of claiming an indication for the treatment of acute mania in bipolar affective disorder. Concomitantly, the sponsor submitted supplement

Supplement 006 was declared approvable it contained safety data that shall appear in Zyprexa®. The sponsor makes several appeals for changes in draft labeling that the Division is considering based on the review of study HGEU from the sponsor's NDA supplement .

II. Data Reviewed:-

- Revised case summaries for patients who died during or with 30-days of terminating treatment in study HGEU
- Revised adverse event tables

Revised case summaries-

Study HGEU in supplement reports 5 deaths in patients during or within 30-days of treatment. The supplement reports that there were 3 patient-deaths in the 15-mg group, and 1 each in the 5 and 10-mg groups. On further review of the cases, the sponsor reports that these patients were not actually exposed to the dose levels that their dose groups indicated. Two of the 15-mg group deaths actually only received up to 10-mg. Patients in the 15-mg treatment group in study HGEU received 5-mg/day for 1-week then 10-mg/week for the second week before reaching a dose of 15-mg/day in the third week.

Patients 006-601 and 023-2312 though assigned to the 15-mg dose group only reached the 10-mg level. The death rate that originally appeared dose dependent was not related to the actual dose that the patient received.

The sponsor also proposed revised adverse event tables that were discussed and shall be submitted in draft labeling as a part of their response to the Division letter to the sponsor that was dated October 28, 1999. One patient (015-1525) was inadvertently assigned to the 15-mg group due to a transcription error but was truly in the placebo group. This does not substantially change the adverse event table.

III. Conclusions and Recommendations

Given that two of the patients who died actually received 10-mg in lieu of 15-mg, the

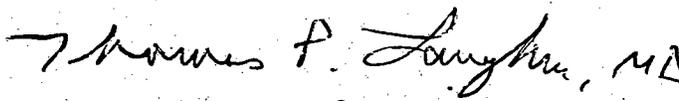
description of the deaths in the PRECAUTION section when the sponsor submits their next version of draft labeling. This is an appropriate change, and shall be considered along with other changes in draft labeling in the sponsor's complete response to the letter of October 28, 1999.


Paul J. Andreason, M.D.

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

2-25-00

Lilly's clarification that there is no dose dependent mortality, along with the fact that there was no unifying mechanism for death in these patients, led us to agree that there is insufficient data at present to support a conclusion of drug-related mortality. Alternatively, we have agreed to strengthening labeling with findings suggesting a different tolerability profile in patients with Alzheimer's Disease (see my 2-25-00 memo to file).


TL, PDP

MEMORANDUM

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

DATE: February 25, 2000

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

SUBJECT: Recommendation for Approval Action for Zyprexa (olanzapine) for the treatment of manic or mixed episodes in bipolar disorder

TO: File NDA 20-592/S-006
[Note: This memo should be filed with the 12-22-99 response to our approvable letter.]

1.0 BACKGROUND

In our 10-28-99 approvable letter, we requested a phase 4 commitment to conduct additional studies in pediatric patients with bipolar disorder. We also requested additional information regarding studies HGEH and HGEW, i.e., a breakdown of the number of patients enrolled by each episode type (manic or mixed), and a table listing patients and visits for which total YMRS scores were treated as missing. Finally, we attached our proposal for labeling.

Lilly responded to our approvable letter with a 12-22-99 submission, including an alternative labeling proposal and responses to the other questions and requests in our letter.

-Regarding pediatric studies, Lilly agreed to submit a pediatric development plan within 120 days of the approvable letter.

-Regarding the breakdown of episode types for the 2 positive studies, these were as follows:

-HGEH 2	Manic 19%	Mixed 81%
-HGGW	Manic 43%	Mixed 57%

-Regarding missing data, there were no instances in which it was necessary to exercise the rule and exclude YMRS data.

The review team, up to the level of Team Leader, interacted with the sponsor over a period of several weeks, including an exchanges of draft labeling and a teleconference in order to resolve the differences in labeling. On 2-15-00, we faxed version AP1ZYPLB.DOC to Lilly, and they responded

with a 2-18-00 counterproposal. In a 2-22-00 telcon, we reached final agreement on labeling on all issues except whether or not to change the psychosis indication to schizophrenia. Dr. Katz and I discussed that issue on 2-23-00, and decided to retain the current labeling language for now, as requested by Lilly. The mutually agreed upon final labeling [AP2ZYPLB.DOC] is included with the approval letter.

The following were the 2 major labeling issues that were discussed and negotiated:

-Inclusion of safety findings from study HGEU, a study of olanzapine in patients with psychiatric/behavioral symptoms in association with Alzheimer's Disease:

-In our labeling proposal included with the 10-28-99 approvable letter, we had added a

[]
[]
[]

Upon reexamination of doses actually received, Lilly clarified that there was not dose dependent mortality. That clarification, along with the fact that there was no unifying mechanism for death in these patients, i.e., there were several different causes of death, all common conditions in this very sick and elderly population, led us to agree that the [] []

[] In fact, there is insufficient data at present to support a conclusion of drug-related mortality. Alternatively, we have agreed to strengthening the already existent "Dysphagia" statement under Precautions and the addition under "Use in Patients with Concomitant Illness" the adverse event findings from study HGEU. These findings suggestive of a different tolerability profile in patients with Alzheimer's Disease are also now noted in the "Geriatric Use" subsection under Precautions.

-Changing the psychosis indication to focus exclusively on schizophrenia:

-We had considered changing the psychosis indication from "management of the manifestations of psychotic disorders" to simply the "treatment of schizophrenia," as part of a policy shift on psychotropic indications. However, Lilly expressed great concern that competitors, formulary committees, and others might misuse this labeling difference for their product relative to other antipsychotics. Alternatively, we have decided to attempt to effect this change as a class labeling action.

