

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-520/S-012

Trade Name: **SYMBYAX**

Generic Name: **Olanzapine and Fluoxetine Hydrochloride**

Sponsor: **Eli Lilly & Company**

Approval Date: 03/19/2009

Indications: Acute treatment of:

- Depressive Episodes Associated with Bipolar I Disorder in adults
- Treatment Resistant Depression (Major Depressive Disorder in adults who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode) patients.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 21-520/S-012

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-520/S-012

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-520/S-012, 20-592/S-039, 21-086/S-021

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

Dear Dr. Phillips:

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 Symbyax (olanzapine/fluoxetine) capsules (NDA 21-520), Zyprexa (olanzapine) tablets (NDA 20-592), and Zyprexa Zydis (olanzapine) tablets (NDA 21-086).

We acknowledge receipt of your submissions dated September 19, 2008, December 1, 2008, February 23, 2009, February 27, 2009 and March 17, 2009.

Your submission of September 19, 2008 constituted a complete response to our August 1, 2008 action letter.

These supplemental new drug applications propose Risk Evaluation and Mitigation Strategies (REMS) and provide for the following changes to product labeling:

For Symbyax (fluoxetine/olanzapine):

- The addition of a new indication, acute treatment of treatment resistant depression (TRD)
- The addition of a Medication Guide

For Zyprexa and Zyprexa Zydis:

The addition of the following language to the Indications and Usage section, regarding concomitant use of fluoxetine and olanzapine:

- acute treatment of depressive episodes associated with Bipolar Disorder
- acute treatment of treatment resistant depression

The addition of a Medication Guide for Zyprexa and Zyprexa Zydis.

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

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, **“SPL for approved NDA 21-520/S-012, NDA 20-592/S-039, & NDA 21-086/S-021.”**

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. For administrative purposes, designate this submission **“Final Printed Carton and Container Labels for approved NDA21-520/S-012, 20-592/S-039, and 21-086/S-021”** Approval of this submission by FDA is not required before the labeling is used.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for the Symbyax application because the condition of TRD is not applicable to the pediatric population in sufficient numbers to study.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

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) if 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)). This provision took effect on March 25, 2008.

Since the approvals of Zyprexa on September 30, 1996, Zyprexa Zydis on April 6, 2000, and Symbyax on December 24, 2003, we have become aware of new safety information from analysis of data indicating increased risks of hyperglycemia, hyperlipidemia, and weight gain associated with

olanzapine use, as noted in our August 1, 2008, letter. Therefore, we consider this information to be “new safety information” as defined in FDAAA.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Symbyax, Zyprexa, and Zyprexa Zydis pose serious and significant public health concerns requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients’ safe and effective use of Symbyax, Zyprexa, and Zyprexa Zydis. FDA has determined that Symbyax, Zyprexa, and Zyprexa Zydis are products that have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients’ decisions to use, or continue to use Symbyax, Zyprexa, and Zyprexa Zydis. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Symbyax, Zyprexa, and Zyprexa Zydis.

Your proposed REMS for Symbyax, Zyprexa, and Zyprexa Zydis, submitted on February 27, 2009, and appended to this letter are approved. The REMS consists of the Medication Guides included with this letter and the timetable for submission of assessments of each of the REMS included in your February 27, 2009 submission.

Your assessment of each of the REMS should include an evaluation of:

- a. Patients’ understanding of the serious risks of Symbyax, Zyprexa, and Zyprexa Zydis.
- b. A report on periodic assessments of the distribution and dispensing of each Medication Guide in accordance with 21 CFR 208.24.
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

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

- **NDA 21-520, NDA 20-592 or NDA 21-086 - REMS ASSESSMENT**
- **NEW SUPPLEMENT FOR NDA 21-520, NDA 20-592 or NDA 21-086
PROPOSED REMS MODIFICATION
REMS ASSESSMENT [if included]**

If you do not submit electronically, please send 5 copies of submissions containing REMS assessments or proposed modifications of the REMS.

**POSTMARKETING COMMITMENT: STUDIES SUBJECT TO REPORTING
REQUIREMENTS OF 21 CFR 314.80**

We remind you of your following postmarketing commitment agreed upon in your submission dated September 19, 2008. This commitment is listed below.

1. Long-Term Efficacy Studies

Since TRD is a chronic illness, you are required to assess the longer-term effectiveness and safety of Symbyax in TRD. You have agreed to submit the results of this trial during the first quarter of 2015.

