

- ☐ How the participants will be recruited
- ☐ How and how often the surveys will be administered
- ☐ Explain controls used to minimize bias
- ☐ Explain controls used to compensate for the limitations associated with the methodology

- o The survey instruments (questionnaires and/or moderator's guide).
- o Any background information on testing survey questions and correlation to the messages in the Medication

Guide.

Sincerely,
Rimmy



Appendix A.pdf (62
KB)

*Renmeet Grewal, Pharm.D., LCDR USPHS
Team Leader, Senior Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838*

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/s/

Renmeet Grewal
3/16/2009 03:33:47 PM
CSO

David, Paul A

From: David, Paul A
Sent: Friday, February 20, 2009 5:54 PM
To: 'Christine Ann Phillips'
Cc: David, Paul A
Subject: More Work on the Project

Attachments: REMS template app A B 1-23-09.doc

Hello Christine,
Our Division of Risk Management (DRISK) is requesting that Lilly respond to the items, below, for your pending Zyprexa and Symbyax applications. Of course, we are on a time constraint, and we would appreciate a prompt response.
Regards,
Paul

- We are aware that the sponsor was not provided with a REMS template prior to submission of the REMS as part of their Complete Response. As a result, the proposed REMS does not follow the recommended format.
- We request that the sponsor revise and resubmit the proposed REMS to follow the template that the review division provides. We are attaching the REMS template below.
- We recommend the REMS goal be revised for [Zyprexa (olanzapine)] or [Symbyax (olanzapine and fluoxetine)], as follows:
The goal of the REMS is to inform patients of the serious risks associated with the use of [Zyprexa (olanzapine)] or [Symbyax (olanzapine and fluoxetine)], including the risks of hyperglycemia, hyperlipidemia, and weight gain.
- The sponsor's proposed timetable for assessments annually after approval of the REMS is acceptable; however, the assessments must be submitted separately and not as part of a Periodic Safety Update Report (PSUR). The sponsor should submit for review a detailed plan to evaluate patients' understanding about the safe use of [Zyprexa (olanzapine)] or [Symbyax (olanzapine and fluoxetine)] at least 2 months before they plan to conduct the evaluation. The submission should include:
 - All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of [Zyprexa (olanzapine)] or [Symbyax olanzapine and fluoxetine]. This should include, but not be limited to:
 - Sample size and confidence associated with that sample size
 - How the sample will be determined (selection criteria)
 - The expected number of patients to be surveyed
 - How the participants will be recruited
 - How and how often the surveys will be administered
 - Explain controls used to minimize bias
 - Explain controls used to compensate for the limitations associated with the methodology
 - The survey instruments (questionnaires and/or moderator's guide).
 - Any background information on testing survey questions and correlation to the messages in the Medication Guide.

- The sponsor needs to provide the information needed (methodology) to assess the effectiveness of the REMS for [Zyprexa (olanzapine)] or [Symbyax (olanzapine and fluoxetine)], as stated above, including an evaluation of:
 - Patients' understanding of the serious risks of [Zyprexa (olanzapine)] or [Symbyax (olanzapine and fluoxetine)]
 - A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
 - A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Of note, the sponsor's submitted

(b) (4)

This may not be used in place of actual assessments because the participants did not receive the approved Medication Guide.



REMS template app
A B 1-23-09....

CAPT Paul A. David, R.Ph.
Chief, Project Management Staff
Division of Psychiatry Products/HFD-130
Food and Drug Administration
10903 New Hampshire Avenue, Building 22, Room 4100 .
Silver Spring, Maryland 20993-0002

Phone: 301-796-1058
Fax: 301-796-9838
paul.david@fda.hhs.gov

11/25/08

APPENDIX A- REMS TEMPLATE

<<If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.>>

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

11/25/08

- A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;
- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following: Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval.

11/25/08

APPEARS THIS WAY ON ORIGINAL

11/25/08

Appendix B

REMS Supporting Document Template

This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Background
2. Goals
3. Supporting Information on Proposed REMS Elements
 - a. Additional Potential Elements
 - i. Medication Guide
 - ii. Patient Package Insert
 - iii. Communication Plan
 - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
 - c. Implementation System
 - d. Timetable for Assessment of the REMS
4. Information Needed for Assessments
5. Other Relevant Information

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/s/

Paul David
2/20/2009 06:04:47 PM
CSO

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, February 11, 2009 5:01 PM
To: 'Roland W Usher'
Cc: Bates, Doris J; Updegraff, Kimberly; Grewal, Renmeet
Subject: Important Notice: Psychopharmacologic Drugs Advisory Committee Meeting, June 9-10, 2009 [Zyprexa]

Importance: High

{Dear Mr. Usher: Please forward the attached notice to Dr. Phillips and Dr. Brophy as soon as possible; I am forwarding the message via your address for security reasons. Thank you very much!}

Dear Dr. Phillips and Dr. Brophy:

I am forwarding this message to your attention through Mr. Usher, to assure a secure email link for its transmission.

The Office of Drug Evaluation I / Division of Psychiatry Products has scheduled a Psychopharmacologic Drugs Advisory Committee (PDAC) meeting for June 9-10, 2009. The committee will discuss multiple supplemental NDAs, including your submissions:

NDA 21-592/S-040: Zyprexa (olanzapine) for the acute second line treatment of manic or mixed episodes associated with bipolar I disorder or schizophrenia in adolescents.

Arrangements for this PDAC are being managed by Dr. Kimberly Updegraff, Regulatory Health Project Manager, Division of Psychiatry Products. Please contact Dr. Updegraff directly with any specific questions you may have.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

Updegraff, Kimberly

From: Greeley, George
Sent: Thursday, August 20, 2009 7:19 AM
To: Updegraff, Kimberly
c: Stowe, Ginneh D.
Subject: NDA 20-592 Zypresa

Importance: High

Hi Kimberly,

The Zyprexa (olanzapine) partial waiver/assessment product was reviewed by the PeRC PREA Subcommittee on July 22, 2009. The Division recommended a partial waiver from birth to 12 years of age because too few children with disease/condition to study and completed studies for children 13-17 years of age.

The PeRC informed the Division that an expansion of the patient population is not a PREA trigger. The pediatric page for this supplement should reflect an assessment only.

The PeRC agreed the Division in the review of the assessment for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
0903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

 Please consider the environment before printing this e-mail.

Updegraff, Kimberly

From: Diaz, Jessica M
Sent: Friday, October 16, 2009 4:15 PM
To: Simon, Sarah
Cc: Dempsey, Mary; Updegraff, Kimberly; Karwoski, Claudia B; Griffiths, LaShawn
Subject: RE: NDA 020592 Zyprexa REMS Assessment/Modification Submission

Importance: High

Hello Sarah,

Good afternoon. Regarding the Zyprexa NDA 020592 REMS Assessment/Modification Submission from Eli Lilly and Company. We, DRISK, have reviewed the submission and the changes are in keeping with our recommendations in the Addendum dated 10-06-2009. The REMS Assessment/Modification Submission submitted by the applicant on 10/13/2009 is acceptable.

Please feel free to contact DRISK with any follow-up questions or concerns.

Best Regards,

Jess

LCDR Jessica M. Diaz, RN, BSN
Patient Product Information Reviewer
Division of Risk Management
FDA-CDER-OSE
301-796-4908 (Office)

-----Original Message-----

From: Simon, Sarah
Sent: Friday, October 16, 2009 3:08 PM
To: Updegraff, Kimberly
Cc: Dempsey, Mary; Diaz, Jessica M
Subject: RE: NDA 020592 Zyprexa REMS Assessment/Modification Submission

Hi Kim,

I got notification of this submission the other day and so Mary Dempsey and Jess Diaz are looking into it. They are still determining whether an email acknowledgement of acceptance of the changes will be sufficient or if a new review assignment will be generated. I will certainly pass along Drisk's decision on how they are going to handle it. Thank you for making sure I was aware of the submission!

Enjoy your weekend,
Sarah

-----Original Message-----

From: Updegraff, Kimberly
Sent: Friday, October 16, 2009 2:53 PM
To: Simon, Sarah
Cc: Updegraff, Kimberly
Subject: NDA 020592 Zyprexa REMS Assessment/Modification Submission

Dear Sarah,

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Tuesday, October 21, 2008 9:04 AM
To: 'Christine Ann Phillips'
Subject: FW: Zyprexa, Symbyax, Prozac submission in response to AE letter

Please forgive me. A correction to the PDUFA date: March 19, 2009.

Regards,
Rimmy

From: Grewal, Renmeet
Sent: Tuesday, October 21, 2008 8:58 AM
To: 'Christine Ann Phillips'
Subject: Zyprexa, Symbyax, Prozac submission in response to AE letter

Hi Christine,

Regarding your submission dated and received on September 19, 2008. After an initial review of the submission the agency has decided this is a complete response to the August 1, 2008 approvable letter. This is considered a class 2 submission and the PDUFA date is March 19, 2008, however if the agency completes its review prior to this date we will take an action.

Sincerely,
Rimmy

*Renmeet Grewal, Pharm.D., LCDR USPHS
Senior Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838*

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/s/

Renmeet Grewal
10/21/2008 09:06:54 AM
CSO

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Tuesday, October 21, 2008 8:58 AM
To: 'Christine Ann Phillips'
Subject: Zyprexa, Symbyax, Prozac submission in response to AE letter

Hi Christine,

Regarding your submission dated and received on September 19, 2008. After an initial review of the submission the agency has decided this is a complete response to the August 1, 2008 approvable letter. This is considered a class 2 submission and the PDUFA date is March 19, 2008, however if the agency completes its review prior to this date we will take an action.

Sincerely,
Rimmy

*Renmeet Grewal, Pharm.D., LCDR USPHS
Senior Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
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/s/

Renmeet Grewal
10/21/2008 09:02:36 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION		
TO (Division/Office): OSE/DRISK Attn: Mary Dempsey			FROM: OND/ODE1/DPP; HFD-130 From: Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager Through: Thomas Laughren, M.D., Division Director		
DATE 9/25/08	IND NO.	NDA NO. 20-592/s-039/040/041 21-520/012, 21-086/021, 18-936/077	TYPE OF DOCUMENT REMS: addition of a Medguide	DATE OF DOCUMENT 9/19/08	
NAME OF DRUG Olanzapine		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE PDUFA: 3-19-09 WANT TO ACT SOONER	
NAME OF FIRM: Eli Lilly					
REASON FOR REQUEST I. GENERAL					
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE/ADDITION ☐ MEETING PLANNED BY ☐ PRE-NDA MEETING ☐ END OF PHASE II MEETING ☐ RESUBMISSION ☒ SAFETY/EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☐ OTHER (SPECIFY BELOW):					
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH ☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):			STATISTICAL APPLICATION BRANCH ☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS					
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE IV STUDIES			☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
☐ CLINICAL			☐ PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Hi Mary, This is a response to an approvable letter sent (8-1-08) to the sponsor including a REMS to respond with a MEDGUIDE. The sponsor has responded to our approvable letter. Since this contains a medguide we are coding it a 6 month clock however we would like to act on these supplements sooner. I have attached the links to the sponsor's response. The network location for Zyprexa is : \\FDSWA150\NONECTD\N20592\S_040\2008-09-19 The network location for Symbyax is : \\FDSWA150\NONECTD\N21520\S_012\2008-09-19 The network location for Prozac is : \\FDSWA150\NONECTD\N18936\S_075\2008-09-19 If you have any further questions please contact me at either renmeet.grewal@fda.hhs.gov or 301-796-1080. Thanks, Rimmy					
SIGNATURE OF REQUESTER Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager 301-796-1080 Renmeet.grewal@fda.hhs.gov			METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

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/s/

Thomas Laughren
9/25/2008 05:47:53 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592/S-049
NDA 21-086/S-028
NDA 21-253/S-033

Eli Lilly and Company
Attention: Catherine A. Melfi, Ph.D.
Scientific Director, Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Melfi:

We acknowledge receipt of your supplemental new drug applications dated July 8, 2008, and received July 9, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) tablets (NDA 20-592), Zyprexa Zydis (olanzapine) orally disintegrating tablets (NDA 21-086), and Zyprexa IntraMuscular (olanzapine) injection (NDA 21-253).

Reference is also made to an FDA letter dated June 16, 2008 notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antipsychotic drugs. This information pertained to the warning regarding use of antipsychotics and increased mortality in elderly patients with dementia-related psychosis.

Your supplemental applications provide for revisions to the labeling for the Zyprexa product line consistent with our June 16, 2008 letter.

This supplemental new drug applications provide for the following changes to product labeling:

Under the **BOXED WARNING** section, the addition of a warning regarding increased mortality in elderly patients with dementia-related psychosis. [This new section will be added to the beginning of the label with bolded font and enclosed in a black box.]

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis —

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death)

or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Zyprexa (olanzapine) is not approved for the treatment of patients with dementia-related psychosis (*see* **WARNINGS**).

Under **WARNINGS** the language below will be implemented in bolded font in the **WARNINGS** section as the first paragraph in this section.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis —

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Zyprexa is not approved for the treatment of patients with dementia-related psychosis (*see* **BOXED WARNING**).

We have completed our review of these supplemental applications, and they are approved, effective on the date of this letter, for use as recommended in the above agreed-upon labeling text.

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(I)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). 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 supplements NDAs 20-592/S-049, 21-086/S-028, & 21-253/S-033.**”

In addition, within 21 days of the date of this letter, amend any pending applications for this NDA with content of labeling in structured product labeling (SPL) format to include the changes approved in these applications.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter and that the revised labeling be reflected in the next printing of the labeling. While you may use labeling already printed, we request that revised labeling accompany any newly shipped product within 60 days from the date of this letter.

Failure to make these changes promptly could make your product misbranded under Sections 201(n) and 502(a) of FDCA.

PROMOTIONAL MATERIALS

You must promptly revise all promotional labeling and advertising for this product to make it consistent with the labeling changes described above. These revisions should include prominent disclosure of the important new information described in the **BOXED WARNING** section that appear in the revised package labeling.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Psychiatry Products and two copies of both the promotional materials and the package insert(s) directly 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

LETTERS TO HEALTH CARE PROFESSIONALS

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

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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 LCDR Sonny Saini, Pharm. D., Safety Project Manager, at (301) 796-0532.

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

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/s/

Thomas Laughren
8/14/2008 08:25:40 PM

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF New Drugs
DIVISION OF Psychiatry Products**

NDAs: 21-520 (S-012), 20-592 (S-039, S-040, S-041), 21-086 (S-021)
PRODUCTs: Symbyax (fluoxetine/olanzapine) capsules
Zyprexa (olanzapine) tablets
Zyprexa Zydis
SPONSOR: Eli Lilly
REVIEWER: Mitchell Mathis, M.D.
DATE: July 31, 2008

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) for an approved drug if the FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)(2)]. Section 505-1(a) provides the following factors:

- A. The estimated size of the population likely to use the drug involved;
- B. The seriousness of the disease or condition that is to be treated with the drug;
- C. The expected benefit of the drug with respect to such disease or condition;
- D. The expected or actual duration of treatment with the drug;
- E. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- F. Whether the drug is a new molecular entity.