I believe that Lilly has submitted sufficient data to support the conclusion that Zyprexa is effective and acceptably safe in the short-term treatment of acute manic and mixed episodes associated with Bipolar I Disorder. I recommend that we issue the attached approval letter with the version of labeling for which we were able to reach mutual agreement with the sponsor.

cc:
Orig NDA 20-592/S-006
HFD-120
HFD-120/TLaughren/RKatz/PAndreason/EHearst/DBates

DOC: MEMZYPMN.AP1

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

Medical Review #2 (2/25/00)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-006

ADMINISTRATIVE and CORRESPONDENCE

Exclusivity Checklist

NDA: <u>20-592/S-006</u>			
Trade Name: <u>ZYPREXA</u>			
Generic Name: <u>OLANZAPINE</u>			
Applicant Name: <u>ELI LILLY & COMPANY</u>			
Division: <u>DNDP, HFD-120</u>			
Project Manager: <u>DORIS J. BATES, PH.D.</u>			
Approval Date:			
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?			
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.			
a. Is it an original NDA?	Yes	<input type="checkbox"/>	No <input checked="" type="checkbox"/>
b. Is it an effectiveness supplement?	Yes	<input checked="" type="checkbox"/>	No <input type="checkbox"/>
c. If yes, what type? (SE1, SE2, etc.)	<u>SE1</u>		
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	<input checked="" type="checkbox"/>	No <input type="checkbox"/>
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.			
Explanation:			
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:			
Explanation:			
d. Did the applicant request exclusivity?	Yes	<input checked="" type="checkbox"/>	No <input type="checkbox"/>
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	<u>THREE (3)</u>		
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.			
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes	<input type="checkbox"/>	No <input checked="" type="checkbox"/>
If yes, NDA #			
Drug Name:			
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.			
3. Is this drug product or indication a DESI upgrade?	Yes	<input type="checkbox"/>	No <input checked="" type="checkbox"/>
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).			

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.		Yes	<input checked="" type="checkbox"/>	No
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.		<input checked="" type="checkbox"/>		<input type="checkbox"/>
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product		OLANZAPINE (IN PSYCHOSIS)		
NDA #		20-592 (ORIGINAL)		
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.		Yes		No
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)		<input checked="" type="checkbox"/>		<input type="checkbox"/>
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability				

studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

<input checked="" type="radio"/> Yes		<input type="radio"/> No	
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IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

<input checked="" type="radio"/> Yes		<input type="radio"/> No	
--------------------------------------	--	--------------------------	--

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

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

<input checked="" type="radio"/> Yes		<input type="radio"/> 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.

<input type="radio"/> Yes	<input checked="" type="radio"/> 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?

<input type="radio"/> Yes	<input checked="" type="radio"/> No		
---------------------------	-------------------------------------	--	--

If yes, explain:

c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:	FID-MC-HGEH
Investigation #2, Study #:	FID-MC-HGGW
Investigation #3, Study #:	/

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

not redemonstrate something the agency considers to have been demonstrated in an already approved application.

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

Investigation #1	HGEH	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
Investigation #2	HGGW	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
Investigation #3		Yes	<input type="checkbox"/>	No	<input type="checkbox"/>

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

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

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

Investigation #1	HGEH	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
Investigation #2	HGGW	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
Investigation #3		Yes	<input type="checkbox"/>	No	<input type="checkbox"/>

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

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

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

Investigation #1	HGEH
Investigation #2	HGGW
Investigation #3	

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

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

Investigation #1	HGEH	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
IND#:	28,705				

Explain:

Investigation #2	HGGW	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
IND#:	28,705				

Explain:

Investigation #3	Yes	No	
IND#:			
Explain:			
<p>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?</p>			
Investigation #1	Yes	No	
IND#:			
Explain:			
Investigation #2	Yes	No	
IND#:			
Explain:			
Investigation #3	Yes	No	
IND#:			
Explain:			
<p>c. Notwithstanding an answer of "yes" in (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.)</p>			
If yes, explain:		Yes	No <input checked="" type="checkbox"/>



Signature of PM/CSO

Dr. J. P. ... Ph.D.

Date:

17 September 1999 and 25 February 2000

Signature of Division Director

[Signature]

Date:

cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac



PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>20592</u>	Trade Name:	<u>ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/</u>
Supplement Number:	<u>6</u>	Generic Name:	<u>OLANZAPINE</u>
Supplement Type:	<u>SE1</u>	Dosage Form:	
Regulatory Action:	<u>AP</u>	Proposed Indication:	<u>mania associated with bipolar disorder</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Inadequate for ALL pediatric age groups
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

initial entry 01-SEP-98 NA action 02-OCT-98 resubmission S-006 12-APR-99 updated comments 15-SEP-99 AE action 28-OCT-99 resubmission 22-DEC-99 updated comments 25-FEB-00

there is a pediatric commitment for the initial indication (antipsychotic) but not for the pending indication (mania). The resubmission includes a commitment to submit a proposed pediatric development plan within 120 days of the AE letter (February 26, 2000)