FINAL REPORT SUBMISSION: March 31, 2015

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled “**Postmarketing Study Commitment Protocol**”, “**Postmarketing Study Commitment Final Report**”, or “**Postmarketing Study Commitment Correspondence.**”

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
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

INTRODUCTORY PROMOTIONAL MATERIALS

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

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

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 Renmeet Grewal, Pharm.D., Senior 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

Enclosure: REMS, Product labeling & Medication Guide

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/s/

Thomas Laughren
3/19/2009 03:59:08 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-520/S-012

OTHER ACTION LETTERS



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-520/S- (b) (4) /S-012/S- (b) (4) /S- (b) (4)

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

Dear Dr. Phillips:

Please refer to your supplemental new drug application dated September 28, 2006 (S-012), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbyax (fluoxetine/olanzapine) 3/25mg, 6/25mg, 12/25mg, 6/50mg, & 12/50mg capsules.

We acknowledge receipt of your submissions dated:

(b) (4)

Your submission of February 1, 2008 constituted a complete response to our March 28, 2007 action letter.

This supplemental new drug application provides for the use of Symbyax (fluoxetine/olanzapine) capsules for acute treatment of treatment resistant depression (TRD).

We also acknowledge the following supplements incorporated into the label:

(b) (4)

(b) (4)

(b) (4)

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

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENT

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)). This provision took effect on March 25, 2008.

Since Symbyax was approved in 2003, for the treatment of depressive episodes associated with bipolar disorder, we have become aware of new safety information from analysis of data related to an increased risk of hyperglycemia, hyperlipidemia, and weight gain associated with olanzapine use. This information was not available when Symbyax was granted marketing authorization for the treatment of depressive episodes associated with bipolar disorder. Therefore, we consider this information to be “new safety information” as defined in FDAAA.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that 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 Symbyax. FDA has determined that Symbyax is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients’ decisions to use Symbyax. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Symbyax.

You must revise and submit your Medication Guide to include the metabolic risks of Symbyax. Your proposed REMS must contain your revised Medication Guide and a timetable for submission of assessments of the REMS. The timetable for assessment of the REMS shall be no less frequent than 18 months, 3 years, and 7 years after the REMS is approved. Your assessment of the REMS should include an evaluation of:

- a. Patients’ understanding of the serious risks of Symbyax
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

In accordance with section 505-1, you are required within 120 days of the date of this letter to amend your supplements with a REMS prior approval supplement containing your proposed REMS.

Use the following designator to prominently label all submissions, including supplements, relating to this REMS:

SUPPLEMENT FOR NDA 21-520 PROPOSED REMS

POSTMARKETING STUDY COMMITMENT: LONG-TERM EFFICACY STUDIES

We acknowledge your commitment to conduct a study to evaluate the longer term effectiveness of olanzapine-fluoxetine combination (OFC; Symbyax) in treatment-resistant depression (TRD) in your correspondence, dated August 30, 2007. Review of the proposed outline of the study design for Study H6P-MC-HDAY submitted August 30, 2007, has revealed a major design limitation that needs to be modified. (b) (4)

(b) (4) In order to seek a labeling claim, the patients must be stabilized for (b) (4) on OFC (b) (4) before randomization to double-blind treatment in Study Period III. The (b) (4) stabilization period must be prospective, (b) (4) Please submit a full protocol with the (b) (4) week OFC stabilization period prior to randomization including a complete statistical analysis plan for review.

Since TRD is a chronic illness, you are required to assess the longer-term effectiveness of Symbyax in TRD. Accordingly, we will require that you submit your plan for studying, as a Postmarketing Commitment, the effect of Symbyax in reducing the risk of relapse in acutely remitted patients with TRD. We ask that you commit to submitting these results no later than 3 years after the date of approval of this supplemental application.

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 Renmeet Grewal, Pharm.D., Senior 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
8/1/2008 05:45:57 PM



NDA 21-520/S-012

Eli Lilly & Company
Attention: Robin Pitts 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, received September 29, 2006 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbyax (olanzapine/fluoxetine) 3 mg/25 mg, 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50 mg (mg equivalent olanzapine/mg equivalent fluoxetine) capsules.

We acknowledge receipt of your amendments dated November 8, 28, 2006, December 11, 14, 2006, and February 5, 20, 2007.