ZYPREXA (olanzapine) is approved for the treatment of schizophrenia as well as bipolar mania (monotherapy or in combination with lithium or valproate) in adults. SYMBYAX (olanzapine and fluoxetine in combination) is approved for the treatment of depressive episodes associated with Bipolar Disorder in adults.

The Division of Psychiatry Products (DPP) became aware of new treatment emergent safety signals of hyperglycemia, hyperlipidemia, and significant weight gain associated with olanzapine treatment. These data were presented in recent supplements for Zyprexa to treat adolescent schizophrenia and manic or mixed episodes of Bipolar I Disorder, and in a supplement for SYMBYAX to treat treatment resistant depression. Lilly provided additional data regarding hyperglycemia, hyperlipidemia, and significant weight gain associated with olanzapine treatment in submissions on September 10, 2007, October 4, 2007, November 1, 2007, December 19, 2007, February 1, 2008, February 5, 2008, May 12, 2008, and June 4, 2008. These data indicate that patients across the age spectrum

taking olanzapine are at increased risk of clinically important hyperglycemia, hyperlipidemia, and weight gain.

These new data have led DPP to conclude that olanzapine should be reserved for second line use in adolescents only after patients have failed to respond to already approved products. In addition, DPP has determined that patients (regardless of age and diagnosis) and their caregivers should be provided with a Medication Guide to help them understand these risks and how to manage them (including monitoring requirements for body weight as well as recommended serum glucose and lipid monitoring). After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of ZYPREXA and SYMBYAX outweigh the risks. As part of the REMS, DPP has determined that a Medication Guide should be developed to ensure patients and their caregivers are fully informed about the risks of olanzapine use.

- A. The number of patients with Schizophrenia or Bipolar Disorder in the United States is estimated to be about 6 million. Treatment resistant depression is estimated to afflict 4 million Americans.
- B. Schizophrenia, Bipolar Disorder, and treatment resistant Major Depressive Disorder represent major psychiatric illnesses which if left untreated result in enormous personal, family, and social disability.
- C. Use of ZYPREXA AND SYMBYAX to treat these disorders results in better control of symptoms, decreased hospitalizations, and return to more normal function.
- D. The expected duration of therapy with ZYPREXA or SYMBYAX is indefinite and may be lifelong.
- E. Known serious risks associated with the use of olanzapine include increased mortality and increased risk of stroke in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, hyperglycemia, hyperlipidemia, weight gain, tardive dyskinesia, orthostatic hypotension, seizures, impaired cognitive and motor function, and hyperprolactinemia.
- F. Olanzapine is not a new molecular entity.

In accordance with section 505-1 of the 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 AND SYMBYAX 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 these products. FDA has determined that ZYPREXA AND SYMBYAX are products that have serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use,

ZYPREXA OR SYMBYAX. In addition, patient labeling could help prevent serious adverse effects related to the use of the product.

The Medication Guide is being requested from sponsor due to the new safety information described above, and is will be considered to be part of a REMS. A timetable for submission of assessments of the REMS is also required, and shall be no less frequent than 18 months, 3 years, and 7 years after the REMS is approved.

The only elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of New Drugs

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/s/

Thomas Laughren
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MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592/S-039
NDA 20-592/S-040
NDA 20-592/S-041
NDA 21-520/S-012
NDA 21-086/S-021
NDA 18-936/S-077

Eli Lilly & Company
Attention: Christine A. Phillips, Ph.D., RAC
Manager, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Phillips:

We acknowledge receipt on February 1, 2008 of your February 1, 2008 resubmission to your supplemental new drug application S-012 for Symbyax (olanzapine / fluoxetine), NDA 21-520. We acknowledge receipt on February 4, 2008 of your February 4, 2008 resubmissions to your supplemental new drug applications S-039 for Zyprexa (olanzapine) Tablets, NDA 20-592, S-021 for Zyprexa (olanzapine) Zydis, NDA 20-186, and S-077 for Prozac (fluoxetine) Capsules, NDA 18-936. We also acknowledge receipt on February 5, 2008 of your February 5, 2008 resubmissions to your supplemental new drug applications S-040 and S-041 for NDA 20-592.

We consider these submissions to be complete, Class 2 responses to:

- our March 28, 2007 action letter for NDA 21-520 / S-012,
- our April 30, 2007 action letter for NDA 20-592 / S-040 and S-041, and
- our September 21, 2007 action letter for NDA 20-592 / S-039, NDA 21-086 / S-021, and NDA 18-936 / S-077.

Therefore, the user fee goal dates for these submissions will be:

- August 1, 2008 for NDA 21-520 S-012,
- August 4, 2008 for NDA 20-592 / S-039, NDA 21-086 / S-021, and NDA 18-936 / S-077, and
- August 5, 2008 for NDA 20-592 S-040 and S-041.

We do, however, request that you resubmit proposed labeling for all six supplements as soon as possible. We note that the proposed labeling currently provided in the resubmissions incorporates all Changes Being Effected language for the respective products that has been submitted to the Agency later than the March 28, 2007, April 30, 2007, or September 21, 2007 action letters, respectively, but that the labeling text does not highlight these CBE-related changes. We therefore request that you resubmit proposed labeling to these six supplemental applications that highlights all changes to labeling text that are not, at present, approved, for each product in question. Please annotate the

NDA 20-592/S-039
NDA 20-592/S-040
NDA 20-592/S-041
NDA 21-520/S-012
NDA 21-086/S-021
NDA 18-936/S-077

Page 2

marked up labeling to indicate which changes arise from submitted CBE language and which changes are responses to our March 28, 2007, April 30, 2007, or September 21, 2007 action letters.

If you have any questions, call either LCDR Renmeet Grewal, Pharm. D., Regulatory Project Manager, or Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 796-2260.

Sincerely,

{See Appended Electronic Signature Page}

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

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/s/

Thomas Laughren
2/26/2008 08:22:49 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592/S-039, 21-086/S-021, & 18-936/S-077

Eli Lilly & Company
Attention: Catherine A. Melfi, Ph.D.
Scientific Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Melfi:

Please refer to your supplemental new drug applications dated September 28, 2006, received September 29, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) tablets, Zyprexa Zydis (olanzapine) orally disintegrating tablets, and Prozac (fluoxetine hydrochloride) capsules.

We acknowledge receipt of your resubmission dated January 4, 2007, and received January 5, 2007.

We additionally acknowledge receipt of your submission dated March 21, 2007.

These supplemental new drug applications provide for the use of Zyprexa (olanzapine) tablets, Zyprexa Zydis (olanzapine) orally disintegrating tablets, and Prozac (fluoxetine) capsules for the co-administration of Zyprexa and Prozac for the treatment resistant depression (TRD).

We completed our review of these applications, and they are approvable. Before these applications may be approved, however, you must address the following deficiency:

Clinical studies for the TRD indication were submitted to the Symbyax (olanzapine/fluoxetine) application, NDA 21-520/S-012. The addition of TRD language to each of the individual components is dependent on this application. Therefore, we cannot approve these applications until we take an approval action on NDA 21-520/S-012 (Symbyax for treatment resistant depression).

Once we take a final action on the Symbyax TRD application, we encourage you to resubmit the above supplements.

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. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. 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.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, call LCDR Renmeet Grewal, Pharm.D. Senior Regulatory Project Manager., at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

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

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/s/

Thomas Laughren
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**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 29, 2007

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approvable actions for Zyprexa Pediatric Supplements for bipolar disorder (acute mania) and schizophrenia

TO: File NDA 20-592 (S-040 [bipolar] and S-041 [schizophrenia])
[Note: This overview should be filed with the 10-30-06 original submission of these supplements.]

1.0 BACKGROUND

Zyprexa (olanzapine) is an atypical antipsychotic (5HT₂ and D₂ receptor antagonist) that is approved for both schizophrenia and bipolar disorder in adults, including maintenance claims for both. We issued a written request (WR) for both indications, and these supplements are a response to that WR. The 10-30-06 response includes the results from acute studies in mania (HGIU) and schizophrenia (HGIN), and also pediatric PK data from study HGMP.

2.0 CHEMISTRY

The only CMC issue requiring review was environmental assessment. The sponsor sought and was granted a categorical exclusion.

3.0 PHARMACOLOGY

There were no pharm/tox issues requiring review for these supplements.

4.0 BIOPHARMACEUTICS

The sponsor utilized pk data from a formal pk study (HGMP) and also from 3 other studies (HGCS, HGCR, and HGCG) to characterize olanzapine pk in adolescents. Based on these data,

they concluded that overall olanzapine pk was similar in adolescents and adults, and that the one observed difference was greater exposure (by 27%) due to lower weights. Dr. Jackson from OCP agreed, except that he felt that the increased exposure by 27% was an underestimate. He estimated that exposure was increased by about 30-63%. This difference has resulted in a slight modification to the labeling regarding exposure.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review focused on 2 short-term, multicenter, double-blind, placebo-controlled, flexible-dose (2.5 to 20 mg/day), randomized, efficacy and safety studies in adolescents (ages 13-17). One of these studies was in patients with acute mania in bipolar I disorder (HGIU) and the other in schizophrenia (HGIN).

5.1.1 Study HGIU (Acute Mania in Bipolar I Disorder)

This was a 3-week study in bipolar I disorder patients with acute manic or mixed episodes. It was mostly conducted in the US (23 sites) but had 2 sites in Puerto Rico as well. N=161 patients were randomized, and the randomization was 2:1 for olanzapine vs placebo. The mean modal olanzapine dose was 10.7 mg, and the mean daily dose was 8.9 mg. The overall dropouts for this trial favored olanzapine (20% for olanzapine vs 35% for placebo). Of these, the dropouts were mostly for lack of efficacy (11% for olanzapine vs 30% for placebo). The primary endpoint was change from baseline to endpoint on an Adolescent Structured YMRS (total score) and the primary analysis was ANCOVA (LOCF). The results on this analysis were highly favorable to olanzapine ($p < 0.0001$), as were the results for the MMRM ($p=0.0004$) and the OC ($p=0.0013$). Drs. Alfaro, Kong, and Khin all considered this a positive study, and I agree.

5.1.2 Study HGIN (Acute Schizophrenia)

This was a 6-week study in adolescent patients with schizophrenia. It was conducted partly in the US (20 sites, comprising 53% of the total sample) and partly in Russia (5 sites, comprising 47% of the total sample). N=107 patients were randomized, and the randomization was 2:1 for olanzapine vs placebo. The mean modal olanzapine dose was 12.5 mg, and the mean daily dose was 11.1 mg. The overall dropouts for this trial again favored olanzapine (32% for olanzapine vs 57% for placebo). Of these, the efficacy dropouts were most striking, with a 51% loss due to lack of efficacy for placebo compared to only 14% for olanzapine. This finding by itself is almost enough, in my view, to convince one of the benefits of olanzapine in this condition. The primary endpoint was change from baseline to endpoint on a children's version of the BPRS (BPRS-C) total score, and the primary analysis was ANCOVA (LOCF). The overall results on this analysis were highly favorable to olanzapine ($p = 0.003$). However, there were 2 aspects to the data that the review team found troubling, resulting in conclusions by Drs. Alfaro, Kong, and Khin that this should be considered a negative study. Their concerns were as follows:

Highly Non-Significant Results on the MMRM and OC Analyses

Dr. Kong conducted an MMRM analysis as a sensitivity analysis, which yielded a p-value of 0.72. An OC analysis was also highly non-significant result ($p=0.95$).

Comment: In my tertiary evaluation, I found this discrepancy between LOCF and MMRM quite unusual, in my experience, and asked for further exploration. As it turned out, Dr. Kong's MMRM analysis was quite discrepant with the sponsor's MMRM analysis ($p=0.015$). Upon further evaluation, Dr. Kong discovered that the program he had used to conduct the analysis included, as a default, a variance-covariance structure that required independence between the repeated observations for any subject. This is an unusual requirement, and not the variance-covariance structure that we generally recommend. In fact, we almost always recommend an unstructured variance-covariance structure, i.e., the same one used by the sponsor, and a goodness-of-fit exploration for different variance-covariance structures revealed the best fit for this structure. Thus the biometrics group has now recommended that we accept the sponsor's highly significant MMRM result (see addendum to original biometrics review).

Regarding the OC analysis, this remains a discrepancy with the LOCF and the revised MMRM analyses. However, I am not as troubled by this outcome on the OC analysis. As noted, the dropouts on placebo were very substantial, and I'm inclined to view the patients completing a study such as this to 6 weeks on placebo as quite different than the remaining patients. I think the diagnosis of schizophrenia in this younger population is challenging, and likely results in the inclusion of some patients who improve spontaneously, and thus, are doing as well as drug-treated patients at 6 weeks simply because they represent a very different group of patients. This, I think the OC results for this trial can be largely discounted.

Treatment by Geographic Region Interaction

A second problem for the review team was a finding that the positive results were coming predominantly from the Russian sites. For this study, the total sample was roughly split between these 2 regions. Although olanzapine was favored over placebo numerically in both regions, the data from the Russian sites appeared to be driving the overall result:

- For the US patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -21 and -15, respectively ($p=0.258$).
- For the Russian patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -17 and -3, respectively ($p=0.003$).
- So the treatment effect in olanzapine patients was roughly the same in both regions, however, the placebo response was much larger in the US sites compared to the Russian sites.

Comment: In addition to the difference in outcome by region, Dr. Alfaro expressed concern that the Russian sites were far more successful in recruiting patients than the US sites. Implicit in such a concern is a suggestion of a problem in study conduct. It is important to note that we did have DSI inspect the Russian sites, and they found no evidence for fraud. It is also important to point out that there are alternative explanations for more successful recruitment at the Russian sites and also a more successful outcome. The sites may have been drawing patients from larger catchment areas than US sites, many of which were single investigators. There also may have been less competition for patients than is the case in the US. There are numerous studies ongoing in the US, and routine treatment is likely also more readily available in the US than in Russia. These same factors may also explain the different results. If difficulty in recruitment in the US sites led to enrollment of a more heterogeneous group of subjects, this could have led to a higher placebo response rate. It is possible that the Russian patients were the more representative schizophrenic patients who typically have very little response to placebo. There is also the expressed concern about relying primarily on non-US data for an approval action. Although I agree this is generally a concern, I think it is more a concern for an initial claim than it is in this case, where we already have a very strong prior belief that olanzapine is an effective treatment for schizophrenia, based on an abundance of positive data in adults. In summary, while I agree this geographic discrepancy is a concern, I do not think it is, by itself, a sufficient justification for a nonapproval action, when the trial is positive overall on the primary analysis and on the MMRM. Nevertheless, we will ask the sponsor to further address our concern about this discrepancy.