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DORIS BATES

Doris Bates
 Signature

25 Feb 00
 Date

1. The submitted FPL (hard copy version, review jacket) was carefully compared to the WORD file for the same labeling by the CSO and found to match.
2. A line by line comparison of the current label DV 3555 DVP (WORD file. Attachment 2) to the agreed-upon labeling (AP3ZYPLB.DOC, Attachment 1) was performed using the subroutine "track changes" in MS WORD. This comparison (Attachment 3) indicated the following minor changes (all described with reference to AP3ZYPLB.DOC):
 - DOCUMENT HEADER: "Final Labeling" deleted on all pages, pamphlet code added to p.1.
 - DESCRIPTION: Line spacing changes.
 - CLINICAL PHARMACOLOGY: Minor changes related to formatting (line spacing, font changes from italic to normal to preserve uniform appearance of headings/subheadings).
 - INDICATIONS AND USAGE: Line spacing changes.
 - CONTRAINDICATIONS: Line spacing changes.
 - WARNINGS: Line spacing changes.
 - PRECAUTIONS: Line spacing changes; Use in Patients With Concomitant Illnesses changed to Use in Patients With Concomitant Illness.
 - ADVERSE REACTIONS:
 - Overall: Line spacing changes;
 - insertion of the word "a" into the last sentence, fifth paragraph, to read "... to gain a complete understanding..."
 - One apparent spurious change: replacement of the word "studied" in last sentence, sixth paragraph, by itself (possible spacing error).
 - Tables: formatting / layout changes, no content change.
 - *Other Adverse Events* section: minor changes in font, spacing for consistent appearance.
 - DRUG ABUSE AND DEPENDENCE: Line spacing changes.
 - OVERDOSAGE: Line spacing changes.
 - DOSAGE AND ADMINISTRATION: Line spacing changes, spurious changes related to possible spacing errors (apparent replacements of a word or term by the identical word or term).
 - HOW SUPPLIED: Line spacing changes, spurious changes related to possible spacing errors (apparent replacement of a word or term by the identical word or term).
 - ANIMAL TOXICOLOGY: Line spacing changes.
 - DOCUMENT END: addition of text revision date, change FDA filename code to Lilly pamphlet code, line spacing changes

Recommendation: It is recommended that the submitted FPL be acknowledged and retained as identical to the agreed-upon labeling provided with the approval letter of March 17, 2000.

Reviewer: Doris J. Bates, Ph.D., RPM _____

Concurrence: John S. Purvis, Chief, Project Management Staff _____

attachments (for copy to original NDA file after review concurrence):

1. Agreed-upon labeling text from AP letter
2. Printout of WORD file as submitted by firm (pamphlet code DV 3555 DVP)
3. Printout of "Track Changes" WORD file comparing the DV 3555 DVP WORD file with the agreed-upon labeling text
4. Review Jacket: submitted FPL hardcopy, DV 3555 DVP

CC:

Orig NDA (with attachments as above) SE1--006, SLR-008
HFD-120 Division File
HFD-120/Purvis/Bates/Hardeman
HFD-120/20-592/s-006 action package, labeling subsection

d:...\supps\20592\s006\ackretn.doc

ZYPREXA® (OLANZAPINE)
BIPOLAR MANIA EFFICACY SUPPLEMENT
CSO ADMINISTRATIVE AND LABELING REVIEW

SUBMISSION: NDA 20-592 / SE1-006, SLR-008

DATES: S-006: December 3, 1997 (original submission), April 12, 1999 (response to NA letter), December 22, 1999 (response to AE letter).

S-008: August 26, 1998.

APPLICANT: Eli Lilly and Company

DOSAGE FORM AND STRENGTH: Tablets, 2.5, 5.0, 7.5, 10.0, 15.0, 20.0 mg (20 mg not marketed)

INDICATION(S): original indication: antipsychotic. S-006 provides for use of olanzapine in the treatment of acute manic or mixed episodes in bipolar disorder.

SCOPE OF REVIEW: This labeling review addresses:

- changes in the **approved** package insert since submission of SE1-006; see ADMINISTRATIVE HISTORY and CSO Labeling Review..
- changes between the most recent **approved** package insert, cited above, and the **agreed-upon labeling** negotiated between DNDP and the applicant; see ADMINISTRATIVE HISTORY and CSO Labeling Review.

This review has also surveyed the following supplements, submitted and / or approved in the same interval, to validate that they **did not** have or require associated labeling changes. They are not described in the ADMINISTRATIVE HISTORY.

- S-005, manufacturing supplement for changes in contract manufacture of the drug substance, submitted 24SEP97 and approved 04DEC97. There are no related labeling disclosures required for this change.
- S-007, manufacturing supplement for addition of a new bulk packaging site for the drug product, submitted 19DEC97 and approved 23MAR98. The requirement for disclosure of the name and place of business of the manufacturer, packer, **or** distributor of the drug product, per 21 CFR 201.10, does not apply to bulk packaging.

NOTE: Final Printed Labeling will be submitted following approval of this supplement and must be identical to the agreed-upon labeling enclosed with the approval letter. A separate CSO review (Acknowledge and Retain) will compare the FPL to the agreed-upon labeling when received.

MATERIAL REVIEWED / SUPERSEDED:

1. (reviewed): APPROVED package insert PV 2965 AMP (revision of November 19, 1998 to correct a misspelling of the trademark) (text provided by S. Hardeman, CSO)
2. (reviewed) APPROVED package insert PV 3330 AMP (revision of June 29, 1999) (text provided by S. Hardeman, CSO, and by Lilly). This insert includes the 15 mg tablet (S-004) and was approved after PV 2965 AMP was implemented; these two approved inserts were compared to identify any unapproved changes.
3. (superseded) DRAFT Package insert PV 2963-F AMP (first draft of proposed bipolar text, submitted December 3, 1997) **This draft is superseded by draft insert PV 3330-A AMP.**
4. (superseded) DRAFT package insert PV 3330-A AMP (second draft of proposed bipolar text, December 22, 1999, based on PV3330AMP and including geriatric safety and use text based on data provided in [] (see Administrative History)). **This text is superseded by the agreed upon labeling text as confirmed in writing by Lilly on February 29, 2000.**
5. (superseded) DRAFT proposed changes to text in Geriatric Use section (S-008, August 26, 1998, S. Hardeman, CSO; See Administrative History). **This text is superseded by the draft insert PV 3330-A AMP and the agreed upon labeling text as confirmed by Lilly on**

- WARNINGS: No observed changes.
- PRECAUTIONS: No observed changes.
- ADVERSE REACTIONS: No observed changes.
- DRUG ABUSE AND DEPENDENCE: No observed changes.
- OVERDOSAGE: No observed changes.
- DOSAGE AND ADMINISTRATION: No observed changes.
- HOW SUPPLIED: Changes in PV3330 in agreement with the addition of the 15 mg tablet:
 - blue film coating
 - bottles of 30 (15 mg only) added
 - 15 mg tablet description added to master table
- ANIMAL TOXICOLOGY: No observed changes.

