

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**20-592/S034**

**21-086/S015**

**21-253/S015**

***Trade Name:*** Zyprexa Tablets  
Zyprexa Zydis  
Zyprexa IntraMuscular

***Generic Name:*** (olanzapine)  
(olanzapine orally disintegrating)  
(olanzapine for injection)

***Sponsor:*** Eli Lilly and Co., Inc

***Approval Date:*** September 13, 2005

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**APPROVAL LETTER**



## CLINICAL PHARMACOLOGY

### Pharmacodynamics

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin 5HT<sub>2A/2C</sub>, 5HT<sub>6</sub>, (K<sub>i</sub>=4, 11, and 5 nM, respectively), dopamine D<sub>1-4</sub> (K<sub>i</sub>=11-31 nM), histamine H<sub>1</sub> (K<sub>i</sub>=7 nM), and adrenergic α<sub>1</sub> receptors (K<sub>i</sub>=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT<sub>3</sub> (K<sub>i</sub>=57 nM) and muscarinic M<sub>1-5</sub> (K<sub>i</sub>=73, 96, 132, 32, and 48 nM), respectively. Olanzapine binds weakly to GABA<sub>A</sub>, BZD, and β adrenergic receptors (K<sub>i</sub>>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<sub>2</sub>) 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<sub>2</sub> may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M<sub>1-5</sub> receptors may explain its anticholinergic-like effects. Olanzapine's antagonism of histamine H<sub>1</sub> receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α<sub>1</sub> 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

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/s/

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

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**MEDICAL REVIEW(S)**

## Review and Evaluation of Clinical Data

<b>Supplemental NDA</b>	NDA 20-592 SLR-034 NDA 21-086 SLR.-015
<b>Sponsor:</b>	Elli Lilly and Co.
<b>Drug:</b>	Olanzapine: Zyprexa® (oral tablets) Zyprexa® Zydis® (orally disintegrating tablet)
<b>Material Submitted:</b>	Prior Approval Labeling Supplement
<b>Correspondence Date:</b>	6/1/2005
<b>Stamp Date:</b>	6/2/2005

### I. Proposed Changes and Rationale/Documentation.

The purpose of this review is to assist the Team Leader and the Division Director in the regulatory processing of these Labeling Supplement NDA submissions (hard copy submission).

#### Proposed Labeling Changes in the Indications and Usage Section

The sponsor wants to add the term "mixed" to the Bipolar I-acute mania indication for the combination therapy subsection under "Indications and Usage" in labeling, as copied below (copied from page 7 of proposed-marked, labeling changes, provided in Attachment 1 of the submission):

Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA after achieving a responder status for an average duration of two weeks was demonstrated in a controlled trial (*see Clinical Efficacy Data under CLINICAL PHARMACOLOGY*). 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*).

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.

The efficacy of ZYPREXA in combination with lithium or valproate was established in two placebo-controlled (6-week) trials 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 sponsor explains that the term "mixed" was inadvertently left out "during labeling discussions" of proposed labeling for the efficacy supplement NDA 20-592 S018.

The following reasons for the proposed labeling change were found in the "Note-to-the-Reviewer" section of the current submission:

1. The sponsor notes that the second sentence of the subsection on the combination treatment indication (as shown above) describes the pivotal efficacy trials as including acute "mixed or manic" Bipolar I patients (see above copied labeling

text). Therefore, the insertion of “mixed” into the first sentence of this subsection (as above) would add “clarity,” according to the sponsor.

2. The sponsor notes that the monotherapy indication in this section of labeling uses the terms, acute “mixed” and “mania” for describing the indication in Bipolar I patients. This approved indication was supported by trials that included acute “mixed” and “manic” Bipolar I patients, similar to the patient population for the combination therapy trials that supported the combination treatment indication (except that the subjects of the combination treatment trials had to be “inadequately controlled” on lithium or valproate monotherapy, as described in approved labeling). Therefore, the insertion of “mixed” into the first sentence of this subsection (as above) would be more “consistent,” with the approved language for the monotherapy indication.

The undersigned reviewer also notes that the above pivotal efficacy trials supporting each of the monotherapy and combination treatment indications used the same primary efficacy variable, “a reduction of Y-MRS total score,” as described in approved labeling (as shown on page 5 of the sponsor’s marked version of proposed labeling in Attachment 1 of the submission).

## **II. Conclusions and Recommendations**

The sponsor’s proposal is acceptable for reasons that follow.

The patient population in pivotal trials for the combination treatment indication included acute mixed or manic patients, as with the monotherapy trials (except patients had to be valproate or lithium treatment resistant in the combination treatment trials). The total score on the Y-MRS was the primary efficacy variable for pivotal trials for both indications. On the basis of positive efficacy results the monotherapy indication was approved by the Division (DNDP) for acute mania or mixed Bipolar I. The combination treatment trials were also positive. Therefore, it is reasonable to describe the combination therapy indication as for the treatment of acute “mixed,” or manic Bipolar I, similar to that which is approved for the monotherapy indication.

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Karen Brugge, M.D.  
Medical Reviewer,  
FDA CDER ODE1 DNDP HFD 120

cc: HFD120, HFD 120/ P Andreason/K Brugge/D Bates/T Laughren

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/s/

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Karen Brugge  
7/26/05 03:38:24 PM  
MEDICAL OFFICER

Paul Andreason  
8/1/05 01:02:17 PM  
MEDICAL OFFICER

I agree with Dr Brugge that the term "mixed"  
may be added to the Indications section of  
labeling for Bipolar I mania. I think that  
this is consistent with our previous descriptions and  
it is already described in this manner in  
the clinical trials section.

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**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



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/s/  
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Doris Bates

8/31/2005 03:45:12 PM

CSO

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Entered in DFS on date of transmission.