5.1.3 Summary of Efficacy

There is unanimous agreement within the review team on the positive outcome for study HGIU. For study HGIN, I disagree with the review team on the recommendation for a nonapproval action. One of the concerns, namely Dr. Kong's original finding on the MMRM, has now been addressed, and we are in agreement that an appropriate MMRM analysis yields a highly significant outcome. On the issue of geographic differences in outcome, I disagree that this is of sufficient concern to justify a nonapproval action. Nevertheless, we will ask the sponsor to further address this concern.

5.2 Safety Data

Safety data for these supplements were derived from the 2 pivotal controlled trials (HGIU and HGIN), and also from studies LOAY and HGMF. The combined total for these studies was n=454 patients, and this included 89 placebo patients from the 2 controlled trials. Thus, there were 365 olanzapine-exposed patients in this safety database. This included 136 patients who were treated with olanzapine for at least 23 weeks.

There were no deaths among the olanzapine-exposed patients. There were 44 serious adverse events, the majority of which represented a worsening of psychiatric symptoms. Overall, the profile of common and drug-related adverse events included events already well-recognized for olanzapine, i.e., increased appetite and weight gain, somnolence, sedation, fatigue, dizziness, and dry mouth. Other findings included the following:

-Weight Gain: For the 2 short-term trials (HGIU and HGIN), olanzapine patients gained almost 4 kg more than placebo patients ($p < 0.001$). Almost 44% of olanzapine patients gained $> 7\%$ of their body weight compared to only 7% of placebo patients ($p < 0.001$).

-Transaminase Increases: For the 2 short-term trials (HGIU and HGIN), 12% of olanzapine patients compared to only 2% of placebo patients had ALT increases to $> 3 \times \text{ULN}$ ($p = 0.009$). None of these patients had bilirubin abnormalities, and transaminase elevation is a well-known finding for olanzapine.

-Hyperprolactinemia: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in prolactin of 11.44 mcg/L compared to a decrease of -0.16 mcg/L for placebo ($p < 0.001$).

-Hyperlipidemia: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in triglycerides of 29.2 mg/dL compared to a decrease of -4.4 mg/dL for placebo ($p < 0.001$). For total cholesterol, olanzapine patients had a mean increase from baseline of 13.1 mg/dL compared to a decrease of -1.2 mg/dL for placebo ($p < 0.001$).

-Hyperglycemia: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in fasting glucose of 2.7 mg/dL compared to a decrease of -2.9 mg/dL for placebo ($p < 0.001$).

-Heart Rate Increase: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in heart rate of 6.3 bpm compared to a decrease of 5.1 bpm for placebo. These changes were thought to be related to orthostatic changes seen with olanzapine, especially early in treatment.

Summary of Safety Experience with Olanzapine in Adolescents: Overall, the adverse event profile and other safety parameters for olanzapine in the adolescent population is similar to that seen in adult patients treated with this drug, however, with some differences in magnitude. These differences will need to be reflected in labeling. In addition, we have recently asked the sponsor to provide more complete information generally with regard to effects on weight, glucose regulation, and lipid levels so that labeling for olanzapine can be enhanced with regard to these risks.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have asked the sponsor to make a number of changes, and in some cases, provide new information.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they reviewed the literature and found no relevant papers that would add important new information to the existing database regarding the safety of olanzapine in the treatment of schizophrenia or bipolar disorder in adolescents.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, olanzapine is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in adolescents.

8.0 DSI INSPECTIONS

Inspections were conducted at 2 US sites and at 2 Russian sites, and data from these sites were deemed to be acceptable.

9.0 LABELING AND APPROVABLE LETTER

10.1 Labeling

We have included an extensively modified version of labeling with the approvable letter.

10.2 Foreign Labeling

Olanzapine is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in adolescents.

10.3 Approvable Letter

The approvable letter includes our proposed labeling and requests for additional data.

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has submitted sufficient data to support the conclusion that olanzapine is effective and acceptably safe in the treatment of adolescents with schizophrenia and acute mania/mixed episodes in bipolar disorder. However, before we can take an approval action, the sponsor needs to respond to various requests we have made and we need to reach agreement on labeling. Thus, we will issue the attached approvable letter along with our proposal for labeling.

cc:

Orig NDA 20-592/S-040 and 041

HFD-130/TLaughren/MMathis/NKhin/CAlfaro/KKiedrow/DBates/SHardeman

DOC: Zyprexa_Peds_Laughren_AE_Memo.doc

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/s/

Thomas Laughren
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MEDICAL OFFICER



**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

Date: April 19, 2007

To: Thomas Laughren, M.D., Director
Division of Psychiatric Products, HFD-130

Through: Ellis Unger, M.D., Acting Deputy Director
Office of Surveillance and Epidemiology (OSE)

From: OSE Risk Management Team

Drug Name: Zyprexa (olanzapine)

NDA#: 20-592/SE5-040
20-592/SE5-041

Sponsor: Eli Lilly

OSE RCM#: 2006-1170

Subject: Review of proposed Risk Management Plan, submitted October 30, 2006

1 INTRODUCTION

This review follows a request from the Division of Psychiatric Products (DPP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Risk Management Plan (RMP) for oral olanzapine for use in adolescent populations with Schizophrenia or Bipolar Disorder.

Olanzapine (Zyprexa) is an atypical antipsychotic available as oral tablets, oral disintegrating tablets (Zyprexa Zydis), and as an intramuscular injection. It was originally approved on 9/30/1996 for the treatment of schizophrenia in adults. Olanzapine oral tablets are currently approved for the following indications in adults: treatment of schizophrenia, treatment of acute mixed or manic episodes associated with bipolar I disorder, maintenance monotherapy for bipolar I disorder, and combination therapy (with lithium or valproate) for the short-term treatment of acute mixed or manic episodes associated with bipolar I disorder.

Two efficacy supplements were submitted in the pediatric adolescent population (ages 13-17 years old). The Sponsor proposes the following indications, “Schizophrenia in adolescents” and “Acute mixed or manic episodes associated with bipolar I disorder in adolescents.” The current proposed indications are based on two pivotal studies (HGIN for adolescent schizophrenia and HGIU for adolescent bipolar disorder) and a pharmacokinetic study in the adolescent population.

2 MATERIALS REVIEWED

- Risk Management Plan For Zyprexa for oral Olanzapine for Use in Adolescent Populations with Schizophrenia or Bipolar Disorder, Manic or Mixed Episodes, submitted by Eli Lilly
- Alfaro C. Medical Officer’s Clinical Review of Zyprexa (olanzapine) NDA 20-592/SE5-040: Treatment of Bipolar I Disorder in Adolescents; review completion date 4/6/07.
- Alfaro C., Medical Officer’s Clinical Review of Zyprexa (olanzapine) NDA 20-592/SE5-041: Treatment of Schizophrenia in Adolescents; review completion date 4/6/07.
- Proposed Zyprexa Physician Labeling, submitted October 30, 2006.
- Guidance documents:
 - Development and Use of Risk Minimization Action Plans
<http://www.fda.gov/cder/guidance/6358fml.pdf>
 - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
<http://www.fda.gov/cder/guidance/6359OCC.pdf>

3 RESULTS OF REVIEW

3.1 Safety Risks

3.1.1 Sponsor’s Safety Concerns

The Sponsor specifically identified weight gain, sedation, and hyperprolactenemia as risks associated with olanzapine occurring at a higher frequency in the adolescent clinical trial database in comparison to the adult clinical trial database. Hepatic changes were also identified as an identified risk by the Sponsor. Because of the different reference ranges used for hepatic laboratory analyses in adolescent and adult patients, no analyses were performed to compare hepatic results between adolescent and adult patients. Other safety issues including glucose dysregulation and dyslipidemia occurred at lower frequencies in adolescents in comparison to adults. The potential drug interactions with olanzapine adolescents are thought to be similar as in adults.

Information provided in the Sponsor’s safety specification regarding the identified safety issues are summarized in the table below.

Safety Risk	Clinical Trials	Postmarketing
weight gain	• Significantly higher increases in weight gain for olanzapine	341/1450 case reports in adolescents had at least one

Safety Risk	Clinical Trials	Postmarketing
	compared to placebo at every visit - Greater incidence of treatment emergent weight gain $\geq 7\%$ (Placebo controlled trials: 43.5% OLA vs 6.8% PLA). In the entire adolescent database 65% of OLA treated adolescents had weight gain $\geq 7\%$ - Higher incidences of weight gain $\geq 7\%$ in adolescents than adults (65% adolescents versus ~36% adults)	MedDRA term related to weight gain.
sedation	- Overall 158 of 454 (38%) of olanzapine treated patients reported at least 1 sedation event. - Adolescents reported sedation 1.9x and somnolence 1.7x more frequently than adults	227/1450 case reports in adolescents had at least one MedDRA term related to sedation
hyperprolactinemia	55% of all olanzapine exposed patients had abnormally high prolactin levels, one dc'd txt - Higher incidence of high prolactin levels in adolescents (23% vs ~4% in adults)	116/1450 case reports in adolescents had at least one MedDRA term related to hyperprolactinemia
hepatic changes	- No Hy's rule cases - Significantly higher incidence of abnormal elevations in AST, ALT in olanzapine vs placebo treated patients. - No analyses comparing adolescents to adults	- One fatal case – adolescent male found dead; autopsy revealed hepatic steatosis 92/1450 case reports in adolescents had at least one hepatic-related MedDRA term 39% of these had clinically significant elevations (met definition of Hy's rule ALT/AST 3x ULN and TB 1.5 x ULN)
glucose dysregulation	parameters higher in adults in clinical trials	total of 95 postmarketing cases with AEs related to glucose dysregulation; 6 were fatal – the cause of death were reported in 3 diabetic ketoacidosis (2), necrotizing pancreatitis (1)
dyslipidemia	Clinical trials - Triglycerides higher in adolescents, LDL higher in adults	34 lipid related postmarketing reports

3.1.2 DPP Safety Concerns

The DPP medical officer, Cara Alfaro, reiterates the above concerns in her clinical reviews of the supplemental applications. According to the medical officer's review, the most common adverse events (> 5%, olanzapine > placebo) occurring in the pivotal trials were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

She considered weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia to be significant safety signals.

3.2 Sponsor's Proposed Risk Management Plan

3.2.1 Pharmacovigilance Activities

Eli Lilly proposes the following pharmacovigilance activities:



3.2.2 Risk Minimization Activities

Eli Lilly intends to utilize product labeling and customary prescriber education as the risk minimization tools to address all risks in adolescents specified in their submission. They did not propose a Risk Minimization Action Plan (RiskMAP) to address any of the identified risks.

4 DISCUSSION AND CONCLUSION

The Sponsor's goals and overall proposal are consistent with an enhanced pharmacovigilance and routine risk minimization activities. The proposal places particular emphasis on identifying the incidence and prevalence of identified risks and potential risks in adolescents in the postmarketing setting. At present, Zyprexa is marketed with an education-based risk management plan to address the potential medication errors with Zyrtec. There is no risk management plan or RiskMAP to address the safety issues identified in the Sponsor's submission or in the clinical review.

Based on the clinical review and email correspondence with the project manager, DPP plans to take a non-approval action for the schizophrenia indication in adolescents because the efficacy results were only statistically significant in patients enrolled in sites from Russia driven primarily by a low placebo response. DPP is also planning an approvable action for the bipolar indication because a number of requests for safety information and other analyses are required for approval.

Because additional data will be required to assess the primary safety issues described above, OSE will defer comment on the sponsor's submitted risk management plan at this time. A final discussion on the appropriateness of a RMP or Risk MAP will be undertaken after the sponsor submits a complete response to the action taken decided by the FDA.

OSE Risk Management Team

Claudia Karwoski, Pharm.D., Risk Management Team Leader, OSE-IO

Mary Dempsey, Risk Management Program Coordinator, OSE-IO

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/s/

Mary Dempsey
4/19/2007 12:01:46 PM
DRUG SAFETY OFFICE REVIEWER

Ellis Unger
4/19/2007 12:45:11 PM
MEDICAL OFFICER

Bates, Doris J

From: Bates, Doris J
Sent: Monday, March 19, 2007 4:06 PM
To: 'Catherine Melfi'
Cc: Alfaro, Cara; Khin, Ni Aye; Bates, Doris J
Subject: NDA 20-592 S-040 and S-041: Clinical Review Questions
Importance: High

Dear Dr. Melfi:

I am forwarding the following questions from our clinical review team. As previously, I am including the clinical review team members as CC recipients on this message. Please 'reply to all' in your response if you send an initial reply by e-mail; the official submission will need to be amended as well, for recordkeeping purposes.

1. For the Acute Placebo Controlled Combined Database, please provide a subgroup analysis for age (< 15 , ≥ 15) for the variable "weight in kg" similar to Table 2.7.4.70 in the summary-clin-safety document.
 2. Please provide a subgroup analysis for age (< 15 and ≥ 15) and gender for the variable "PCS weight change ($> 7\%$)" for the Acute Placebo Controlled Combined Database.
 3. It appears that the study report for HGIN includes all vital signs analyses for all subgroups (e.g. Table HGIN.14.47) while these analyses are only included in the study report for HGIU if the treatment by subgroups analysis was significant (e.g. HGIU.12.45). Please provide the subgroup analyses for HGIU similar to that provided in Table HGIN.14.47.
 4. In section 2.7.4.7.5 of the summary-clin-safe-app document, analyses are provided for suicide-related adverse events. In reviewing Table APP.2.7.4.7.5.9 (patients with possible suicidal behavior or ideation - combined database), there appear to be 3 cases that do not have narratives listed in this document or in the Table of Significant and Notable Patients document. Please provide case narratives for the following cases: HGMF-008-0805, LOAY-401-4012 and LOAY-407-4077.
 5. In the summary-clin-safe-app document, section 2.7.4.7.1.3.2.6 presents correlation coefficients between weight and a number of factors for the Overall Olanzapine Exposure Combined Database. Please provide these data for the Acute Placebo Controlled Database.
 6. In the summary-clin-safe-app document, section 2.7.4.7.1.3.3 compares data between the adolescent and adult populations. For these population comparisons, the Overall Olanzapine Exposure Combined Database is used. Is a comparison of these populations including only the acute, double-blind trial data available?
 7. In proposed labeling, some adverse events have been removed from the sections "other adverse events observed during the clinical trial evaluation of oral olanzapine" and "other adverse events observed during the clinical trial evaluation of intramuscular olanzapine for injection". In the former section, it appears that all of the frequently occurring AEs ("frequent") have been removed. In both sections, many adverse events that were included in the infrequent and rare categories have been removed. Please provide a justification for removal of these adverse events from proposed product labeling.
-

3/19/2007

Message copied and pasted to WORD and carriage returns inserted, because a software glitch has apparently eliminated automatic line breaks in the email text editor, resulting in text cutoff when the message is converted to .pdf format for DFS.