Agreed upon labeling vs. approved insert PV 3330 AMP, with changes superseding S-008 and including data from []

Draft insert PV 2963 F-AMP was based on approved insert PV 2965. It is superseded by PV 3330-A AMP, which is based on approved insert PV 3330 AMP. Therefore, the changes listed above between the two approved versions of FPL are also reflected in the two successive drafts and have been carried through to the agreed upon labeling for S-006.

Labeling supplement S-008 (see Administrative History) proposed revised language for the Geriatric Use subsection of the package insert. There are also changes to the Geriatric Use subsection and the ADVERSE REACTIONS section of PV 3330-A AMP which were recommended by the Division in connection with []

[] but the patient data generated in connection with it remain relevant to product labeling. In a February 28, 2000 teleconference with John Roth, regulatory project manager at Lilly, it was confirmed that the geriatric language proposed in supplement S-008, is addressed, and therefore may be superseded, by the agreed upon labeling for S-006. See also FAX, February 29, 2000. (attachment 2)

A line by line comparison of the agreed upon labeling for S-006 to prior approved FPL PV 3330 AMP indicates that no additional changes in wording have been made other than those relevant to the following areas, as indicated (underlining) in the marked-up version of agreed upon labeling (attachment 3):

- the proposed indication bipolar mania affects:
 - Description (first line)
 - Clinical Pharmacology (*Pharmacodynamics*)
 - Clinical Efficacy (new subsection Bipolar Mania, with text)
 - Indications and Usage (new subsection Bipolar Mania, with text)
 - Precautions (General – text added to the existing section for Suicide and Drug Interactions)
 - Adverse Reactions (new text in introductory paragraphs, new tables and modifications to contents of existing tables, new information in *Incidence of Adverse Events in Short-Term, Placebo-Controlled Trials* subsection, new information in *Other Adverse Events Observed During the Clinical Trial Evaluation* section, revisions to reported frequency,

February 29, 2000. The S-008 proposed text is Attachment 1 to this review; Lilly's FAX is Attachment 2.

6. (reviewed) FDA / Lilly Agreed Upon Labeling Text (agreement confirmed in writing by Lilly, FAX, February 29, 2000). **This text is Attachment 3 to this review.**
7. (reviewed) Tabular Summary of Labeling Changes (Approved Package Insert), provided by Lilly, March 3, 2000. **This text is Attachment 4 to this review.**

ADMINISTRATIVE HISTORY:

- **Changes to prior approved labeling** made during the review of S-006 include the following other supplements / annual reports which have been approved or accepted:
 - S-004, manufacturing supplement for the 15 mg tablet, submitted 14APR97 and approved 09SEP97; labeling revised 29JUN99 (PV 3330 AMP). This insert declares the 15 mg dosage strength, provides its description and inactive ingredients, and lists bottles of 30 tablets for this strength per CMC supplement SCM-004, approved 09SEP97. (NOTE: the delay in revision of FPL is attributed to delay in market introduction of 15 mg tablets by the applicant. Note also that the 20 mg tablets are not currently marketed.)
 - S-010, CBE labeling supplement for the addition of priapism to a new "Postintroduction Reports" subsection in ADVERSE REACTIONS, submitted 13OCT98 and approved 11JAN99 (PV 2964 AMP).
 - Y-003 (Annual Report) includes Insert PV 2965 AMP which corrects misspelling of the trademark ZYPREXA in PV 2964 AMP, effective 05NOV99.
- **Changes to the current agreed upon labeling** for S-006 also include information related to the following two supplements which have been superseded or withdrawn:
 - S-008, labeling supplement for revision of the Geriatric Use subsection in conformance with the Geriatric Labeling Final Rule, submitted 26AUG98. The revisions proposed in S-008 are addressed and **superseded** by the inclusion of language relevant to [] (see below) in the agreed upon labeling text for the current action (S-006). See CSO Labeling Review and Action Letter.
 - [] [] the supplement provided additional safety and efficacy data which have been incorporated into the agreed-upon final labeling for S-006.
- As noted above, inserts PV 2963-F AMP and 3330-A AMP are draft inserts only and include the applicant's proposed / revised proposed language for the bipolar indication.

CSO LABELING REVIEW:

Approved inserts: PV 2965 AMP vs. PV 3330 AMP.

A line by line comparison of the prior approved label PV 2965 AMP and the current label PV 3330 AMP indicated the following changes (all are described with reference to PV 3330):

- **DESCRIPTION:** 15 mg strength added; "color mixture white" deleted from list of inactives; titanium dioxide listed; FD&C Blue No. 2 Aluminum Lake listed as colorant in tablet coating (15 mg) and printing ink (all other strengths).
- **CLINICAL PHARMACOLOGY:** No observed changes.
- **INDICATIONS AND USAGE:** No observed changes.
- **CONTRAINDICATIONS:** No observed changes.

- severity of AEs by body system within this section)
- Dosage and Administration (Bipolar Mania subsection)
 - superseded supplement S-008 affects:
 - Precautions (*Geriatric Use* text))
 -
 - Precautions (*General - Dysphagia, Use in Patients with Concomitant Illness, Geriatric Use*)
 - Adverse Reactions (including tables, *Other Adverse Events Observed During the Clinical Trial Evaluation* section, revisions to reported frequency, severity of AEs by body system)

Some additional text rearrangements have been incorporated for clarity. See clinical reviews for more detail on the basis of the revisions.

Recommendation: It is recommended that the agreed-upon labeling text be implemented as it stands in the approval letter for NDA 20-592/SE1-006. Implementation of the package insert revisions for S-006 supersedes the Geriatric Labeling text revisions proposed by the applicant in S-008 and includes information relevant to the use of the drug in Alzheimer's dementia, as presented in .