This supplemental new drug application provides for the use of Symbyax (olanzapine/fluoxetine) capsules for Treatment Resistant Depression (TRD).

We completed our review of this application, and it is approvable. Before the application may be approved, however, you must address the following issues:

Updated Information on Risks of Weight Gain, Hyperglycemia, and Hyperlipidemia

A primary concern with this application and the primary basis for our not taking a final action is our view that we lack important safety information needed to adequately update the labeling with all relevant risk information. In particular, we are concerned that the labeling is deficient with regard to information about weight gain, hyperglycemia, and hyperlipidemia that is associated with olanzapine use, whether taken alone or in combination with fluoxetine. You must fully address these concerns before we will be able to take a final action on this application.

Defining what your response will need to be to fully address these concerns will likely involve an interactive process with us over a period of several weeks, because we, first of all, need to fully understand the universe of relevant olanzapine and olanzapine/fluoxetine combination (OFC) studies and their characteristics. Once we better understand this set of studies and what data pertinent to our concerns were collected, we will be in a better position to provide detailed advice on what studies to pool, what data to provide, and what additional analyses to conduct. In characterizing these trials, it will be important to provide details on what data were collected (e.g., plasma glucose, HbA1c, total cholesterol, HDL, LDL, triglyceride, and urine glucose), under what conditions (e.g., fasting vs non-

fasting), the demographic characteristics of the subjects (e.g., pediatric vs adult), and at what intervals. Once we have this information, we will work with you to define what studies to pool, and what data to provide to us and in what format.

Regarding data displays, an overall strategy will be to subgroup patients on the basis of their status at baseline so that clinicians can better understand the risks associated with treatment of patients falling into different risk categories. For example, we note that your proposed Symbyax label includes

(b) (4)

This latter finding was based on a small number of patients in the OFC program, and for this reason, we would like to see such data for the entire olanzapine program. In addition, we were troubled that this important finding was not included in your proposed label. We will want you to provide similar information based on subgroupings of patients on the basis of weight and BMI (for weight change), and lipid findings for the lipid data. We will want you to provide data both on proportions of patients meeting certain on-treatment criteria and also for mean change from baseline.

If you feel you have already aggregated and submitted data to address these concerns, then we ask that you direct us to precisely which submissions these are. If, on the other hand, you have aggregated the appropriate data for your own internal purposes but not submitted them, we ask you to submit them. Your recent February 20, 2007 response to our January 12, 2007 letter regarding the New York Times story has not been particularly helpful in addressing these concerns.

Our overall goal is to improve labeling with regard to these findings so that clinicians will be better informed on what the risks are for their patients. They cannot make reasonable treatment decisions until they have such information. We do not feel that current labeling for either Symbyax or Zyprexa, provides sufficient information on these risks, and we fully intend to insure that these labels are enhanced with the best available information to characterize these risks.

Post Marketing Commitments

Long-Term Efficacy Studies

Since TRD is a chronic illness, you are required to assess the longer-term effectiveness and safety of Symbyax in TRD. Accordingly, we ask for your commitment to submit, as a Postmarketing commitment, the results of this study to evaluate Symbyax's ability to reduce the risk of relapse in acutely remitted patients with TRD. We ask that you commit to submitting these results no later than 3 years after the date of approval of this supplemental application.

Labeling

Please submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling text for the package insert.

In addition, all previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Foreign Regulatory Update/Labeling

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

Request for Safety Update and World Literature Update

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Prior to an approval action, we require an updated report on the world's archival literature pertaining to the safety of Symbyax. Please provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. This report should include only literature not covered in your previous submissions. We will need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Symbyax. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of

articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Promotional Materials

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

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

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 application 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 the Division of Psychiatry Products 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., 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

Enclosure

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/s/

Thomas Laughren
3/28/2007 02:51:39 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-520/S-012

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYMBYAX safely and effectively. See full prescribing information for SYMBYAX.

SYMBYAX (olanzapine and fluoxetine hydrochloride) capsule for oral use

Initial U.S. Approval: 2003

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS AND INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

- See full prescribing information for complete boxed warning.
- Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for Major Depressive Disorder (MDD) and other psychiatric disorders. SYMBYAX is not approved for use in children and adolescents (5.1, 8.4, 17.2).
- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. SYMBYAX is not approved for the treatment of patients with dementia-related psychosis (5.2, 5.18, 17.3).