From: Bates, Doris J
Sent: Thursday, March 08, 2007 1:33 PM
To: 'Catherine Melfi'
Cc: Bates, Doris J; Kong, Fanhui; Alfaro, Cara
Subject: NDA 20-592: S-040, S-041: Additional URGENT Question from statistical review team
Importance: High

Dear Dr. Melfi:

Regarding the two efficacy supplements referenced above, we have another urgent question with respect to the statistical review. Please again feel free to reply via email initially, then amend the supplements accordingly.

It is claimed in the Clinical Study Report, that of the 161 randomized patients, 159 were analyzed for the primary efficacy measure. Two of the patients randomized to receive olanzapine did not have a post baseline observation that could be used for the primary efficacy analysis.

In addition, the primary analysis, LOCF mean change from baseline to Endpoint of the YMRS total score, was conducted without data from patients in Site 021.

Appendix 16.1.9 gives a list of patients who were excluded from efficacy analyses.

However, the primary efficacy results in the Study Report were based on the whole set of 161 patients. The YMRS total score data set provided to the Agency contained all 161 patients, with none excluded due to lack of baseline efficacy measure or post baseline efficacy measure.

Please clarify which set[s] of data, and how many patients in the respective dataset[s], were included in the performance of which specific analyses. If you could provide the patient numbers and site numbers, per dataset, for those patients excluded from the respective datasets/analyses, this would be very helpful.

Please feel free to contact me if you have any questions. I have again included both clinical and statistical reviewers in the CC line, along with myself, to speed any reply sent via email.

Thank you, and best regards,

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 18, 2007

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: NDA 20-592/SE5-040 (bipolar I disorder, acute mania)
NDA 20-592/SE5-041 (schizophrenia)
(This overview should be filed with the 10-30-2006 submission)

SUBJECT: Zyprexa (olanzapine)
Recommendation of 1) an approvable action - treatment of bipolar I disorder, acute mania in adolescents; and 2) a non-approvable action - treatment of schizophrenia in adolescents.

1. BACKGROUND

Zyprexa (olanzapine) is an atypical antipsychotic agent, approved in the U.S. for treatment of schizophrenia and bipolar disorder, mania or mixed episodes, as monotherapy (both acute and maintenance) or combination therapy in adults. It is available as oral 2.5, 5, 10, 15, or 20 mg strength tablets; 5, 10, 15, or 20 mg oral disintegrating tablets (Zydis). The usual oral dose range is 10-20 mg/day. Zyprexa intramuscular injection is indicated for agitation associated with schizophrenia and Bipolar I Mania. The recommended dose in these patients is 10 mg injection. Currently, none of the available atypical antipsychotic drugs are approved for treatment of schizophrenia or bipolar disorder in adolescents.

The Agency has issued a written request on 11/30/2001 under 505A(c) [patent or exclusivity protection] that the sponsor to conduct clinical trials for two indications: schizophrenia and bipolar disorder in adolescents. It was further amended on 4/9/02 (timeframe to submit study reports by 11/30/2006), 7/3/02 [informing notification requirement to the FDA when pediatric studies be initiated or not agree to conduct the requested studies according to the BPCA provision new section 505(d)(4)(A)], 5/7/04 (to include ethnic and racial minorities in accordance to the BPCA) and 6/29/05 (conduct as acute inpatient or outpatient trial).

The sponsor submitted the above referenced supplemental NDAs for schizophrenia and bipolar claim in adolescents on 10/30/2006. The application included the efficacy and safety result from protocols F1D-MC-HGIN and F1D-MC-HGIU for schizophrenia and bipolar indications, respectively. In addition, the sponsor also included PK results from study F1D-MC-HGMF.

The data submitted was reviewed by Cara Alfaro, Pharm.D., Clinical Reviewer, DPP (review dated 4/6/2007), Andre Jackson, Ph.D., Clinical Pharmacologist, Office of Clinical Pharmacology (review dated 3/27/07) and Fanhui Kong, Ph.D., Statistics Reviewer, Office of Biostatistics (review dated

4/6/2007). An environmental assessment review (dated 1/17/2007) was performed by Janice Brown, Ph.D., Office of New Drug Quality Assessment.

2.0 CHEMISTRY

No new CMC information required for review in this submission except environmental assessment issues. A categorical exclusion was requested and granted.

3.0 PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology issues required for review in this submission.

4.0 CLINICAL PHARMACOLOGY

Based on results from study F1D-MC-HGMF (Study HGMF) and other existing adolescent pharmacokinetic data from studies F1D-MC-HGCS, F1DMCHGCR, F1D-MC-HGGC, and F1D-SB-LOAY, the sponsor submitted a study report in which olanzapine pharmacokinetics in adolescents was characterized. I would refer to Dr. Jackson's review for detail.

In brief, the sponsor reported that olanzapine pharmacokinetics was similar in adolescents and adults. The sponsor also claimed in their proposed labeling that (b) (4)

However, Dr. Jackson noted that due to the poor quality of the prediction of the true steady-state values with the model, only the observed range of steady-state values was used. As Dr. Jackson pointed out in his review that in clinical studies, most adolescents had a lower average body weight compared to adults, resulting in an average range of olanzapine exposure that was approximately 30-63% higher in adolescents than adult patients. Dr. Jackson provided labeling comments to reflect these findings.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the result of two short-term double-blind, placebo-controlled, randomized, efficacy and safety studies of olanzapine: one in the treatment of the adolescents (ages 13 to 17) with schizophrenia (Study HGIN); and the other study in the treatment of the adolescents with Bipolar I Disorder, Acute Mania or Mixed Episodes (Study HGIU).

The sponsor indicated that the result of each study supported for the treatment claim. Both Drs. Alfaro and Kong in their reviews indicated that only study HGIU support the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Study HGIN, however, does not seem to provide data to support the effectiveness claim of olanzapine in the treatment of schizophrenia in adolescents.

I would briefly describe the study design and then discuss the primary efficacy analysis results in the following subsection.

5.1.2 Summary of Studies Pertinent to Efficacy Claim

5.1.2.1 Study F1D-MC-HGIN (Schizophrenia)

This study was a multicenter, randomized, double-blind, placebo-controlled, flexible dose study in adolescent with schizophrenia, with a 6-week acute period. The primary objective of this study was to assess the efficacy and safety of olanzapine (2.5 to 20 mg/day) compared to placebo in the treatment of adolescents with schizophrenia. After the screening and washout period (2-14 days), subjects were randomized to receive treatment with either olanzapine or placebo for up to 6 weeks of double-blind treatment.

The study was conducted in 20 U.S. centers which enrolled 53% of the study population; and in 5 Russian centers which enrolled 47% of the study population. One hundred and fifteen subjects entered the study. Of these, 107 (72 to olanzapine and 35 to placebo) were randomized and 64 subjects (49 to olanzapine and 15 to placebo) completed the acute phase of the study. Lack of efficacy was the most common reason for early termination in both groups: 18 (51%) patients for the placebo group; and 10 (14%) in the olanzapine group. 7.9% of study patients discontinued due to an adverse event.

Seventy two percent (N=77) of the patients were Caucasian; 22% were Africa-Americans; and 3% Hispanics. Seventy percent (N=75) were male and 30% (N=32) were female. 66% (N=71) were between 12 and 16 years and 33.6% (N=36) were 17 yrs of age; mean age of 16.1 yrs. There was no difference in demographic and baseline disease characteristics between the olanzapine and placebo groups.

The primary efficacy endpoint was the change from baseline to endpoint (up to 6 weeks double-blind treatment) in the anchored version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score. The ITT data set included all randomized subjects who received at least one dose of assigned study medication, and had at least one post-baseline efficacy assessment. The LOCF analysis was considered primary, but OC was also done. The ANCOVA was the statistical model employed, with covariate baseline scores, treatment and country factors. The protocol allowed interim analysis that the interim analysis result consistent with the final analysis results at $\alpha=.0294$ level. According to the sponsor, there was no interim analysis conducted. Dr. Kong confirmed the primary efficacy results on LOCF dataset. He also applied MMRM as a sensitivity analysis. The results are as follows:

Efficacy Results on BPRS Total Scores for Study HGIN in ITT population (LOCF):

	Mean Baseline BPRS (SD)	LS Mean Change from Baseline (SD)	Difference between LS Means and C.I.; P-values (vs. placebo)
Olanzapine N=72	50.3	-19.3 (1.91)	-10.1 (-16.7, -3.5); p=0.003
Placebo N=35	50.1	-9.1 (2.73)	

Efficacy Results on BPRS Total Scores for Study HGIN (MMRM):

	Mean Baseline BPRS (SD)	LS Mean Change from Baseline (SD)	Difference between LS Means and C.I.; P-values (vs. placebo)
Olanzapine N=72	50.3	-24.7 (1.70)	-1.25 (-8.11, 5.61); p=0.72
Placebo N=35	50.1	-23.5 (3.06)	

Efficacy Results on BPRS Total Scores for Study HGIN (OC):

	Mean Baseline BPRS (SD)	LS MeanChange from Baseline (SD)	Difference between LS Means and C.I.; P-values (vs. placebo)
Olanzapine N=50	50.3	-24.4 (1.82)	-0.25 (-7.9, 7.4); p=0.95
Placebo N=15	50.1	-24.1 (3.35)	

According to Dr. Kong's assessments, there does not seem to have an advantage of olanzapine over placebo. Both the OC and MMRM showed highly non-significant results. Although the LOCF yields highly significant efficacy result, this procedure is reliable only when efficacy measures are stable over the study period. Given the high percentages of patient dropout as indicated in Drs. Kong and Alfaro's reviews, there seemed an impact on reliability of efficacy result in this study. Dr. Kong noted in his review that olanzapine reduced the BPRS-C total score in both the dropout group and the non-dropouts groups, while placebo reduced the score only in the non-dropouts group, not in the dropouts group. Although this phenomenon was observed in both US and Russia, the primary endpoint, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia ($p = 0.003$) but not the sites in the United States ($p = 0.258$). As Dr. Alfaro pointed out in her review, the sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia (see also section 5.1.3. Treatment Effect by Country).

Comment:

Both Drs. Alfaro and Kong did not consider this study as a positive study for olanzapine in treatment of schizophrenia in adolescents, and I agree with them.

5.1.2.2 Study F1D-MC-HGIU (Bipolar I Disorder)

This study was a multicenter, randomized, double-blind, placebo-controlled, flexible dose study of olanzapine (2.5 to 20mg/day) in adolescents with Bipolar I Disorder, acute mania or mixed episodes. After the screening and washout period (2-14 days), subjects were randomized to receive treatment with either olanzapine or placebo for 3 weeks of double blind treatment.

The study was conducted in 23 centers in the United States and 2 centers in Puerto Rico. Two hundred and three subjects entered the study. Of these, 161 (107 to olanzapine and 54 to placebo) were randomized and 120 subjects (85 in olanzapine and 35 in placebo) completed the acute phase of the study. The most common reason for the early withdrawal in both treatment groups was the lack of efficacy which had a total of 28 subjects (17.4%): 16 patients in the placebo group and 12. The difference between the two treatment groups is statistically significant ($p=0.007$). 14.5% of study patients discontinued due to an adverse event.

Seventy percent ($N=112$) of the patients were Caucasian, 16% ($N=26$) Hispanics and 9% ($N=15$) were Africa-Americans. More than half were male ($N=85$). 81% were between 12 and 16 years of age and 9.3% ($N=15$) were 17 yrs of age; mean age of 15.1 yrs. There was no difference in demographic characteristics between the olanzapine and placebo groups at baseline. The treatment groups, however, differed at baseline on measures of disease characteristics. Patients in the placebo group had greater numbers of previous manic, depressive, and mixed episodes. Patients in the olanzapine treatment group had much higher baseline scores on the CGI Severity for Depression;

more numbers reported in terms of history of psychiatric hospitalizations and paternal history of psychosis.

The primary efficacy endpoint was change from baseline to endpoint in the Adolescent Structured Young-Mania Rating Scale (YMRS) total score. The ITT data set included all randomized subjects who received at least one dose of assigned study medication, and had at least one post-baseline efficacy assessment. The LOCF analysis was considered primary, but OC was also done. The ANCOVA was the statistical model employed, with covariate baseline scores, treatment and country factors. Dr. Kong confirmed the primary efficacy results on LOCF dataset. He also applied MMRM as a sensitivity analysis.

Efficacy Results on YMRS Total Scores for Study HGIU in ITT population (LOCF):

	Mean Baseline BPRS (SD)	LS Mean Change from Baseline (SD)	Difference between LS Means and C.I.; P-values (vs. placebo)
Olanzapine N=105	33.1	-17.8 (0.87)	-7.7 (-10.7, -4.6); p<0.0001
Placebo N=54	32	-10 (1.53)	

Both MMRM and OC showed similar results, p=0.0004 and p=0.0013, respectively.

Comment:

Both Drs. Alfaro and Kong consider this study as a positive study for efficacy of olanzapine in treatment of bipolar I disorder, acute mania, in adolescents. I agree with them.

5.1.3 Comments on Other Important Efficacy Issues

Dose Response Relationship

Since both studies conducted were flexible dose (2.5 to 20 mg olanzapine) trials by design, there is no adequate data to address dose response for efficacy. The mean daily dose of olanzapine was 8.9 mg and in bipolar study and in schizophrenia study was 11.1 mg.

Treatment Effect by Country

The primary endpoint of schizophrenia study HGIN, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia (p = 0.003) but not the sites in the United States (p = 0.258). The sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia.

Study HGIN	Placebo	Olanzapine
USA	N=19	N=38
Mean Change From Baseline of BPRS-C Total (SD)	-15.0 (18.3)	-21.2 (16.3)
Russia	N=16	N=34
Mean Change From Baseline of BPRS-C Total (SD)	-2.6 (17.4)	-17.4 (14.5)

There were about 89% patients in US and only 11% patients in Puerto Rico in bipolar study HGIU.

Predictors of Efficacy in Subgroup Populations

Exploratory analyses in order to detect subgroup interactions on the basis of gender (M,F), age (<15 yrs, ≥15 yrs) and race (Caucasian, non-Caucasian). As stated in Dr. Kong's review, there were no

statistically significant effects in any of these subgroups in both studies although the effect was numerically larger in males compared to females; and in ≥ 15 yr age group than < 15 yrs.