Reviewer: Doris J. Bates, Ph.D., RMO



Concurrence: John S. Purvis, Chief, Project Management Staff



attachments (for copy to original NDA file after review concurrence):

1. S-008 Cover Letter
2. FAX from applicant, 29FEB2000
3. Agreed-upon labeling (printout)
4. Labeling change summary from applicant, March 3, 2000

NDA 20-592 / SE1 - 006, SLR-008
ZYPREXA® (olanzapine) Bipolar Disorder

PAGE 5
CSO Labeling Review

CC:
Orig NDA (with attachments as above) SE1-006, SLR-008
HFD-120 Division File
HFD-120/Purvis/Bates
HFD-120/20-592/s-006 action package, labeling subsection

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FACSIMILE TRANSMISSION

Eli Lilly and Company
Lilly Research Laboratories

U.S. Regulatory Affairs
Phone No. (317) 276-5185
FAX (317) 276-1652

CONFIDENTIAL

CONFIDENTIAL



TO: Dr. Doris Bates

FROM: John Roth

COMPANY: FDA

PHONE #: 317-433-3523

FAX #: 1-301-594-2859

DATE: 3-3-00

Number of Pages: 3
(Including cover sheet)

Message: Doris - As we discussed, I'm faxing
the labeling summary for versions PV2963AMP
and later. Please let me know if this is the
information you need. Thanks for your help and
enjoy your weekend.

IMPORTANT CONFIDENTIALITY NOTICE

The documents accompanying this telecopy transmission contain confidential information belonging to the sender which is legally protected. The information is intended only for the use of the individual or entity named below. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this telecopy information is strictly prohibited. If you have received this telecopy in error, please immediately notify us by telephone (collect) to arrange for return of the telecopied documents to us.

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

Correspondence : Fax re: Labeling (3/3/00)

NDA 20-592/8006

FACSIMILE TRANSMISSION**Eli Lilly and Company
Lilly Research Laboratories**U.S. Regulatory Affairs
FAX (317) 276-1652

CONFIDENTIAL

CONFIDENTIAL

**To: Doris Bates, Ph.D., FDA****FAX #: 301-594-2859****Date: February 29, 2000****From: Greg Brophy, Ph.D, Eli Lilly & Co.****Phone #: 317-277-3799****Re: NDA 20-592 – Zyprexa® (olanzapine) – Supplement 006 (Bipolar Mania)****Agreement with FDA's Labeling Edits Faxed to Lilly on February 28, 2000****Agreement with FDA's Proposal to Supercede S008 with S006**

This fax is in response to:

- The Division's February 28, 2000 fax of revised labeling for the subject supplemental NDA incorporating the suggested editorial corrections suggested in our February 28, 2000 fax.
- The proposal made by Dr. Doris Bates of the Division to supercede the *Geriatric Use* subsection labeling changes proposed in Lilly's previously submitted Geriatric Labeling Supplement (S008 to NDA 20-592; submitted August 26, 1998) with the currently agreed upon *Geriatric Use* subsection labeling in the subject supplemental NDA.

We have reviewed the Division's faxed labeling incorporating our suggested editorial corrections and are in total agreement with this version.

We have also considered the Division's proposal to supercede S008 with the currently agreed upon *Geriatric Use* subsection labeling in the subject supplemental NDA. The primary reason for submitting S008 was to comply with the geriatric final rule (Federal Register Notice, August 27, 1997, Docket No. 89N-0474). It is our understanding from the Division's proposal that you consider the currently agreed upon labeling in the subject supplemental NDA to be in compliance with the geriatric final rule. Accordingly, we are in full agreement with your proposal to supercede S008 with the currently agreed upon labeling in the subject supplemental NDA.

We thank you very much for your continued cooperation during the review of this application. Please call Dr. John Roth at (317) 433-3523 or me at (317) 277-3799 if there are any questions.



Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

**PHASE 4 COMMITMENT
FDA Response Requested**

February 25, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-592, ZYPREXA® (olanzapine) – S006 (Bipolar Mania)

We are enclosing our plan to address the Phase 4 commitment requested in your October 28, 1999 approvable letter for the referenced supplemental NDA. The enclosed Note to Reviewers provides a brief overview of our plan, and the enclosed Attachment provides a more detailed summary. We are requesting the Division's review and response regarding the acceptability of our proposed plan for its intended purpose.

We thank you for your continued cooperation and assistance and ask that you please call Dr. John Roth at (317) 433-3523 or me at (317) 277-3799 if there are any questions. We look forward to working with you on this important matter.

Sincerely,

ELI LILLY AND COMPANY

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

Enclosure

Redacted 21 page(s)

of trade secret and/or

confidential commercial

information from

*Administrative +
Correspondence: Phase 4 Commitment (2/25/00)*

**Meeting Minutes, Discussion of Response to AE Letter
NDA 20-592/SE1-006
Zyprexa (olanzapine) in Treatment of Bipolar I Disorder
Eli Lilly & Co.**

Date/Time/Site: 5 January 2000, 10:00 a.m., WOC II 4037

Participants: R. Katz, T. Laughren, P. Andreason, J. Ware (meeting recorder).

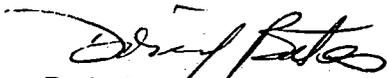
Draft: 25 February 2000, by D. Bates

Final:

Background: An approvable letter, with draft labeling, was issued for this supplement on October 28, 1999. Lilly notified the Division of their intent to amend the supplement in a letter dated October 26, 1999. Additional information on safety of the drug in the Alzheimer's Dementia population was provided by Lilly on November 24, 1999 and the response to the approvable letter was received December 23, 1999. The response package includes the complete revised labeling proposals from the applicant, and was distributed to Drs. Katz, Laughren, Hearst, Andreason, Mosholder, and Burkhart for further reference.