RECENT MAJOR CHANGES

Boxed Warning: Increased Mortality in Elderly Patients with Dementia-Related Psychosis	08/2008
Indications and Usage:	
Depressive Episodes Associated with Bipolar I Disorder (1.1)	03/2009
Treatment Resistant Depression (1.2)	03/2009
Dosage and Administration:	
Depressive Episodes Associated with Bipolar I Disorder (2.1)	03/2009
Treatment Resistant Depression (2.2)	03/2009
Specific Populations (2.3)	03/2009
Warnings and Precautions:	
Elderly Patients with Dementia-Related Psychosis (5.2)	08/2008
Hyperglycemia (5.4)	03/2009
Hyperlipidemia (5.5)	03/2009
Weight Gain (5.6)	03/2009
Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions (5.7)	03/2009
Activation of Mania/Hypomania (5.9)	03/2009
Orthostatic Hypotension (5.11)	03/2009
Seizures (5.13)	03/2009
Hyponatremia (5.15)	03/2009
Potential for Cognitive and Motor Impairment (5.16)	03/2009
Use in Patients with Concomitant Illness (5.18)	03/2009
Hyperprolactinemia (5.19)	03/2009
Laboratory Tests (5.23)	03/2009

INDICATIONS AND USAGE

SYMBYAX® combines olanzapine, an atypical antipsychotic and fluoxetine, a selective serotonin reuptake inhibitor, indicated for acute treatment of:

- Depressive Episodes Associated with Bipolar I Disorder in adults (1.1)
- Treatment Resistant Depression (Major Depressive Disorder in adults who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode) (1.2)

DOSAGE AND ADMINISTRATION

- Once daily in the evening, generally beginning with 6 mg/25 mg (2.1, 2.2)
- The starting dose of SYMBYAX 3 mg/25 mg – 6 mg/25 mg should be used in patients predisposed to hypotensive reactions, hepatic impairment, or with potential for slowed metabolism. Escalate dose cautiously (2.3)
- Consider using a lower dose for pregnant women during the third trimester (2.3)

- Discontinue gradually (2.4)
- The safety of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical trials (2.1, 2.2)

DOSAGE FORMS AND STRENGTHS

- Capsules: 3 mg/25 mg, 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50 mg (mg equivalent olanzapine/mg equivalent fluoxetine) (3)

CONTRAINDICATIONS

- Do not use with an MAOI or within 14 days of discontinuing an MAOI due to risk of drug interaction. At least 5 weeks should be allowed after stopping SYMBYAX before starting treatment with an MAOI (4, 7.1)
- Do not use with pimozide due to risk of risk of drug interaction or QT_c prolongation (4, 7.9)
- Do not use with thioridazine due to QT_c interval prolongation or potential for elevated thioridazine plasma levels. Do not use thioridazine within 5 weeks of discontinuing SYMBYAX (4, 7.8)

WARNINGS AND PRECAUTIONS

- Clinical Worsening and Suicide Risk* Monitor for clinical worsening and suicidal thinking and behavior (5.1)
- Elderly Patients with Dementia-Related Psychosis* Increased risk of death and increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) (5.2)
- Neuroleptic Malignant Syndrome* Manage with immediate discontinuation and close monitoring (5.3)
- Hyperglycemia* In some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking olanzapine. Patients taking SYMBYAX should be monitored for symptoms of hyperglycemia and undergo fasting blood glucose testing at the beginning of, and periodically during, treatment. (5.4)
- Hyperlipidemia* Undesirable alterations in lipids have been observed. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically during, treatment (5.5)
- Weight gain* Potential consequences of weight gain should be considered. Patients should receive regular monitoring of weight (5.6)
- Serotonin Syndrome and Neuroleptic Malignant Syndrome (NMS)-like Reactions* Have been reported with SYMBYAX. Discontinue and initiate supportive treatment (5.7)
- Allergic Reactions and Rash* Discontinue upon appearance of rash or allergic phenomena (5.8)
- Activation of Mania/Hypomania* Screen for Bipolar Disorder and monitor for activation of mania/hypomania (5.9)
- Tardive Dyskinesia* Discontinue if clinically appropriate (5.10)
- Orthostatic Hypotension* Orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, may occur especially during initial dose titration. Use caution in patients with cardiovascular disease or cerebrovascular disease, and those conditions that could affect hemodynamic responses (5.11)
- Seizures* Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold (5.13)
- Abnormal Bleeding* May increase the risk of bleeding. Use with NSAIDs, aspirin, warfarin, or drugs that affect coagulation may potentiate the risk of gastrointestinal or other bleeding (5.14)
- Hyponatremia* Has been reported with SYMBYAX in association with syndrome of inappropriate antidiuretic hormone (SIADH) (5.15)
- Potential for Cognitive and Motor Impairment* Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery (5.16)
- Hyperprolactinemia* May elevate prolactin levels (5.19)
- Long Elimination Half-Life of Fluoxetine* Changes in dose will not be fully reflected in plasma for several weeks (5.21)
- Laboratory Tests* Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment (5.23)