Duration of Treatment

The studies conducted were for short-term use of Olanzapine in the treatment of adolescent schizophrenia and bipolar disorder. There is no data pertinent to the long-term efficacy in this submission. Since these disorders are chronic illnesses, it would be good to have data from a longer term study. However, Olanzapine is approved for maintenance treatment in adults with schizophrenia or bipolar disorder. We could infer the efficacy data from adult maintenance trials to adolescent population. According to the 05-30-2002 meeting minute, we agreed to grant a waiver for bipolar maintenance studies in adolescents.

5.1.4 Conclusions Regarding Efficacy Data

I concur with both Drs. Kong and Alfaro's recommendation and conclusion that the data from study HGIN did not seem to support the schizophrenia claim; and that results from study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with acute mania in Bipolar I Disorder.

5.2 Safety Data

5.2.1 Safety Database

Dr. Alfaro's safety review was based on an integrated database covering Acute Database from both pivotal double-blind studies (HGIN - 6weeks; and HGIU - 3 weeks) ; and the Overall Combined Database from the 26 week open label extension phase of HGIN and HGIU, other open label studies (HGMF and LOAY). A total of 268 patients (179 olanzapine; 89 placebo) were enrolled in the Acute Placebo-Controlled Database and 454 patients were included in the Overall Combined Database. Total exposure of olanzapine in adolescents was 48,946 patient-days.

As requested in the Written Request letter, there were sufficient numbers of adolescents enrolled in the 26 week open label phase that followed the double blind trials. Eighty-two subjects from the bipolar study HGIU received olanzapine during this open-label phase for > 23 weeks ($n = 30$, 23-26 weeks; $n = 52$, > 26 weeks). Fifty-four subjects from the schizophrenia study HGIN received olanzapine during this open-label phase for > 23 weeks ($n = 19$, 23-26 weeks; $n = 35$, > 26 weeks).

There were no deaths reported in the olanzapine treatment group in the double-blind studies. A total of 7 SAE reported; 6 patients in the olanzapine treatment arm in the Acute Database for weight increased, migraine, arm fracture, worsening of bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the overall combined database. The majority of these SAEs, 19/35 patients, were listed as worsening of existing psychiatric disorder (schizophrenia, bipolar disorder).

The sponsor also reported data from the postmarketing safety database including 2359 case reports in patients 13 to 17 years of age. There were 27 deaths in the adolescent age group based on the post marketing spontaneous MedWatch reports and the published literature. Based on the limited information provided in these reports, 15 of the cases occurred in the US. Seven of the cases involved completed suicide or possible suicide and five of the cases related to diabetes mellitus,

diabetic coma or diabetic ketoacidosis. Based on the proportion of events (%) in patients 13-17 yrs potential safety signals reported by the sponsor included weight increased, overdose, fatigue, ALT increase, diabetes mellitus and increased appetite.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk). In the double-blind studies, the most common AEs were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (24%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies HGIN and HGIU.

In the schizophrenia trials, 31% of adolescent patients experienced weight gain compared to 6% of adult patients. Somnolence and sedation were experienced by 24% and 15% of adolescent patients compared to < 5% of adult patients. Similar patterns occurred in the bipolar disorder trials except that somnolence was very common in the adult population as well as the adolescent population.

5.2.2.2 Weight Gain

The following table summarizes the significant mean weight changes by mean change in weight to endpoint, mean change in BMI to endpoint and % of patients with $\geq 7\%$ increase in body weight based on the results obtained from the two double-blind studies. Similar results were obtained for OC.

	Olanzapine	Placebo	LS Mean Diff	P-value
Weight (kg)	3.90 (n = 177)	0.24 (n = 88)	3.66	< 0.001
Mean Change to Endpoint (LOCF)				
BMI	1.22	0.05	1.17	< 0.001
Mean Change to Endpoint (LOCF)				
$\geq 7\%$ increase in body weight (%)	43.5%	6.8%	-	< 0.001

A significant mean weight changes from baseline by mean change in weight to endpoint (7.35 Kg), mean change in BMI to endpoint (2.31) and % of patients with $\geq 7\%$ increase in body weight (65%) based on the results from the overall combined database including the open label studies.

For each double-blind study, mean change in weight (kg) was evaluated between the subgroups gender and age. No statistical significant differences were noted between these subgroups. The change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for olanzapine group in study HGIN.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months.

5.2.2.3 Abnormal Laboratory Tests

Liver function tests

The percentage of adolescent patients with ALT baseline $\leq 3 \times$ ULN who had ALT $> 3 \times$ ULN at any time during the acute double blind studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group ($p = 0.009$). The percentage was higher compared to the finding in adults (i.e., 2% in olanzapine group). Six patients discontinued HGIN and HGIU due to increases in liver transaminases (ALT). Four patients had an increase in TBili to > 1.5 times ULN – two in the olanzapine group and two in the placebo group. Six subjects in olanzapine group discontinued due to elevated liver enzymes. There were no subjects who had ALT $\geq 3 \times$ ULN and TBili $\geq 1.5 \times$ ULN.

Comment: The sponsor proposed these LFT abnormalities in adolescents as part of the transaminase elevations subsection under the Warnings/Precautions section of the labeling. I consider this as a reasonable proposal. In the adolescent section, I concur with Dr. Alfaro's recommendation to include the number of patients who discontinued due to elevations in LFTs in the labeling.

Lipid profile (Hypertriglyceridemia, Hypercholesterolemia)

The mean change from baseline to endpoint for triglycerides was 29.2 mg/dL for the olanzapine group and -4.4 mg/dL for the placebo group (LS Mean Diff = 33.6, $p < 0.001$). There were 11 marked outliers noted for elevated triglycerides at any time (> 250 mg/dL). The most significant was an increase from 103 mg/dL at baseline to 1237 mg/dL. A higher percentage of patients in the olanzapine group had a shift from normal to high triglycerides (12.4%) compared to placebo (1.9%) ($p = 0.039$).

The mean change from baseline to endpoint for cholesterol was 13.1 mg/dL for the olanzapine group and -1.2 mg/dL for the placebo group (LS Mean Diff = 14.3, $p < 0.001$). A higher percentage of patients in the olanzapine group had a shift from normal to borderline cholesterol (15.7%) compared to placebo (3.6%) ($p = 0.023$).

Comment: The sponsor proposed labeling changes in this submission, the finding on cholesterol and triglyceride was placed in the Adverse Reactions, laboratory changes subsections. I believe the finding on lipids should be placed more prominently in the labeling. Given other significant findings on weight, liver enzymes and glucose are part of the Warning/Precautions in the labeling, we should consider placing this topic in the same section.

Hyperglycemia

The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). Regarding the percentage of patients with shifts from normal (< 100 mg/dL) to high fasting glucose, it was not significantly different between olanzapine (0/122) and placebo (1/51). Similarly, the percentage of patients with changes in fasting glucose from impaired glucose tolerance (≥ 100 mg/dL and < 126 mg/dL) to high (≥ 126 mg/dL) fasting glucose was not statistically different between olanzapine (2/13) and placebo (0/13).

In the Acute Database, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes). There was no change from baseline to endpoint in this parameter.

Comment: In this adolescent population, olanzapine did not appear to be associated with significant hyperglycemia. This finding could be attributable to initial development of insulin resistance in younger age group before actual increase in glucose level is observed. The finding on HbA1c was not unexpected either since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months.

Current Zyprexa labeling contains standard warning language on hyperglycemia and diabetes for atypical antipsychotics. The sponsor did not propose any changes to this warning section. Given the finding that the adolescent population experienced significant weight gain, it is important that sufficient information on these risks needs to be described in the labeling. Recently, the Division has asked the sponsor to provide more data on the glucose and lipid findings with Zyprexa in our March 28, 2007 approvable letter for Symbyax in treatment resistant depression and in our January 12, 2007 letter regarding the New York Times story. The sponsor has not adequately addressed to our concerns on these issues yet. We should reference these two letters in our action letter.

Hyperprolactinemia

Based on the acute database from the two double-blind studies, the mean change from baseline to endpoint in prolactin was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, $p < 0.001$). The washout period prior to baseline could be as short as 2 days. In study HGIN, 17% (11/64) of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The mean prolactin concentration at the end of study was 55.8 ± 15.8 ng/ml. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study.

It was noted that many patients had elevated prolactin at baseline. For those patients with normal baseline, it was found that 47.4% of patients in the olanzapine group had a treatment-emergent high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$). No significant treatment by gender interaction on prolactin level was found.

Gynecomastia occurred in 1 (0.9%) patient in the olanzapine group and no patients in the placebo group and amenorrhea occurred in no patients in the olanzapine group and 1 (2.4%) patient in the placebo group. As Dr. Alfaro stated in her review, the Overall Combined Database was evaluated since adverse events such as gynecomastia are not expected to occur with acute use but rather more long term use of antipsychotics. In the Overall Combined Database, gynecomastia occurred in 7 (4.3%) of patients (all from schizophrenia trials), galactorrhea occurred in 2 (3.1%) patients with schizophrenia and 1 (1%) patient with bipolar disorder and amenorrhea occurred in 1 (1.5%) patient with schizophrenia and 1 (1%) patient with bipolar disorder. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Comment: The proposed labeling contains the paragraph on hyperprolactinemia from the approved labeling in the Warning/Precaution section. The sponsor did not propose any labeling changes with adolescent data in the Warning section and the Pediatric Use section. We should ask the sponsor that more specific information be included in the Pediatric Use section.

I concur with Dr. Alfaro's recommendation that the sponsor should provide additional analyses on the subset of patients with baseline prolactin within the normal range and also, a subgroup analysis for gender and age. While I note Dr. Alfaro's request to obtain narratives on 8 cases of gynecomastia (1 case in the acute trials and 7 cases in the open trials) and two cases of high prolactin concentrations from study HGIN (1 in acute trial and 1 during the open label). It will be difficult to interpret such data if they came from the open-label phase, but we may be able to note any potential signal. It would be worthwhile to look at the individual narratives in this population, although it will be difficult to distinguish this AE from normal breast development in adolescent female. Given the fact that Dr. Alfaro was unable to identify gender in any of these cases, I have no objection to her request for more information from the sponsor.

Elevated CPK

In Dr. Alfaro's comments to the sponsor section, she recommends that we ask for narrative summaries for cases with CPK >500 U/L in our action letter. From her review, I am not able to identify which one of these CPK elevations were noted during the double-blind treatment. Upon follow up with Dr. Alfaro on this issue, we agree that we could just limit our request to one patient with a CK of 7289 U/L in the acute trial.

5.2.2.4 Vital signs and ECG changes

There was a mean increase in heart rate of 6.3 bpm in adolescents treated with olanzapine compared to a decrease of 5.1 bpm in the placebo group. The sponsor attributed this increase in heart rate to olanzapine's potential for inducing orthostasis. There were no significant changes in ECG parameters including QTc.

5.2.2.5 Extrapyramidal Symptoms

For both HGIN and HGIU, change from baseline to endpoint in the EPS rating scales was similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups. I note Dr. Alfaro's request to the sponsor for case narratives regarding one case of opisthotonus and one case of oculogyration. Since these AEs occurred during the open-label phase, I do not think it is necessary to review these 2 case narratives. It may be difficult to ascertain causality in the open label trials. I also note as part of Dr. Alfaro's request for additional information on how was "treatment-emergent" parkinsonism, akathisia and dyskinesia defined by the respective rating scales, and an analysis of AIMs individual items and total score (change from baseline to endpoint) for the completers in the overall combined database. It is doubtful that further assessment would give any significant result.

5.2.2.6 Suicidality

No completed suicides occurred in the clinical trials. In the acute double-blind studies, 2 events occurred in the olanzapine group (suicidal ideation/behavior – intent unknown and suicidal ideation) and 1 event occurred in the placebo group. These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in

bipolar disorder patients. I agree with Dr. Alfaro that suicidal behaviors or ideation is not uncommon in these patients and it is difficult to interpret any causality to olanzapine therapy in the absence of a placebo comparator. One of the exclusion criteria for HGIU was "patients who have been judged clinically to be at serious suicidal risk". However, Dr. Alfaro noted that three patients (012-1203, 012-1212, and 024-2402) who were rated the maximum score of "7" at baseline (has made a suicide attempt within the last month or is actively suicidal) of the CDRS-R individual item "suicidal ideation." She recommended that we ask the sponsor in the approvable letter to provide more information regarding inclusion of these patients in this study. Given the study results from the acute double-blind phase of the study, I do not think we need to convey this question to the sponsor.

5.2.2.7 Risk Management Plan

The sponsor's proposed risk management plan includes

(b) (4)

The OSE was consulted on this proposed risk management plan. The OSE has stated that they would provide their input on the appropriateness of the RMP after the sponsor submits a complete response to the action letter.

5.2.3 Conclusion Regarding Safety Data

This submission revealed safety findings of Olanzapine in adolescent population in which most AEs consistent with the previously observed AE profile of olanzapine as described in current labeling. The sponsor has included all the percentages in the treatment emergent AE of $\geq 5\%$ and $\geq 2\%$ table as the commonly observed AEs in controlled adolescent clinical trials under the adverse events section of the labeling. I think this portion of their labeling proposal seems acceptable.

Significant safety signals that emerged in these adolescent clinical trial databases were weight gain, hypertriglyceridemia, hypercholesterolemia, hyperprolactinemia and transaminase elevations. Although there are some changes proposed in the labeling by the sponsor, we need to work on the labeling language so that all pertinent safety findings are adequately reflected in the labeling. We have already asked the sponsor for an extensive search for data to address the concerns regarding weight, glucose and lipid profiles in our 1/12/2007 letter and our 3/28/2007 approvable letter for symbyax (olanzapine/fluoxetine combination) in treatment of treatment resistant depression. In our action letter for this set of olanzapine pediatric supplements, we should reiterate related safety concerns and ask the sponsor to make relevant safety changes in the labeling.

6.0 WORLD LITERATURE

The sponsor has provided a literature update pertaining to the safety of Olanzapine. As Dr. Alfaro noted, the sponsor reported that none of the articles would change safety conclusion for olanzapine.

7.0 FOREIGN REGULATORY ACTION

I am not aware of any foreign regulatory action of this drug for adolescent claim.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take these supplemental NDAs to the PDAC.

9.0 DSI INSPECTIONS

DSI data audit inspections were requested for two domestic sites and two Russian sites. DSI did not indicate any major inspectional issues that would impact data integrity on efficacy and safety.

We also informed DSI of GCP non-compliance reported by the sponsor in one clinical trial site 021 for study HGIN (CI: Dr. A. Robb). DSI will decide if further investigation of this clinical investigator site is needed. The sponsor has excluded data from at this site (N=3) in their analysis and reported no impact on efficacy results.

10.0 LABELING AND ACTION LETTER

Since we are recommending a non-approval action on schizophrenia indication, we should delete the labeling language in reference to this efficacy claim. We have made modifications to the proposed labeling and should provide our labeling comments to the sponsor with respect to safety language in labeling, and related safety issues in our action letter. Our modified version of draft labeling in the new PLR format is attached in our action letter for bipolar indication.

