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 5HT₂A/₂C, 5HT₆ (Kᵢ=4, 11, and 5 nM, respectively), dopamine D₁-D₄ (Kᵢ=11-31 nM), histamine H₁ (Kᵢ=7 nM), and adrenergic α₁ receptors (Kᵢ=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT₃ (Kᵢ=57 nM) and muscarinic M₁-M₅ (Kᵢ=73, 96, 132, 32, and 48 nM), respectively. Olanzapine binds weakly to GABAₐ, BZD, and β adrenergic receptors (Kᵢ>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 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 may explain some of the other therapeutic and side effects of olanzapine. Olanzapine’s antagonism of muscarinic M₁-M₅ receptors may explain its anticholinergic-like 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.

In the CLINICAL PHARMACOLOGY: Pharmacokinetics: 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/

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Thomas Laughren
9/13/2005 07:58:31 AM