Discussion: It was agreed by all participants that the December 1999 submission constituted a complete response to the approvable letter.

Decisions/Action Items: The final proposed labeling will be drafted and FAXed to Lilly, with revisions as agreed upon in the December 15, 1999 meeting on the safety package. per Division policy, negative study results will be included in the clinical trials section of the labeling, and secondary outcome measures will not be discussed. A change in the indication from antipsychotic to antischizophrenic will be proposed as part of the final labeling.


Doris J. Bates, PhD, RPM
for the attendees

 2-25-00
Thomas P. Laughren, MD
Team Leader, Psychiatric Drugs
Group

Post meeting note: A teleconference was held on February 22, 2000 between representatives of Lilly and the FDA clinical review team. On February 23, 2000, following a face to face meeting on another olanzapine indication, it was further discussed, and agreed, that the indication would not be revised to antischizophrenic at this time.

NDA 20-592 / SE1-006

Olanzapine in Bipolar I

Resubmission Filing Meeting 2

CC:

HFD-120/Original NDA Efficacy Supplement

HFD-120/Division File

/Katz

/Laughren/Hearst/Andreason/Mosholder

/Burkhart

/Bates *JB 25 FEB 2000*

ELECTRONIC MAIL MESSAGE

Date: 12-Jan-2000 12:45pm EST
From: Doris Bates
BATESD
Dept: HFD-120 WOC2 4034
Tel No: 301-594-5536 FAX 301-594-2859

TO: Thomas Laughren (LAUGHREN)
TO: Earl Hearst (HEARSTE)
TO: Paul Andreason (ANDREASONP)
CC: Andrew Mosholder (MOSHOLDERA)
CC: Greg Burkhardt (BURKHARTG)

Subject: Zyprexa Information FYI and Feedback

NDA 20-592/S-006: Telecon, 12JAN00, 12:30 p.m.
D. Bates to J. Roth, 317.433.3523

This email documents that I have spoken with John Roth of Lilly, re the Zyprexa resubmission of 22DEC99. He is aware that we have accepted this submission as a complete response and are engaged in review.

He informed me that Lilly had strong hopes of resolving further issues very quickly and that the launch date had been tentatively set for the end Feb 2000. He asked if this date was realistic and I noted that, having been out, I could not answer this off the cuff but that I was under the impression there were other related review issues (DDMAC) which would also need to be addressed.

If acceptable, I will follow up to inform him that our time frame for the labeling review is likely to be later than end February.

Please let me know if a telecon or meeting should be needed to address any labeling review issues with the firm.

58.1



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN - 6 2000

NDA 20-592/S-006

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

Dear Dr. Brophy:

We acknowledge receipt on December 23, 1999 of your December 22, 1999 resubmission to your supplemental new drug application for ZYPREXA (olanzapine) Tablets, 2.5, 5, 7.5, and 10mg.

This resubmission contains additional clinical information submitted in response to our October 28, 1999 action letter.

With this amendment, we have received a complete response to our October 28, 1999 action letter.

If you have any questions, call Doris J. Bates, Ph.D., Project Manager, at (301) 594-5536.

Sincerely,

A handwritten signature in dark ink, which appears to be "JSP", is written next to the date "1/6/00".

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA 20-592/S-006
Page 2

cc:

Archival NDA 20-592

HFD-120/Div. Files

HFD-120/D.Bates

HFD-120/Laughren/Andreason/Hearst

JPD 1-6-00

DISTRICT OFFICE

Drafted by: jhw/January 5, 2000

Initialed by:

final:

filename: ZYS6AZAC.LTR

RESUBMISSION ACKNOWLEDGEMENT (AC)

Meeting Minutes, Labeling Discussion
NDA 20-592/SE1-006
Zyprexa (olanzapine) in Treatment of Bipolar I Disorder
Eli Lilly & Co.

Date/Time/Site: 15 December 1999, 2:00 p.m., WOC II 4037

Participants: R. Katz, T. Laughren, P. Andreason, A. Mosholder, E. Hearst, D. Bates (meeting recorder). Absent: G. Burkhart

Draft: 29 December 1999

Final:

Background: The efficacy supplement provides for the use of olanzapine in the treatment of bipolar 1 disorder. An approvable letter, with draft labeling, was issued for this supplement on October 28, 1999. Lilly notified the Division of their intent to amend the supplement in a letter dated October 26, 1999.

On November 12, 1999, Dr. C. Beasley and A. Breier of Lilly participated in a teleconference with Dr. T. Laughren in order to discuss the proposed draft labeling as specifically related to safety in patients with dementia of the Alzheimer's type (study HGEU). In the course of this discussion, Lilly proposed deferral of implementation for these labeling revisions and agreed to provide additional information pertinent to their request. This additional information was received November 24, 1999; it includes

- case reviews of all deaths associated with or occurring within 30 days of the acute double-blind phase of Study HGEU
- a revised comprehensive table of treatment-emergent adverse events in study HGEU. Note that the applicant cites errors in the relevant database for this study as the basis for revision of this table.
- revised tables of treatment-emergent adverse events for study HGEU re:
 1. events with two or more occurrences and more occurrences than placebo
 2. dose-dependent AEs
 3. most frequent AEs in all groups (at least 2x incidence on placebo)
 4. AE incidence in combined groups (at least 2x incidence on placebo)
- case summary data, including CRF safety information, ClinTrace summaries, and MEDWATCH forms, for all patients who died during the acute double-blind portion of the study

The November 24 submission was not intended to be a response to the Division's approvable letter, and was clearly marked as such. That response was received December 23, 1999, includes the complete revised labeling proposals from the applicant, and has been distributed to Drs. Katz, Laughren, Hearst, Andreason, Mosholder, and Burkhart for further reference.