11.0 CONCLUSION AND RECOMMENDATION

I concur with both Drs. Alfaro and Kong that the sponsor has not provided sufficient evidence to convince that olanzapine is effective for treatment of schizophrenia in adolescents. Therefore, I recommend the Division issue a non-approvable letter for this NDA supplement (SE5-041).

Regarding the NDA supplement (SE5-040), results from study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Although there are some changes in the labeling proposed by the sponsor in the submission, we will need more information in order to adequately address the safety findings regarding changes in weight, glucose and lipid profiles. We may need further modification in the labeling to reflect all significant findings. Therefore, I recommend that the Division issue an approvable action letter with our labeling comments.

Cc: HFD-130/Laughren/Mathis/Alfaro/Bates
File: NK/NDA20592/Memo_SE5_040041_peds_042007.doc

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/s/

Ni Aye Khin
4/19/2007 01:45:57 PM
MEDICAL OFFICER

**MEMORANDUM
SERVICES**

DEPARTMENT OF HEALTH AND HUMAN

**PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: 4/12/2007

TO: Doris Bates, Ph.D., Regulatory Project Manager
Ni Khin, M.D., Medical Team Leader
Division of Psychiatric Products, HFD-130

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good-Clinical Practice Branch I
Division of Scientific Investigations

FROM: Khairy Malek, Medical Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-592:SE5-040 and SE5-041

APPLICANT: Eli Lilly & Co., Inc.

DRUG: Zyprexa (olanzapine)

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of mania in adolescents with bipolar 1 disorder and
adolescents with schizophrenia.

CONSULTATION REQUEST DATE: December 1, 2006

DIVISION ACTION GOAL DATE: April 30, 2007

PDUFA DATE: April 30, 2007

I. BACKGROUND:

Olanzapine is a psychotropic agent approved by the FDA in 1996 in the treatment of psychotic disorders including schizophrenia and also approved for the treatment of acute manic episode associated with adult bipolar 1 disorder.

The two new supplements are for the same indications in the pediatric population and the protocols included adolescents 13-17 years old. Supplement SE5-040, protocol F1D-MC-HGIU(a) is titled "Olanzapine Versus Placebo in the Treatment of Mania in Adolescents with Bipolar 1 Disorder". Supplement SE5-041, protocol F1D-MC-HGIN(c) is titled "Olanzapine Versus Placebo in the Treatment of Adolescents with Schizophrenia"

Four sites were chosen for inspection; two sites investigated the 2 protocols and two sites, in Moscow, investigated one study, the schizophrenia treatment in adolescents only.

Summary Report of U.S. and Foreign Inspections

II. RESULTS (by protocol/site):

Name of CI (M.D.)	Location	Protocol	Inspection Date	EIR Received Date	Final Classification
Robert Riesenber	Atlanta, GA	HGIU HGIN	1/29- 2/5/07	4/6/07	NAI
Melissa DelBello	Cincinnati OH	HGIU HGIN	2/5- 2/21/07	3/19/07	NAI
Leonid Bardenstein	Moscow Russia	HGIN	2/19- 2/22/07	Draft only received (not final)	VAI
Valery Kransov	Moscow Russia	HGIN	2/26- 3/2/07	Draft only received (not final)	VAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

A. Protocol # HGIU

1. Robert Riesenber-Atlanta Georgia

At this site 7 subjects were randomized and completed the double-blind period of the study. Four subjects # 2701, 2704, 2705 and 2708 did not complete the open-label period due to adverse events or lost to follow-up.

There was no limitation of the inspection.

The field investigator reviewed the records of three subjects and no violations of the federal regulations were observed.

The data from this site can be used in support of the NDA supplement.

2. Melissa DelBello-Cincinnati, Ohio

At this site 15 subjects were enrolled in the study. The field investigator reviewed all the records of the subjects in the study. No violations were observed.

There was no limitation of the inspection.

The data from this site can be used in support of the NDA supplement.

B. Protocol HGIN:

1. Robert Riesenberg-Atlanta, Georgia

At this site 5 subjects enrolled in the study. Subject # 2002 terminated early during the double-blind phase of the study, subject # 2005 was lost to follow up during the open-label phase of the study, and the other three completed the study. The field investigator reviewed the records of three subjects and no violations were observed.

There was no limitation of the inspection.

The data from this site can be used in support of the NDA supplement.

2. Melissa DelBello-Cincinnati, Ohio

At this site six subjects enrolled in the study. The field investigator audited all the records in the study. No violations were observed.

There was no limitation to the inspection.

The data generated from this site can be used in support of the NDA.

3. Leonid Bardenstein-Moscow, Russia.

At this site ten subjects were enrolled, but 6 subjects completed the double-blind portion of the study. Four subjects were discontinued during that phase, 2 due to physician perceived lack of efficacy, 1 due to subject perceived lack of efficacy and one because of elevated liver enzymes. Nine subjects completed the open-label period of the study (all except the one with elevated liver enzymes).

The field investigator reviewed the records of all subjects in the study. Few protocol violations were observed:

- Three subjects (# 9101, 9102 and 9103) were enrolled in the study before all the laboratory reports were available to the CI, but none of them had prolactin levels above 200 ug/L (as it appeared later).

- Subject # 9109 was started at the beginning of the open-label period on 20 mg olanzapine instead of the protocol required 2.5-5 mg with gradual increase.

There was no limitation of the inspection.

The data generated from this site can be used in support of the NDA supplement, and the above stated protocol violations will not affect the validity of the data.

4. Valery Kransov-Moscow, Russia

At this site, 10 subjects were enrolled; 7 subjects completed the double-blind period II. Two subjects had early withdrawal due to perceived lack of efficacy and one for protocol violations. The same 7 subjects completed the open-label portion of the study. The field investigator audited all the records of the subjects. A protocol violation was observed:

- Three subjects (#9101, 9407, and 9408) were enrolled in the study before all the laboratory results were received and reviewed before enrolling in the study as required by the protocol.

There was no limitation of the inspection.

The data obtained from this site can be used in support of the NDA supplement and the protocol violation mentioned above will not affect the validity of the data.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The studies were generally well conducted in all the four sites. We did not receive the final EIRs from the Moscow inspections. An addendum will be generated if there is any conclusion changes.

The data from all the studies can be used in support of the NDA supplement.

I reviewed the EIRs and the few laboratory reports sent by the field investigator from 2 sites (Dr. Riesenbergs' site in Moscow and Dr. Brandenstein site in Atlanta, and I observed a tendency of elevation in the liver enzymes in five subjects and probably also the lipids (2 subjects at Dr. Riesenbergs' site), in this age group. The division may have made a more thorough analysis than mine.

Khairy Malek
Medical Officer

{See appended electronic signature page}

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Khairy Malek
4/16/2007 01:29:13 PM
MEDICAL OFFICER

Constance Lewin
4/16/2007 01:53:44 PM
MEDICAL OFFICER

Constance Lewin
4/16/2007 02:00:30 PM
MEDICAL OFFICER

Bates, Doris J

From: Bates, Doris J
Sent: Thursday, March 08, 2007 4:55 PM
To: 'Catherine Melfi'
Cc: Alfaro, Cara; Kong, Fanhui; Bates, Doris J
Subject: RE: NDA 20-592 S-040, S-041: Additional Questions
Importance: High

Dear Dr. Melfi:

We have additional questions from our clinical reviewer for these supplements, which I am forwarding below:

These questions pertain to the Acute Placebo-Controlled Combined Database:

1. It is unclear whether there was greater weight gain in patients with lower BMI at baseline (and visa versa). Please provide an analysis of weight gain based on the patient's baseline BMI to address this question.
2. Please provide the numbers of patients in both the placebo and olanzapine treatment groups who were obese (BMI > 30) at baseline and at end of study. Was there a statistical difference?
3. Please provide a subgroup analysis for laboratory data (similar to the summary in Table 2.7.4.33 in summary-clin-safety). Include all olanzapine patients who gained greater than 3.9 kg (mean weight gain from baseline) compared to all placebo patients.

As with prior questions, I am including the clinical and statistical reviewers as CC recipients; please feel free to reply via email prior to amending the supplements with a formal response.

Please feel free to contact me if you have any questions concerning this message,

Sincerely,

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

3/8/2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA# 20-592/S-039
18-936/S-077
21-086/S-021

Eli Lilly and Company
Attention: Robin Wojcieszek, R.Ph.
Associate Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Wojcieszek:

Please refer to your supplemental new drug application dated September 28, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) tablets (20-592/S-039), Zyprexa Zydis tablets (21-086/S-021), and Prozac (fluoxetine) capsules (18-936/S-077).

Reference is also made to an Agency letter dated November 27, 2006, refusing to file these applications.

We acknowledge receipt of your resubmission dated January 4, and received January 5, 2007.

As previously communicated to you, the Agency concurs with your proposed alternative labeling as well as the justification provided in the briefing package. Therefore, these applications have been filed under section 505(b) of the Act as of March 6, 2007 in accordance with 21 CFR 314.101(a).

Additionally, these applications have been designated as a standard review priority classification and, as such, the user fee goal date will be November 5, 2007.

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

NDA 20-592/S-039, 18-936/S-077, & 21-086/S-021

Page 2

If you have any questions, call Renmeet Grewal, Pharm.D., Regulatory Project Manager, at (301) 796-1080.

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

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/s/

Thomas Laughren
3/7/2007 08:11:27 AM

Bates, Doris J

From: Bates, Doris J
Sent: Monday, March 05, 2007 11:36 AM
To: 'Catherine Melfi'
Cc: Bates, Doris J; Alfaro, Cara
Subject: NDA 20-592 S-040 / S-041: Additional Clinical Questions
Importance: High

Good morning Dr. Melfi:

I have the following questions from our clinical reviewer regarding the above referenced pediatric supplements.

1. In the brief summary for study HGCS, it is noted that 2 patients experienced the adverse event "intentional injury". Please provide brief summaries for these two events.

2. For study HGGC, were there any serious adverse events? The synopsis states that no patients experienced serious adverse events associated with cardiac abnormalities or weight gain - but there is no mention of other SAEs that may have occurred in this trial.

3. For the adult studies HGDH and HGGF that included adolescent patients, please submit narratives for the serious adverse events (per Table 2.7.4.4 in the summary-clin-safety document).

For the adult studies HGGF and HGKL, please submit narratives for the discontinuations due to adverse event cases.

4. For patient HGIU-028-2804, the narrative indicates that she experienced bilateral galactorrhea while hospitalized for a recurrence of bipolar symptoms. Please provide the prolactin concentrations that were obtained by the hospital (pending at time patient was discharged).

5. Patient HGMF-003-0304 had the SAE "exacerbation of bipolar illness with positive suicidal ideation". However, it appears that this was coded to the preferred term "bipolar disorder". Why weren't both verbatim terms coded to preferred terms - i.e. bipolar disorder and suicidal ideation?

6. For the discontinuations due to the adverse event "weight gain" in the acute and combined databases, please provide weight data for the post-study follow-up visits. Some of the narratives have this information, but the majority indicate that the adverse event had resolved without providing weight data.

I am also including a comment from our reviewer, verbatim as I received it: please feel free to share this comment with all to whom it might apply...

3/5/2007

I also wanted to thank the Sponsor for the narratives provided in this submission. These are among the best narratives I have seen from Sponsors and I truly appreciate the effort that was obviously put into the organization of them.

Please feel free to contact us if you have any questions regarding this message. If you wish to reply by email, please reply to all, as I have included the clinical reviewer as a CC recipient on this message to facilitate that process. Please amend the supplemental NDAs with any information provided by email, as we need the official documents to reflect all additions to the file.

Thank you, and best regards,

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

3/5/2007

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, February 21, 2007 3:06 PM
To: 'Catherine Melfi'
Cc: Bates, Doris J; Kong, Fanhui; Alfaro, Cara; 'Robin Pitts Wojcieszek'
Subject: NDA 20-592 S-040 and S-041: URGENT Statistics Questions
Importance: High

Dear Dr. Melfi:

I have received the following urgent questions from our statistical review team. Please provide an initial response via return email, to facilitate our review, if possible; we will need amendments submitted to the supplements for the record.

I have included the clinical and statistical reviewers as CC recipients to minimize routing delays on your response, and I have copied Ms. Wojcieszek to facilitate routing for you at Lilly.

For Study HGIN: please provide

- (a) the IND numbers and the **serial numbers** and their **submission dates** for the study **protocol and its amendments A, B, C**, along with **those for the SAP**;
- (b) please indicate whether an interim analysis was performed, and, if so, please indicate when this was done and provide results;
- (c) please provide any available correspondence, etc. to demonstrate that the full SAP was submitted to the Division, and reviewed, prior to data unblinding. [If the SAP was modified in any way based on Division feedback, this should also be indicated]

For Study HGIU: please provide

- (a) the IND numbers and the **serial numbers** and their **submission dates** for the study **protocol and its amendments A**, along with **those for the SAP**;
- (b) any available correspondence, etc. to demonstrate that the full SAP was submitted to the Division, and reviewed, prior to data unblinding. [If the SAP was modified in any way based on Division feedback, this should also be indicated].

Please feel free to contact me if you have any questions about this message.

With best regards,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

2/21/2007

Bates, Doris J

From: Bates, Doris J
Sent: Monday, February 12, 2007 4:54 PM
To: 'Catherine Melfi'
Cc: 'Robin Pitts Wojcieszek'; Bates, Doris J
Subject: RE: Follow-up; NDA 20-592; S-040 and S-041
Attachments: PLR POSSIBLE CONTENT FORMAT DEFICIENCIES.pdf

Hi Dr. Melfi:

Thanks for your very timely inquiry. I will not be here tomorrow; am going to be home riding out the predicted ice storm and, unfortunately, not available online. I plan to be working, but it will involve reading and scheduled teleconferences only. Under the circumstances I wanted to contact you before leaving today:

1. We have realized that because of the inclusion of the Zydis and IM formulations in a common PI, we need you to submit a one page letter to each of these INDs to cover a labeling supplement for the transition to PLR format. We realize that the Zydis formulation is bioequivalent to the tablet, so that our review of the tablet data can be extended to the Zydis form without the need for a second clinical review or user fee. For the IM formulation, there is no intended claim related to pediatric use, and therefore the only change is in the labeling format, as regards this dosage form.

One letter, referencing all three NDA numbers and adding the Zydis and IM labeling submissions, should address this. We will, of course, be acting simultaneously on all submissions on the already established PDUFA date for S-040 and S-041 to NDA 20-592. This is purely a bookkeeping detail [but one we need to address], to cover the labeling format change for the other two dosage forms under their respective NDAs.