ADVERSE REACTIONS

Most common adverse reactions (≥5% and at least twice that for placebo) are disturbance in attention, dry mouth, fatigue, hypersomnia, increased appetite, peripheral edema, sedation, somnolence, tremor, vision blurred, and weight increased (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- **Monoamine Oxidase Inhibitor (MAOI)** SYMBYAX is contraindicated for use with MAOI's, or within 14 days of discontinuing an MAOI due to risk of drug interaction. At least 5 weeks should be allowed after stopping SYMBYAX before starting treatment with an MAOI (4, 7.1)
- **Pimozide** SYMBYAX is contraindicated for use with pimozide due to risk of risk of drug interaction or QT_c prolongation (4, 7.9)
- **Thioridazine** SYMBYAX is contraindicated for use with thioridazine due to QT_c interval prolongation or potential for elevated thioridazine plasma levels. Do not use thioridazine within 5 weeks of discontinuing SYMBYAX (4, 7.8)
- **Drugs Metabolized by CYP2D6** Fluoxetine is a potent inhibitor of CYP2D6 enzyme pathway (7.9)
- **Tricyclic Antidepressants (TCAs)** Monitor TCA levels during coadministration with SYMBYAX or when SYMBYAX has been recently discontinued (7.9)
- **CNS Acting Drugs** Caution is advised if the concomitant administration of SYMBYAX and other CNS-active drugs is required (7.2)
- **Antihypertensive Agent** Enhanced antihypertensive effect (7.9)
- **Levodopa and Dopamine Agonists** May antagonize levodopa/dopamine agonists (7.9)
- **Benzodiazepines** May potentiate orthostatic hypotension and sedation (7.8, 7.9)
- **Clozapine** May elevate clozapine levels (7.9)
- **Haloperidol** Elevated haloperidol levels have been observed (7.9)
- **Carbamazepine** Potential for elevated carbamazepine levels and clinical anticonvulsant toxicity (7.9)

- **Phenytoin** Potential for elevated phenytoin levels and clinical anticonvulsant toxicity (7.9)
- **Alcohol** May potentiate sedation and orthostatic hypotension (7.9)
- **Serotonergic Drugs** Potential for Serotonin Syndrome (5.7, 7.3)
- **Triptans** There have been rare postmarketing reports of Serotonin Syndrome with use of an SSRI and a triptan (5.7, 7.4)
- **Tryptophan** Concomitant use with tryptophan is not recommended (5.7, 7.5)
- **Fluvoxamine** May increase olanzapine levels; a lower dose of the olanzapine component of SYMBYAX should be considered (7.8)
- **Drugs that Interfere with Hemostasis** (e.g., NSAIDs, Aspirin, Warfarin, etc.): May potentiate the risk of bleeding (7.6)
- **Drugs Tightly Bound to Plasma Proteins** Fluoxetine may cause shift in plasma concentrations (7.9)

-----USE IN SPECIFIC POPULATIONS-----

- **Pregnancy** SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1)
- **Nursing Mothers** Breast feeding is not recommended (8.3)
- **Pediatric Use** Safety and effectiveness of SYMBYAX in children and adolescent patients have not been established (8.4)
- **Hepatic Impairment** Use a lower or less frequent dose in patients with cirrhosis (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 03/2009

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS AND INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Suicidality and Antidepressant Drugs — Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of SYMBYAX or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SYMBYAX is not approved for use in pediatric patients. [See *Warnings and Precautions (5.1)*, *Use in Specific Populations (8.4)*, and *Patient Counseling Information (17.2)*].