Discussion: It was noted that the geriatric dementia population is highly vulnerable to aspiration pneumonia. Although the applicant presents detailed case histories for all five deaths associated with the acute double-blind phase of the study, and argues that these deaths follow markedly different clinical courses, the Division observed that dysphagia are which increase the risk of aspiration in precisely this population. Also, it was noted that, although the five deaths occurred at markedly different times during or within 30 days of the acute double-blind phase of the study, all five patients who died had been

receiving drug during this phase; there were deaths in all dose groups (5, 10, 15 mg) with a slight excess in the mid-dose group (3 deaths as opposed to one each in the low and high-dose groups).

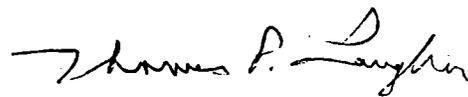
Decisions/Action Items: It was agreed that, based on the data provided by the applicant, the Division can make the following changes to the proposed olanzapine labeling:

-
-
- strengthen the language related to dysphagia in the Precautions section of labeling
-

In addition, it was agreed that we would request Lilly to evaluate the five deaths from the standpoint of total exposure time, ranked by dose. Finally, it was noted that risperidone use appears to carry similar risks for the geriatric dementia population; the Division will therefore address the risperidone labeling at this time.

A letter will be drafted conveying the new proposals for labeling revisions and our request for further evaluation of the five deaths, as discussed above.


Doris J. Bates, PhD, RPM
for the attendees

 2-3-00
Thomas P. Laughren, MD
Team Leader, Psychiatric Drugs
Group

Post meeting note: Because the applicant's complete response to the Division's approvable letter has now also been received by the Division, action on both submissions may be combined if appropriate. There is no official classification of response types for efficacy supplements; an internal review timetable of six months or less generally applies.

CC:

HFD-120/Original NDA Efficacy Supplement

HFD-120/Division File

/Katz

/Laughren/Hearst/Andreason/Mosholder

/Burkhart

/Bates

HFD-710/Jin/He

1/13/00

2/29/99



Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

December 22, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

RESPONSE TO APPROVABLE LETTER

Re: NDA 20-592, Zyprexa® (olanzapine) – S006 (Bipolar Mania)

We are providing the following complete response to your October 28, 1999 approvable letter for the referenced supplemental NDA. Please note our October 29, 1999 submission to the referenced NDA notifying you of our intent to amend the referenced supplement.

Attachment 1 provides our response to your proposal for the revised labeling of Zyprexa. Included is our revised labeling proposal, as well as a detailed explanation of our suggested revisions to your proposal. An electronic copy of our revised labeling proposal is also being provided for convenience on the enclosed computer diskette (WORD 6.0 format).

Attachment 2 provides our response to your request related to pediatric studies.

Attachment 3 provides our response to your request for additional information for Studies HGEH and HGGW.

In light of our ongoing labeling discussions with the Division, draft copies of introductory promotional materials are not yet available. However, final materials will be submitted with Form 2253 at the time of first use pursuant to regulatory requirements.

We respectfully request a meeting or conference call with Division representatives to discuss any disagreements concerning our draft labeling response or to clarify any other issues prior to the approval of the referenced supplemental NDA.



Eli Lilly and Company
Pharmaceutical Division

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

November 23, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

**Re: NDA 20-592, Zyprexa® (Olanapine) – Supplement 006 (Bipolar Mania) –
General Correspondence**

Please refer to your October 28, 1999 approvable letter for the referenced supplemental NDA. Please refer also to the November 12, 1999 telephone conversation between Dr. Tom Laughren (FDA) and our Drs. Charles Beasley and Alan Breier. In this conversation certain aspects of the draft labeling accompanying your October 28 letter were discussed. It was agreed that Lilly would promptly submit information pertinent to this discussion.

This submission is not a response to the October 28 approvable letter for bipolar mania. In the future a complete response to that approvable letter will be submitted.

The attached document provides the information we committed to provide in the November 12 conference call.

Your prompt review of the information provided herein would be appreciated.

Please call Dr. Al Webber at (317) 276-4255 or me at (317) 277-3799 if there are any questions. Thanks you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY



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

cc: Dr. Doris Bates (six sets of two volumes, shrink-wrapped)

FACSIMILE TRANSMISSION**Eli Lilly and Company
Lilly Research Laboratories**

U.S. Regulatory Affairs
FAX (317) 276-1652

CONFIDENTIAL**CONFIDENTIAL****To: Doris Bates, Ph.D., FDA****FAX #: 301-594-2859****Date: 23 August 1999****From: Greg Brophy, Ph.D, Eli Lilly & Co.****Phone #: 317-277-3799****Re: NDA 20-592 – Zyprexa® (olanzapine) – Supplement 006 (Bipolar Mania)****Labeling teleconference scheduled for 10:30 AM, Tuesday, February 22, 2000**

This is regarding the teleconference scheduled for Tuesday, February 22, 2000, to discuss Lilly's response to the Division's labeling proposal for the subject supplemental NDA, which was faxed to Lilly on Tuesday, February 15, 2000. We are providing a list of the anticipated participants and a summary of the points we plan to discuss during this teleconference. It is our understanding that the Division will telephone Lilly to initiate the teleconference. The telephone number for the meeting room we will be using at Lilly is 317-276-6682.

Teleconference Participants

FDA

Paul Andreason, M.D.; Doris Bates, Ph.D.; Earl Hearst, M.D.; Tom Laughren, M.D.