2. Regarding your question on coding, PMs have not been trained to address coding issues; we don't code SLR and we don't code PLR. I would therefore recommend having your coding experts take any coding related questions directly to the Labeling Review Team committee. I can get you contact information later this week, if you aren't able to locate them on the CDER web page [you would search on SEALD, they are the Study Endpoint And Labeling Development group, I believe, and I think they have an externally accessible site. I am also attaching a link to the labeling guidance information below, from which it may be possible to work back to their main page.] I do understand the basic issue, but I don't have the detailed knowledge to provide any solutions -- nor does anyone else in the Division, for which I apologize.

3. Regarding general labeling issues, we now have in hand a list of the most commonly identified labeling deficiencies, which I am attaching to this email. The standard language meant to accompany our transmission of this list to applicants is provided below.

Our Study Endpoints and Label Development (SEALD) Team have created (attached) a list of the most frequently encountered PLR format/content deficiencies. We are asking you to verify that none of these deficiencies are in your PLR labeling submitted on October 30, 2006. If you find, at the conclusion of your PLR review, that there are deficiencies in your submitted PLR labeling, please amend your application to correct these deficiencies. Additionally, please note that this is not an exhaustive list and you are also encouraged to review our PLR guidance documents located at the following internet address:

<http://www.fda.gov/cder/regulatory/physLabel/default.htm>

3/5/2007

We request that you complete this review and respond to this e-mail within 30 days of receipt of this message.

4. I plan to follow up with you later this week, weather permitting. We will be starting our substantive review of labeling earlier than usual in the review cycle, because of the format change; this does not imply any conclusions regarding efficacy, but is due solely to the format change.

Best regards and I hope you all avoid the ice storm in IN; on a side note, you may want to share the PLR deficiencies list with Robin and the SYMBYAX TRD team, since it is also pertinent there.

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

From: Catherine Melfi [mailto:MELFI_CATHERINE@LILLY.COM]
Sent: Monday, February 12, 2007 4:15 PM
To: Robin Pitts Wojcieszek; Bates, Doris J
Subject: Follow-up; NDA 20-592; S-040 and S-041

Hi Doris:

I just wanted to follow up on our teleconference on January 29 where we discussed the review of the pending supplements for the pediatric indications for Zyprexa. On the teleconference, you had mentioned that you use a template to go over the submitted labeling in PLR format, and I was hoping that it might be possible for you to send us a copy of that template so that we can be sure our PLR submissions follow appropriate formatting for greater ease of review.

Also, my team is working through the coding for the Highlights section of the Zyprexa label in PLR format. I am wondering if you can provide any insight as to how and when coding of the Highlights section needs to be finalized. We're finding that in some cases, there is no appropriate coding available in the current dictionaries, and we also need guidance on how class labeling is to be coded. Do you know if Divisions are requiring labels to have all of the Highlights coding mapped prior to approval, or is the final coding something that can be worked out after approval?

As we work through this together, let me know what I can do to make things easier for you, and any insights you can provide regarding status of the review and details regarding working through PLR would be greatly appreciated.

Thanks!

Cathy

PS (Big winter storm warning for Indianapolis through Tuesday, so there may not be many people in the office tomorrow. I will have access to e-mail whether I'm in the office or at home, so should be available regardless.)

Catherine A. Melfi, Ph.D
U.S. Regulatory Affairs
Phone 317-277-2905 Fax 317-276-1652
Mobile (b) (6)

3/5/2007

email: melfi@lilly.com

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3/5/2007

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 14, 2007

TO: Administrative File

FROM: LCDR Renmeet Grewal, PharmD
Regulatory Project Manager, DPP

SUBJECT: NDA 18-936/S-077, Prozac (fluoxetine HCl) Capsules
NDA (b) (4)/S-039, Zyprexa (olanzapine) Tablets
NDA 21-086/S-021, Zyprexa Zydis (olanzapine) Tablets

- The above three supplemental NDAs were submitted as efficacy supplements along with sNDA 21-520/S-012 (Symbyax) for the treatment of Treatment Resistant Depression (TRD). All four efficacy supplements were classified as priority reviews.
- The Agency filed sNDA 21-520/S-012 but refused to file the above three sNDAs since clinical studies for the TRD indication were only conducted with the Symbyax formulation.
- Eli Lilly (the sponsor) sent in a meeting request dated 1-4-07, and received 1-5-07, to discuss why the Agency refused to file the above three sNDAs. The meeting package was comprised of a justification for placing the combination product into each of the labelings for the individual products as well as an alternative labeling proposal to describe this information.
- The Agency granted the meeting. During the pre-meeting, it was decided, given the alternative labeling proposal and justification, the Agency would file these applications.
- The sponsor was informed that the 1-4-07 meeting package would constitute the resubmission date.
- The sponsor was also informed that these supplements would be coded as a standard review classification since approval was linked to the Agency's review of the Symbyax TRD applications.
- The DR was informed to change the UF coding to clinical data by reference.

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/s/

Renmeet Grewal
2/15/2007 09:38:50 AM
CSO

From: Grewal, Renmeet
To: "Robin Pitts Wojcieszek";
CC: Bender, William;
Subject: sNDAs 20-592/S039, 18-936/077, and 21-086/021
Date: Friday, February 09, 2007 10:50:03 AM
Attachments:

Hi Robin,

Regarding sNDAs 20-592/S039, 18-936/077, and 21-086/021, we concur with your justification that these supplements can be filed. As such, we are placing the additional code of resubmission (RS) with your meeting package submission dated 1-4-07, and received 1-5-07, which will reopen the clock for these applications.

However, your 1-4-07 submission proposed alternative labeling for these applications. We are requesting that you amend these applications with your alternative labeling to each of the sNDAs.

Sincerely,
Rimmy

*Renmeet Grewal, Pharm.D., LCDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838*

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/s/

Renmeet Grewal
2/9/2007 10:54:58 AM
CSO

Bates, Doris J

From: Bates, Doris J
Sent: Monday, January 29, 2007 11:07 AM
To: 'Catherine Melfi'
Cc: Bates, Doris J; Alfaro, Cara
Subject: N 20-592 S-040, S-014: Questions from Clinical Reviewer

Good morning Dr. Melfi:

Per our teleconference this morning, I am sending you the questions received from our clinical reviewer below: if you have any questions please feel free to contact me, and as always, we welcome 'e-desk' copies of any reply if it is convenient for you to do so. I have included Dr. Alfaro on the CC list here to facilitate her receipt of any reply via email.

Please provide patient baseline severity of illness and statistical analysis for US vs. Russia sites (similar to HGIN.11.2 but comparing US vs. Russia). Include the following variables: age of onset of illness, # of previous schizophrenia episodes, total hospitalization, length of current episode, days since last hospitalization, psychiatric hospitalization, CGI-S, BPRS-C subscales, BPRS-C total score, PANSS subscales, and PANSS total score

Do study reports for HGIN and HGIU include information regarding the adverse events associated with patient drop-outs? Please indicate where this information may be found.

In table HGIN.11.2, it is noted that the minimum value for age for Age of Illness Onset was 5 years old for each treatment group. Please provide the study numbers for all patients with an age of illness onset < 10 years old and CRFs for these patients.

In table HGIN.11.2, it is noted that the minimum value for the Length of Current Episode is "0" - please clarify.

For Psychiatric Hospitalization in table HGIN.11.2, please clarify whether this is past or current hospitalization.

Please provide # of prior psychiatric hospitalizations for both treatment groups with statistical analysis for this variable.

Thank you, and best regards,

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

1/29/2007

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, January 17, 2007 1:34 PM
To: 'Catherine Melfi'
Cc: Bates, Doris J; Alfaro, Cara; Kong, Fanhui
Subject: NDA 20-592 S-040 and S-041: Clinical Reviewer Questions [Statistically Related]
Importance: High

Good afternoon Dr. Melfi,

I have received the following questions from our clinical reviewer regarding the above referenced supplemental NDAs:

-
1. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF analysis (similar to table HGIN 14.20 for OC analysis) - with and without site 021.
 2. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF and OC analysis for the US and Russia sites separately.
 3. Provide patient baseline demographics and analysis for US vs. Russia sites (similar to HGIN.11.1 but comparing US vs. Russia).
 4. It is noted that 50 patients were randomized at the 5 sites in Russia - 10 patients per site. Is it coincidental that 10 subjects were randomized at each of these sites? Were caps specified to the investigators such that each site could randomize no more than 10 patients?
-

Please feel free to contact me if you have any questions regarding this email. If you wish to send us a courtesy electronic copy of your reply, I have included Drs. Alfaro and Kong in the CC list so that a 'reply to all' will reach all of us simultaneously.

Thank you and best regards,

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

1/17/2007

NDA REGULATORY FILING CHECKLIST

NDA #	20-592	Efficacy Supplement Type SE-	5	Supplement #	040
NDA #	20-592	Efficacy Supplement Type SE-	5	Supplement #	041

Trade Name: Zyprexa
Established Name: olanzapine
Strengths: 2.5, 5.0, 7.5, 10, 15 and 20 mg
Indication(s): SE5-040, pediatric bipolar disorder
SE5-041, pediatric schizophrenia
Applicant: Eli Lilly & Co., Inc.
Agent for Applicant: none needed, US firm
Date of Application: October 30, 2006
Date of Receipt: October 31, 2006
Date of Filing Meeting: December 15, 2006
Filing Date: December 29, 2006 [but decision made 12-15-06 and conveyed to firm]
PDUFA Date: April 30, 2007

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☐ P ☒
Resubmission after withdrawal? original Resubmission after refuse to file? original
Chemical Classification: (1,2,3 etc.) 6
Other (orphan, OTC, etc.) not applicable

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2)

- application? YES ☒ NO ☐
If yes, explain:
NDA 21253 intramuscular injection exclusivity expires 29MAR2007,
NDA 21086 orally disintegrating tablet exclusivity for long term tx of bipolar disorder expires 14JAN2007
NDA 20592 tablet exclusivity for long term tx of bipolar disorder expires 14JAN2007
- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒
 - Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
If yes, explain:
 - Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
 - Was form 356h included with an authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. agent must sign.
 - Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
If no, explain:
 - If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Additional comments:
 - Patent information submitted on form FDA 3542a? YES ☒ NO ☐
Not included in original submission. Requested and received as an amendment prior to filing date.
Forms were requested and received for both indications.
 - Exclusivity requested? YES, ☒ 3 three Years NO ☐
Three years of exclusivity were requested for each of the two indications.

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
 - Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."
 - Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
 - Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☐ NO ☐
Not applicable; there are no chemistry changes requiring a CMC section, only an EA.
 - PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
Corrected in COMIS per PM request.
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. *Yes*
- List referenced IND numbers: *IND 28,705 only*
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ NO ☒
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
Not applicable YES ☐ NO ☐
- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☒ NO ☐
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☐
Not applicable
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
N/A ☒ YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐

**This is a representation of an electronic record that was signed electronically and
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/s/

Doris Bates

1/4/2007 03:35:37 PM

CSO

One filing checklist for both SE5 submissions under a
common Written Request.

Zyprexa (olanzapine): Pediatric Bipolar, Pediatric Schizophrenia: Priority Review Supplements

NDA FILING MEETING MINUTES
NDA 20-592 SE5-040, SE5-041
Zyprexa (olanzapine): Pediatric Bipolar, Pediatric Schizophrenia
Priority Review Supplements

DATE: 15 December 2006

BACKGROUND: Zyprexa is approved as tablets, orally dissolving tablets, and an intramuscular injection, for schizophrenia, agitation associated with schizophrenia (i.m. formulation) and bipolar disorder. These two supplements are submitted in response to a Pediatric Written Request and the firm seeks exclusivity.

Participants and Reviewers (including those [not present] at filing meeting) :

Discipline

Division Director
Deputy Director
Clinical Team Leader and Reviewer:
Secondary Medical:
Statistical Team Leader: and Reviewer
Pharmacology Team Leader and Reviewer:
Statistical Pharmacology:
Chemistry PAL and Reviewer
Environmental Assessment (if needed):
Biopharmaceutics Team Leader and Reviewer:
DSI:
Regulatory Project Management:
HFD-130 Clinical Safety:
ODS Clinical Safety (RiskMAP-IO):
DDMAC:

Participants

Thomas P. Laughren, M.D.
[Mitchell Mathis, M.D.]
Ni Aye Khin, M.D. / Cara Alfaro, Pharm.D.
not applicable
Peiling Yang, Ph.D. / Fanhui Kong, Ph.D.
not applicable
not applicable
[Janice Brown, Ph.D.]
[Janice Brown, Ph.D.] [categorical exclusion]
Ray Baweja, Ph.D. / Andre Jackson, Ph.D.
[Khairy Malek, Ph.D.]
Doris J. Bates, Ph.D.
not applicable
Mary Dempsey
not applicable

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES, consult sent ☒ NO ☐
international sites need to be inspected; DSI was notified.
- RiskMAP Consult Needed? YES, consult sent ☒ NO ☐
screening review by ODS-IO: RiskMAP is routine pharmacovigilance, and acceptable; a detailed review will not be needed.
- Advisory Committee Meeting needed? YES, date if known NO ☒

STATISTICS FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

Zyprexa (olanzapine): Pediatric Bipolar, Pediatric Schizophrenia: Priority Review Supplements

CHEMISTRY

FILE ☒

REFUSE TO FILE ☐

Categorical exclusion was omitted, has been requested and received.

ELECTRONIC SUBMISSION: No comments.

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

☐

The application is unsuitable for filing. Explain why:

☒

The application, on its face, appears to be sufficiently well-organized and indexed to be suitable for filing.

☐

No filing issues have been identified.

☒

Clinical review issues have been identified and are to be communicated by Day 74.

Comments: The RPM determined that the application, when submitted, was lacking Patent Information [form 3542a] and Environmental Assessment information. These are filing issues [submission materially complete on face]. The RPM contacted the firm and both missing components were submitted and received prior to the filing meeting.

Clinical review comments will be incorporated into the filing letter, which must be signed by the DD to issue on or before January 12, 2007.

Milestones for this project:

Filing date: 12-29-06.

74-day letter date: 1-12-2007.

Pediatric Exclusivity Board Date: 1-10-07. Exclusivity Pkg due to PEB: 1-1-07.

PEB Exclusivity Finding Due Day 90: 1-29-07.

Midcycle meeting: 2-12-2007.

Internal Deadline for reviews to Team Leaders: 3-26-07

Internal Deadline for reviews to Clinical TL: 4-09-07

Internal Deadline for package to Dr. Laughren: 4-16-07

Clinical and Clinical Pharmacology Summaries Due for Web Release by Day 175: 4-24-2007

PDUFA date: 4-30-2007

Doris J. Bates, Ph.D.

