021-253_ORIG APPROVAL_ PACKAGE.

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
21-253

Trade Name: Zyprexa IntraMuscular olanzapine for Injection

Generic Name: Olanzapine

Sponsor: Eli Lilly and Company

Approval Date: March 29, 2004

Indications: Provides for the treatment of agitation associated with schizophrenia and bipolar I mania.

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APPLICATION NUMBER:

21-253

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	X
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology Review(s)	X
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative/Correspondence Document(s)	X

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APPLICATION NUMBER:

21-253

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-253

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

Dear Dr. Brophy:

Please refer to your new drug application (NDA) dated June 15, 2000, received June 16, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa IntraMuscular (olanzapine) for Injection.

We acknowledge receipt of your submission dated October 31, 2003, which constituted a complete response to our action letter of March 29, 2001.

This new drug application provides for the use of Zyprexa IntraMuscular (olanzapine) for Injection for the treatment of agitation associated with schizophrenia and bipolar I mania.

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

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 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 submission "**FPL for approved NDA 21-253.**" Approval of this submission by FDA is not required before the labeling is used.

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 are deferring submission of your pediatric studies for ages 13 to 17 years until November 30, 2006.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Deferred pediatric study under PREA for the treatment of agitation associated with schizophrenia in pediatric patients (adolescent schizophrenia) ages 13 to 17.

   Final Report Submission: November 30, 2006

2. Deferred pediatric study under PREA for the treatment of agitation associated with acute mania, as part of bipolar I disorder, in pediatric patients (adolescent bipolar disorder) ages 13 to 17.

   Final Report Submission: November 30, 2006

Submit final study reports to this NDA. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated "**Required Pediatric Study Commitments**".

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We grant a two year expiry.

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, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

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

Enclosure (labeling)

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

/s/

Russell Katz
3/29/04 12:03:48 PM

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APPLICATION NUMBER:

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APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-253

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

Dear Dr. Brophy:

Please refer to your new drug application (NDA) dated June 15, 2000, received June 16, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa IntraMuscular (olanzapine) for Injection.

We acknowledge receipt of the following submissions:

September 1, 2000	October 11, 2000	October 16, 2000
November 30, 2000	December 1, 2000	December 8, 2000
December 20, 2000	January 5, 2001	January 8, 2001
January 16, 2001	January 26, 2001	March 7, 2001
March 9, 2001	March 15, 2001	March 23, 2001

Please refer to your submission of March 9, 2001, submitted in response to our letter of February 27, 2001, in which we asked several questions related to the microbiology portion of your application. Your responses to our February 27, 2001, letter will be reviewed with your response to this action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, we have the following comments and requests for information:

Chemistry Deficiencies

As you know, you have received a Warning Letter from the Director of the Agency's Detroit District Office, dated 3/2/01, informing you of serious deviations from the Current Good Manufacturing Practice regulations in your firm's —— drug manufacturing operations located in Building —— on the Indianapolis campus. That letter outlined examples of the deficiencies found, with further deficiencies detailed in the FD 483 issued to you at the conclusion of the inspection performed from 1/29-2/23/01. Until you have responded to those deficiencies, and you have heard from the Agency that your responses are acceptable, this application cannot be approved.

Foreign Regulatory Update/Labeling

We require a review of the status of all olanzapine actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If olanzapine has been approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for olanzapine along with English translations when needed.

World Literature Update

Prior to the approval of olanzapine intramuscular, we require an updated report on the world archival literature pertaining to the safety of olanzapine. This report should include only literature not covered in your previous submissions. We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of olanzapine. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in pre-clinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the attached labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which should be 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.

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 submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
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 any 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.

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, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

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

47 page(s) of revised draft labeling has been redacted from this portion of the review.

Attachment A