



NDA 22-173

**NDA APPROVAL**

Eli Lilly and Company  
Attention: Gregory T. Brophy, Ph.D.  
Director, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your new drug application (NDA) received April 30, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zyprexa Relprevv (olanzapine) For Extended Release Injectable Suspension 210 mg, 300 mg, and 405 mg.

We acknowledge receipt of your submissions dated April 16, 2009, May 13, 2009, May 29, 2009, June 12, 2009, July 1, 2009, July 15, 2009, August 12, 2009, August 27, 2009, September 10, 2009, and December 2, 2009.

Your March 11, 2009 submission constituted a complete response to our December 15, 2008 action letter.

This new drug application provides for the use of Zyprexa Relprevv (olanzapine) For Extended Release Injectable Suspension for the treatment of schizophrenia in adults.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

#### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not

likely to be used in a substantial number of pediatric patients. The safety and effectiveness of oral ZYPREXA in the treatment of schizophrenia has been established in short-term studies in adolescents (ages 13 to 17 years).

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Zyprexa Relprevv (olanzapine) to ensure the benefits of the drug outweigh the risks of serious complications related to post-injection delirium/sedation syndrome (PDSS) listed in the labeling.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Zyprexa Relprevv (olanzapine) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Zyprexa Relprevv (olanzapine). FDA has determined that Zyprexa Relprevv (olanzapine) is a product for which patient labeling could help prevent serious adverse effects and has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use Zyprexa Relprevv (olanzapine). Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Zyprexa Relprevv (olanzapine).

We have also determined that a communication plan is necessary to support implementation of the REMS.

Pursuant to 505-1(f)(1), we have also determined that Zyprexa Relprevv (olanzapine) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate these risks listed in the labeling.

Your proposed REMS, submitted on March 11, 2009, amended on July 15, 2009, August 27, 2009, and September 10, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following information:

- a. Healthcare providers and patients' (or caregiver) understanding of the serious risks and conditions of safe use of Zyprexa Relprevv (olanzapine) through surveys.
- b. A description of specific measures that would be taken to increase awareness if surveys of healthcare providers indicate that provider awareness is not adequate.
- c. An assessment of enrollment and discontinuation statistics for certified prescribers, certified dispensers, and patients enrolled in the registry:

1. The number of patients enrolled in the Zyprexa Relprevv (olanzapine) Patient Care Program Registry (during the reporting period and cumulative).
  2. The number of person-years for enrolled patients.
  3. The number of patients who received Zyprexa Relprevv (olanzapine) that were not enrolled (during the reporting period and cumulative).
  4. The number of patients who stopped receiving Zyprexa Relprevv (olanzapine) (during the reporting period and cumulative).
  5. The number of prescribers enrolled in Zyprexa Relprevv Patient Care Program (during the reporting period and cumulative).
  6. The number of pharmacies enrolled in the Zyprexa Relprevv Patient Care Program.
  7. The number of pharmacies that dispensed Zyprexa Relprevv (olanzapine) that were not enrolled (during the reporting period and cumulative).
  8. The number of health care settings enrolled in the Zyprexa Relprevv Patient Care Program.
- d. Assessment of compliance with the requirement that Zyprexa Relprevv (olanzapine) is only dispensed from certified dispensers. This summary will include an assessment of the amount of drug shipped to each site compared to actual prescriptions dispensed and monitoring of variations in ordering patterns.
- e. Assessment of pharmacy and health care setting compliance to include, number and summary of instances where pharmacies and health care settings dispensed Zyprexa Relprevv (olanzapine) directly to the patient and corrective actions taken.
- f. Assessment of Healthcare setting compliance including:
1. Compliance with submission of completed Single or Multiple Patient Injection Forms.
  2. Evaluation of compliance with monitoring conditions through review of injection form and PDSS form responses.
    - Was the patient observed for at least 3 hours post-injection?
    - Was the patient accompanied from the facility?
    - Once a PDSS event was suspected, was the patient's monitoring initiated in a facility capable of resuscitation?
- Responses will be analyzed to determine the compliance level with these required monitoring conditions.
- g. Number of cases of PDSS reported during the reporting period and cumulatively.
- h. A narrative summary and analysis of all cases of PDSS (reported during the reporting period) based upon data provided by prescribers and healthcare facility staff reported on forms submitted to Lilly as part of the Zyprexa Relprevv (olanzapine) Patient Care Program Registry or information reported spontaneously to Lilly.
- i. Based on the information provided, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed will be included with each REMS assessment report.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are

meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Assessments of an approved REMS must also include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 22-173 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 22-173  
PROPOSED REMS MODIFICATION  
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 22-173  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA

2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

**DISSOLUTION METHOD AND SPECIFICATIONS**

The agreed upon dissolution method and specifications are:

1% Sodium Lauryl Sulfate in USP buffer pH 6.8 medium using USP Apparatus 4 (or Ph.Eur.2.9.3 Flow-Through Apparatus) at 3 ml/min flow rate.

**210 mg:**

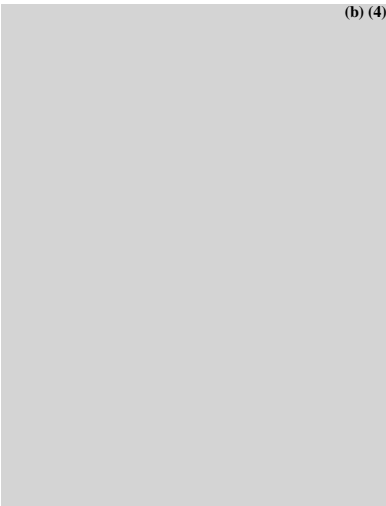
- % released at 30 minutes
- % released at 2 hours
- % released at 8 hours

**300 mg:**

- % released at 30 minutes
- % released at 2 hours
- % released at 8 hours

**405 mg:**

- % released at 30 minutes
- % released at 2 hours
- % released at 8 hours



**EXPIRY**

A 36 month expiry period is granted based on the available stability data.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm> that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “**SPL for approved NDA 22-173.**”

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels as agreed upon in your communication dated July 29, 2009 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 22-173.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **PROPRIETARY NAME**

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Psychiatry Products do not object to the use of the proprietary name, Zyprexa Relprevv (olanzapine), for this product.

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If, following issuance of the “Dear Health Care Professional” letter included as part of your REMS communication plan, you issue an additional letter communicating important safety related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to this NDA, to [CDERMedWatchSafetyAlerts@fda.hhs.gov](mailto:CDERMedWatchSafetyAlerts@fda.hhs.gov), and to the following address:

MedWatch  
Food and Drug Administration  
Suite 12B-05  
5600 Fishers Lane  
Rockville, MD 20857

### **REPORTING REQUIREMENTS**

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

### **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive

copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

If you have any questions, call Keith Kiedrow, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1924.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.

Director

Division of Psychiatry Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Enclosures

Content of Labeling

Medication Guide

REMS

DHCP Letter

REMS Program Materials

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22173	----- ORIG-1	----- ELI LILLY CO	----- ZYPREXA/ADHERA

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS P LAUGHREN  
12/11/2009