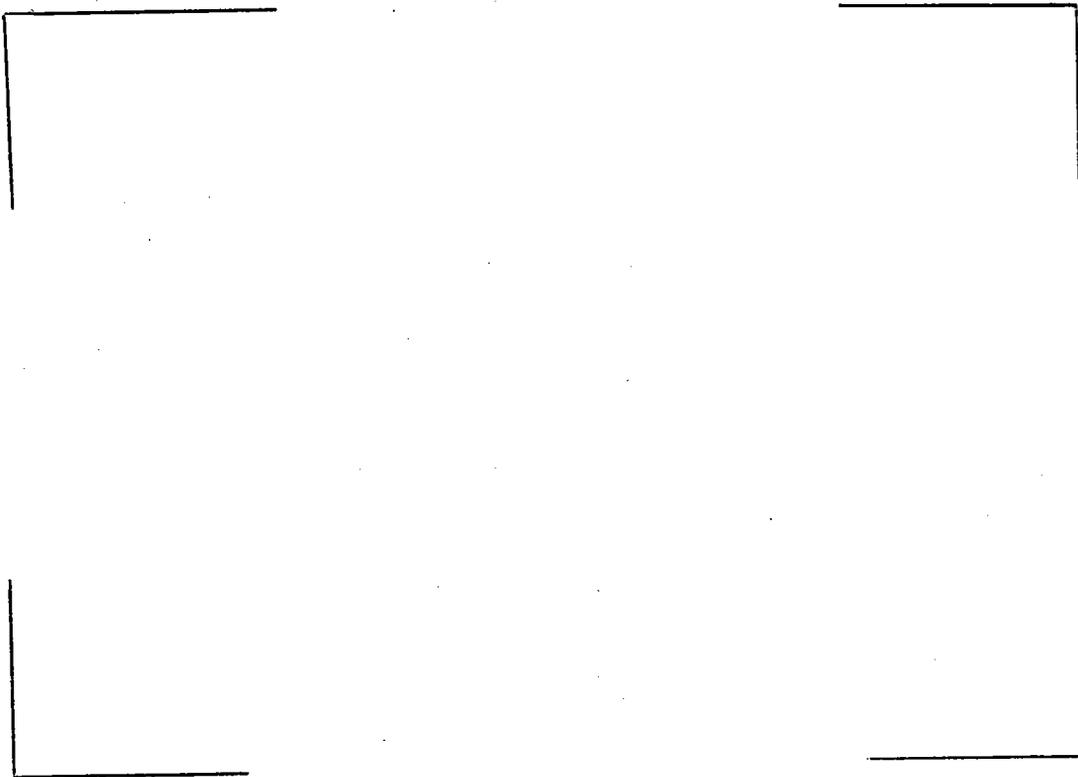
Lilly

Robert Baker, M.D.; Alan Breier, M.D.; Charles Beasley, M.D.; Greg Brophy, Ph.D.; John Hayes, M.D.; Jack Jordan; John Roth, Ph.D.; Todd Sanger, Ph.D; Mauricio Tohen, M.D.

Discussion Topics

We have carefully reviewed the Division's proposed labeling text and appreciate the Division's timely and thorough review. We agree for the most part with the Division's proposed labeling. However, as summarized below, there are a few proposed revisions we wish to discuss further during the teleconference. Our labeling proposals pertaining to each of the discussion topics are provided as attachments. In our labeling proposals, all text previously agreed to by the Division is shown in normal font. Changes from the revised labeling in the Division's February 15, 2000 fax are shown as strike-through font for deletions and as double-underlined font for additions.

1.



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

*Administrative &
Correspondence: Labeling Teleconference (8/23/99)*



Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

April 12, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn.: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-592, Zyprexa® (olanzapine) – Amendment to Supplement 006

Enclosed is an amendment to Supplement 006 (for the referenced NDA), submitted December 3, 1997. Supplement 006 received a not-approvable letter dated October 2, 1998.

The enclosed provides the results from study HGGW. It also provides a complete response to the October 2, 1998 not-approvable letter.

This amendment is formatted and organized according to 21 CFR §314.50 and follows the "Guideline for the Format and Content of the Clinical and Statistical Section of New Drug Applications" and the "Guidelines on Formatting, Assembly, and Submitting New Drug and Antibiotic Applications." Cross-referencing to NDA 20-592 supports the enclosed amendment. Items 11 and 12 of the application, the Case Report Tabulations and the Case Report Forms, are provided as an electronic-only archival copy in accordance with the "FDA Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs".

The electronic archival copy of Items 11 and 12 is contained on one CDROM. This CD-ROM is being sent to the Center for Drug Evaluation and Research Central Document Room in accordance with the "FDA Guidance for Industry Providing Regulatory Submissions in Electronic Format – General Considerations". The CD-ROM has been checked and verified to be free of known viruses. This virus checking software was McAfee VirusScan 3.2.0 using Virus Definitions 3.0.3202 created on 15-Feb-1999.

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Reference is made to the agreement reached April 2, 1999, between Dr. Doris Bates, FDA, and Steve Ward, Lilly, to not submit an electronic copy of the complete NDA in Adobe Acrobat format as a review aid as was previously planned. If at a subsequent time the reviewers desire such an electronic review aid and feel it is appropriate within FDA to request one, Lilly will promptly submit these electronic files as a review aid under separate cover to Dr. Bates.

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

Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Any calls dealing with general issues, clinical reports, labels, or literature should be made to:

J. Alan Webber, Ph.D.
(317) 276-4255
 (home)

(Please address all facsimile (fax) transmission to Dr. Al Webber at (317) 276-1652, or, in his absence, to:

Gregory T. Brophy, Ph.D.
(317) 277-3799
 (home)

Any questions about the electronic submission should be directed to:

Steven T. Ward
(317) 276-2952
 (pager)

On holidays, Saturdays, or Sundays, call Dr. Webber or Dr. Brophy at home using the telephone numbers indicated.

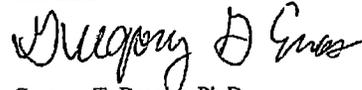
Close liaison between the Lilly personnel listed above will result in any messages, no matter how received, being brought to the attention of all concerned.

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Please call Dr. Al Webber at (317) 276-4255 or me at (317) 277-3799 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

A handwritten signature in black ink, appearing to read "Gregory T. Brophy". The signature is written in a cursive style with a large initial "G".

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

cc: Dr. Doris Bates - one vol. 1, one vol. containing ISE and ISS

Enclosures