Regulatory Project Manager, HFD-130

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/s/

Doris Bates

1/4/2007 03:39:57 PM

One meeting for both submissions under a common Written
Request.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

**FILING COMMUNICATION
ISSUES IDENTIFIED**

NDA 20-592 / S-040
NDA 20-592 / S-041

Eli Lilly & Co., Inc.
Attention: Catherine Melfi, Ph.D.
Scientific Director
U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Melfi:

Please refer to your October 30, 2006 supplemental new drug applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) Tablets, 2.5, 5, 7.5, 10, 15, and 20 mg.

We also refer to your submissions to both sNDAs dated and received November 15, 2006.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, as you were informed on December 15, 2006 in a voice mail from Dr. Doris Bates, Regulatory Project Manager for this Division, these applications have been filed as of that date, under section 505(b) of the Act, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following clinical review issues, and we request that you amend your supplements to respond to these issues. We anticipate that any response submitted in a timely manner will be reviewed during this review cycle, but review decisions will be made on a case-by-case basis at the time we receive the submission.

1. In protocols HGIU and HGIN, height was obtained using "a measuring device supplied by the sponsor" that required calibration. Please provide a description of this measuring device.
2. The primary efficacy analysis in study HGIN excluded data from site 021 due to GCP issues at that site (it is noted that results are similar with and without this site). Please provide details regarding the GCP issues at this site or specify where this information may be found in the study report.
3. In protocol HGIN, it is noted that "The scoring of the anchored version of the BPRS-C is determined by interviews with both the patient and the parent/legal guardian at all visits. The reference score (as recorded in the CRFs) should be the higher of the two scores". Viewing the

CRF, it does not appear that there is an area where the recorder could state the source of the ratings. Are both ratings, patient and parent/legal guardian, available for subjects in this study? If so, please provide these ratings and indicate the primary source for the ratings.

We are providing these comments at this time in order to give you prompt notice of these issues. Our filing review is only a preliminary evaluation of the application and is therefore not indicative of all deficiencies that may be identified during our ongoing review. Issues may be added, deleted, expanded upon or modified as we continue our substantive review of your applications.

If you have any questions, please call Dr. Bates, at (301) 796-2260.

Sincerely,

{See appended electronic signature page}

Thomas P. Laughren, M.D.
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
1/4/2007 09:58:13 PM

Bates, Doris J

From: Catherine Melfi [MELFI_CATHERINE@LILLY.COM]
Sent: Tuesday, December 19, 2006 8:07 AM
To: Jackson, Andre J
Cc: Bates, Doris J
Subject: Assays for NDA 20-592/S-040 and S-041
Attachments: Note to reviewer for methods final dec 18th.doc; F1D-MC-HGCS.pdf; F1D-MC-HGGC.pdf; F1D-MC-HGMF.pdf; emfinfo.txt

Dr. Jackson:

I have obtained supporting documentation regarding the bioanalytical methods for the study reports included in NDA 20-592/S-040 and S-041. The attached Note to the Reviewers provides details on the supporting documentation for each of the four studies. Because we are not able to send zip files over e-mail, I am sending you the information in 3 separate e-mail messages. I will also be submitting the information as an amendment to NDA 20-592/S-040 and S-041. Information to be included in this, plus 2 subsequent e-mail messages is described below.

Included in this e-mail message is:

- The Note to the Reviewers
- 3 bioanalytical methods study reports, one for each of the studies:
 - 1.F1D-MC-HGGC
 - 2.F1D-MC-HGCS
 - 3.F1D-MC-HGMF

In a subsequent e-mail message, I will send the following 2 documents that provide detailed bioanalytical methods information:

- 820-0457: Automated Extraction of Olanzapine (LY170053) in Heparinized Human Plasma. [This report is relevant to all studies]
- 820-0192: The Measurement of Olanzapine in Heparinized Human Plasma [This report is relevant to study HGMF]

In the third e-mail message, I will send the four manuscripts (described in the Note to the Reviewers) that support the bioanalytical methods for study LOAY.

Please let me know if you have further questions or need additional information. I will be out of the office until January 3, but I will be checking e-mail and voicemail while I'm out in case there are any urgent matters.

Cathy Melfi

Catherine A. Melfi, Ph.D
U.S. Regulatory Affairs
Phone 317-277-2905 Fax 317-276-1652
Mobile (b) (6)
email: melfi@lilly.com

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1/18/2007

"Jackson, Andre J" <andre.jackson@fda.hhs.gov>

To melfi@lilly.com

cc

Subject Assays

12/14/2006 09:57 AM

The NDA 20-592 has four studies:

- 1.F1D-MC-HGGC
- 2.F1D-MC-HGCS
- 3.F1D-MC-HGMF
- 4.F1D-SB-LOAY

I have taken a quick look and I did not see any detailed analytical information.

Please look at these submissions and let me know if the analytical data is present and if so where at.

If the data is not at the FDA or not in the project # 1000-0457 report which I called you about, please see that it gets added to the submission.

Please be certain that study dates and assay dates are given so that total storage time can be compared with reported stability data.

Thanks

Andre Jackson

CDER/DCP1

301-796-1545

Please note new E-mail Address:

Andre.Jackson@fda.hhs.gov

1/18/2007

Bates, Doris J

From: Catherine Melfi [MELFI_CATHERINE@LILLY.COM]
Sent: Monday, December 18, 2006 10:50 AM
To: Alfaro, Cara
Cc: Bates, Doris J
Subject: Re: HGIU and HGIN Protocol Submissions
Attachments: emfinfo.txt

Cara:

Thanks for your question. This one is easy. Protocols HGIN and HGIU were submitted to IND 28,705 in a submission dated October 31, 2002; serial number 876.

Our statisticians are validating the programming used to respond to your recent request about exposure numbers. As soon as I get confirmation of the validation, I will send you the response by e-mail. I am not anticipating any problems getting this to you before 1:00 today.

Doris: Should I also submit our response as an amendment to the applications? Our submissions group will have to burn the CDs, etc, so we'd probably submit it later this week. We're also working on sending some site information to DSI as well as working on Dr Jackson's request for the bioanalytical information.

Cathy

Catherine A. Melfi, Ph.D
U.S. Regulatory Affairs
Phone 317-277-2905 Fax 317-276-1652
Mobile (b) (4)
email: melfi@lilly.com

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"Alfaro, Cara" <cara.alfaro@fda.hhs.gov>

12/18/2006 10:35 AM

To Catherine Melfi <MELFI_CATHERINE@LILLY.COM>

CC "Bates, Doris J" <doris.bates@fda.hhs.gov>

Subject HGIU and HGIN Protocol Submissions

Cathy,

There is no hurry on this request. Can you tell me to what IND numbers these protocols were submitted, the dates of the submissions and the serial no. of the submissions? Thank you.
(Yes, I do realize that the protocols are included as addenda to the study reports that I have).

Do you have any questions about our earlier request re: exposure data? Our apologies about needing the information so quickly - as Doris said, we are feeling time pressure as well.

1/18/2007

Thank you.

Cara

Cara Alfaro, Pharm.D., BCPP

Clinical Reviewer

Food and Drug Administration

CDER/Division of Psychiatry Products

10903 New Hampshire Avenue, Building 22, Room 4219

Silver Spring, MD 20993-0002

cara.alfaro@fda.hhs.gov

1/18/2007

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, December 06, 2006 4:38 PM
To: 'Catherine Melfi'
Subject: RE: URGENT: NDA 20-592: S-040 and S-041: Requesting Patent Information on FDA Forms 3542a

Please send two - one for each - I'd rather not take chances at this stage. Sorry I didn't see this sooner, Cathy. Thanks for the quick turnaround.

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

From: Catherine Melfi [mailto:MELFI_CATHERINE@LILLY.COM]
Sent: Wednesday, December 06, 2006 3:38 PM
To: Bates, Doris J
Subject: Re: URGENT: NDA 20-592: S-040 and S-041: Requesting Patent Information on FDA Forms 3542a

Doris: I have contacted our patent attorney to get me the 3542a. I'm not sure how it was left out of the submission, but you're right -- it was left out. Do you need me to send 2 copies (one for each indication), or should I send just one? It would be the exact same document, and in the original submission we only submitted one copy of the information that pertained to both applications. Thanks, and I hope to get something to you very shortly!

Cathy

Catherine A. Melfi, Ph.D
U.S. Regulatory Affairs
Phone 317-277-2905 Fax 317-276-1652
Mobile 317-777-1309
email: melfi@lilly.com

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"Bates, Doris J" <doris.bates@fda.hhs.gov>

12/06/2006 02:42 PM

To Catherine Melfi <MELFI_CATHERINE@LILLY.COM>

cc

Subject: URGENT: NDA 20-592: S-040 and S-041: Requesting Patent Information on F
Forms 3542a

1/18/2007

Hi Cathy

I am going through the submission prior to our filing meeting and realized that I could not locate the patent information forms, FDA 3542a. I found a written statement regarding the patent, but we need these actual forms, signed and submitted for each indication. Can you get these to me by the start of next week? You can .pdf them to me when they're sent in to the official file.

I've attached the template in WORD format for your convenience... thanks!

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

From: Catherine Melfi [mailto:MELFI_CATHERINE@LILLY.COM]
Sent: Friday, December 01, 2006 2:30 PM
To: Bates, Doris J
Cc: Alfaro, Cara; Bates, Doris J; Kong, Fanhui; Malek, Khairy W
Subject: Re: URGENT: NDA 20-592: S-040 and S-041: Requesting a Comprehensive List of Study Sites / Investigators / Patients Randomized / Patients Completing at each site

Hi Doris. I have attached the information you requested. While all of the information is in the supplements, it is not all there in a single document. The attached files include information on sites, investigators, addresses, and number of patients randomized and completed for studies HGIU (S-040, bipolar) and HGIN (S-041, schizophrenia). Please note that we have 2 columns for completed patients -- one column shows the number of patients who completed the acute phase of the study and the other column shows the number of patients who completed the open-label phase. Please let me know if you have any questions or require additional information.

Cathy Melfi

Catherine A. Melfi, Ph.D
U.S. Regulatory Affairs
Phone 317-277-2905 Fax 317-276-1652
Mobile 317-777-1309
email: melfi@lilly.com

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"Bates, Doris J"
<doris.bates@fda.hhs.gov>

11/29/2006 03:10 PM

To: Catherine Melfi <MELFI_CATHERINE@LILLY.COM>
cc: "Bates, Doris J" <doris.bates@fda.hhs.gov>, "Malek, Khairy W" <khairy.malek@fda.hhs.gov>, "A
Cara" <cara.alfaro@fda.hhs.gov>, "Kong, Fanhui" <fanhui.kong@fda.hhs.gov>
Subject: URGENT: NDA 20-592: S-040 and S-041: Requesting a Comprehensive List of Study Sites /

1/18/2007

Investigators / Patients Randomized / Patients Completing at each site

Hi Cathy

As we conduct our filing reviews for these supplements, our reviewers have had difficulty locating a single comprehensive list of sites with investigators, addresses, and patients randomized / completed.

Could you send me this information for both of the pediatric supplements, via reply email, using the Reply to All function so that my colleagues on the CC list receive it as well? This will save us time since our need is urgent.

If the information is already in these submissions, if you could indicate where we can find it, that would also be very helpful.

Again, this is urgent - we need the information, if at all possible, by the end of the day this Friday.

Thanks in advance,

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

1/18/2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-520/S-012
NDA 20-592/S-039
NDA 21-086/S-021
NDA 18-936/S-077

PRIOR APPROVAL SUPPLEMENT

Ely Lilly and Company
Attention: Robin Pitts Wojcieszek, R.Ph.
Associate Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Wojcieszek:

This is a replacement letter for the supplement acknowledgement letter signed on October 11, 2006. In the previous letter, it was stated this application would be reviewed under the provisions of Subpart H (accelerated approval). Please disregard this paragraph. These applications will be reviewed in accordance with our review classification guidance .

We have received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Symbyax (fluoxetine/olanzapine) Capsules
Zyprexa (olanzapine) Tablets
Zyprexa Zydis (olanzapine) Tablets
Prozac (fluoxetine) Capsules

Review Priority Classification: Priority (P)

Date of Application: September 28, 2006

Date of Receipt: September 29, 2006

Our Reference Number: NDA 21-520/S-012
NDA 20-592/S-039
NDA 21-086/S-021
NDA 18-936/S-077

These supplemental applications propose the new indication of treatment resistant depression for Symbyax.

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Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 28, 2006 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be March 29, 2007.

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 note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed, we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the application numbers listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you have any questions, call Renmeet Grewal, Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, MD.
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
10/16/2006 01:29:43 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592/S-039
NDA 21-086/S-021
NDA 18-936/S-077

Eli Lilly and Company
Attention: Robin Wojcieszek, R.Ph.
Associate Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Wojcieszek:

Please refer to your supplemental new drug applications dated September 28, 2006, received September 29, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) tablets (NDA 20-592), Zyprexa Zydis (olanzapine) orally disintegrating tablets (NDA 21-086), Prozac (fluoxetine hydrochloride) capsules (NDA 18-936).

We additionally refer to meetings dated August 18, 1999, April 30, 2002, and December 21, 2005, between Lilly and representatives of the Agency. Although the Agency encourages sponsors to develop fixed dose combinations to help in simplifying dosage regimens, increase compliance and reduce safety concerns, we stated that it would be highly unusual for individual product labeling to be modified to address combination treatment. We agreed that this approach may be reasonable as long as the information was consistent across all of the products, i.e., the combination product and each of the individual products.

However, it is not possible to achieve a Symbyax dose by combining the approved fluoxetine and olanzapine product dosages. We believe that the dosing regimens, proposed in the Zyprexa and Prozac supplements, will confuse prescribers and confound the adequate directions for use in the current individual product labeling. As such, after a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d).

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Renmeet Grewal, Pharm.D., Regulatory Project Manager, at 301-796-1080.

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

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this page is the manifestation of the electronic signature.**

/s/

Thomas Laughren
11/27/2006 11:15:58 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-520/S-012
NDA 20-592/S-039
NDA 21-086/S-021
NDA 18-936/S-077

NDA ACKNOWLEDGMENT

Ely Lilly and Company
Attention: Robin Pitts Wojcieszek R.Ph.
Associate Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Wojcieszek:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Symbyax (fluoxetine/olanzapine) Capsules
Zyprexa (olanzapine) Tablets
Zyprexa Zydis (olanzapine) Tablets
Prozac (fluoxetine) Capsules

Review Priority Classification: Priority (P)

Date of Application: September 28, 2006

Date of Receipt: September 29, 2006

Our Reference Number: NDA 18-936

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 28, 2006 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be March 29, 2007.

We will review this application under the provisions of 21 CFR 314 Subpart H (accelerated approval). Before approval of these applications, you must submit copies of all promotional materials, including promotional labeling as well as advertisements, to be used within 120 days after approval.

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

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NDA 18-936/S-077
Page 2

effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you have any questions, call Renmeet Grewal, Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, MD.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research