DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592 / S-034
NDA 21-086 / S-015
NDA 21-253 / S-015

Eli Lilly and Co., Inc.
Attention: Robin Pitts Wojcieszek, R. Ph.
Associate Director, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285
USA

Dear Ms. Wojcieszek:

Please refer to your supplemental new drug applications (supplemental NDAs) dated June 1, 2005, received June 2, 2005 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) Tablets and Zyprexa Zydis (olanzapine orally disintegrating) tablets. Please also refer to your supplemental NDA submitted September 1, 2005, received September 2, 2005, for Zyprexa IntraMuscular (olanzapine for injection).

These supplemental NDAs provide for revision of labeling in the INDICATIONS AND USAGE, **Bipolar Disorder**, Combination Therapy section of the package insert to add the term "mixed or" between the words "acute" and "manic" in the first sentence.

We also acknowledge receipt of your secure e-mail correspondence dated August 31, 2005 and September 1, 2005. This correspondence references NDA 20-592 S-021 and NDA 21-086 S-005, which were found approvable on December 16, 2003, and acknowledged and retained on August 18, 2005 due to their supersession by the approval of NDA 21-253 on March 29, 2004.

We have completed our review of the above referenced June 1, 2005 supplemental applications, and they are approved.

We also wish to note for the record that specific revisions to the package insert to provide for labeling changes to the CLINICAL PHARMACOLOGY, *Pharmacodynamics* section, CLINICAL PHARMACOLOGY, *Special Populations Race* section, and the PRECAUTIONS, *Nursing Mothers* section, which were included in NDA 20-592 S-021, NDA 21-086 S-005, and your original NDA 21-253, are considered approved consequent to the approval of NDA 21-253.

Following is the approved labeling text for the above referenced sections of the package insert.

In the CLINICAL PHARMACOLOGY section, the first paragraph is modified and the term "-like" is added to the second sentence, third paragraph so that the text overall reads as follows:

CLINICAL PHARMACOLOGY

Pharmacodynamics

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$, (K_i=4, 11, and 5 nM, respectively), dopamine D_{1-4} (K_i=11-31 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors (K_i=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ (K_i=57 nM) and muscarinic M_{1-5} (K_i=73, 96, 132, 32, and 48 nM), respectively. Olanzapine binds weakly to $GABA_A$, BZD, and β adrenergic receptors (K_i>10 μM).

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

Antagonism at receptors other than dopamine and $5HT_2$ may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic-like effects. Olanzapine's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

In the **CLINICAL PHARMACOLOGY: Pharmocokinetics: Special Populations** section: between the Smoking Status and Combined Effects sections, the following statement is added:

Race - In vivo studies have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

In the **INDICATIONS AND USAGE**: **Bipolar Disorder:** Combination Therapy section, the first sentence is revised to include the term "mixed or" as shown:

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

In the **PRECAUTIONS: Nursing Mothers** section, the first sentence, first paragraph is replaced so that the text reads as follows:

Nursing Mothers

In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving olanzapine should not breast-feed.

The final printed labeling (FPL) must include language in the referenced sections that is identical to that presented above. These revisions are terms of the approval of these applications.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this/these submission(s) "**FPL for approved supplements NDA 20-592 / S-034, 21-086 / S-015, and 21-253 / S-015**." Approval of this/these submission(s) by FDA is not required before the labeling is used.

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

MEDWATCH, HFD-410
Food and Drug Administration
VIA Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

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

If you have any questions, please contact Steven D. Hardeman, R.Ph., Acting Chief, Project Management Staff (for the schizophrenia indication), or Doris J. Bates, Ph.D., Regulatory Project Manager (for the bipolar indication), at 301-594-2850.

Sincerely,

(See appended electronic signature page)

Thomas P. Laughren, M.D.
Acting Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Thomas Laughren
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