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. SYMBYAX (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with dementia-related psychosis [see *Warnings and Precautions (5.2, 5.18)* and *Patient Counseling Information (17.3)*].

1 INDICATIONS AND USAGE

1.1 Depressive Episodes Associated with Bipolar I Disorder

SYMBYAX is indicated for the acute treatment of depressive episodes associated with Bipolar I Disorder in adults [see *Clinical Studies (14.1)*].

1.2 Treatment Resistant Depression

SYMBYAX is indicated for the acute treatment of treatment resistant depression (Major Depressive Disorder in adults who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode) [see *Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Depressive Episodes Associated with Bipolar I Disorder

SYMBYAX should be administered once daily in the evening, generally beginning with the 6-mg/25-mg capsule. While food has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of SYMBYAX has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with SYMBYAX in a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg [see *Clinical Studies (14.1)*]. The safety of doses above 18 mg per 75 mg has not been evaluated in clinical studies.

While there is no body of evidence to answer the question of how long a patient treated with SYMBYAX should remain on it, it is generally accepted that Bipolar I Disorder, including the depressive episodes associated with Bipolar I Disorder, is a chronic illness requiring chronic treatment. The physician should periodically reexamine the need for continued pharmacotherapy.

2.2 Treatment Resistant Depression

SYMBYAX should be administered once daily in the evening, generally beginning with the 6-mg/25-mg capsule. While food has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of SYMBYAX has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with SYMBYAX in a dose range of olanzapine 6 to 18 mg and fluoxetine 25 to 50 mg [see *Clinical Studies (14.2)*]. The safety of doses above 18 mg per 75 mg has not been evaluated in clinical studies.

While there is no body of evidence to answer the question of how long a patient treated with SYMBYAX should remain on it, it is generally accepted that treatment resistant depression (Major Depressive Disorder in adult patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode) is a chronic illness requiring chronic treatment. The physician should periodically reexamine the need for continued pharmacotherapy.

2.3 Specific Populations

The starting dose of SYMBYAX 3 mg/25 mg to 6 mg/25 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of SYMBYAX (female gender, geriatric age, nonsmoking status) or those patients who may be pharmacodynamically sensitive to olanzapine. Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. When indicated, dose escalation should be performed with caution in these patients. SYMBYAX has not been systematically studied in patients >65 years of age or in patients <18 years of age [see *Warnings and Precautions* (5.18), *Use in Specific Populations* (8.5), and *Clinical Pharmacology* (12.3, 12.4)].

Treatment of Pregnant Women During the Third Trimester — When treating pregnant women with fluoxetine, a component of SYMBYAX, during the third trimester, the physician should carefully consider the potential risks and potential benefits of treatment. Neonates exposed to SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalizations, respiratory support, and tube feeding. The physician may consider using a lower dose in the third trimester [see *Use in Specific Populations* (8.1)].

2.4 Discontinuation of Treatment with SYMBYAX

Symptoms associated with discontinuation of fluoxetine, a component of SYMBYAX, SNRIs, and SSRIs, have been reported [see *Warnings and Precautions* (5.22)].

3 DOSAGE FORMS AND STRENGTHS

Capsules (mg equivalent olanzapine/mg equivalent fluoxetine):

- 3 mg/25 mg
- 6 mg/25 mg
- 6 mg/50 mg
- 12 mg/25 mg
- 12 mg/50 mg

4 CONTRAINDICATIONS

The use of SYMBYAX is contraindicated with the following:

- Monoamine Oxidase Inhibitors (MAOI) — [see *Drug Interactions* (7.1)]
- Pimozide — [see *Drug Interactions* (7.9)]
- Thioridazine — [see *Drug Interactions* (7.9)]

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with Major Depressive Disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with Major Depressive Disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, Obsessive Compulsive Disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug versus placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1: Suicidality per 1000 Patients Treated

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case

≥65	6 fewer cases
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No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for Major Depressive Disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [see *Warnings and Precautions* (5.22)].

Families and caregivers of patients being treated with antidepressants for Major Depressive Disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for SYMBYAX should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

It should be noted that SYMBYAX is not approved for use in treating any indications in the pediatric population [see *Use in Specific Populations* (8.4)].

5.2 Elderly Patients with Dementia-Related Psychosis

Increased Mortality — Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. SYMBYAX is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning, Warnings and Precautions* (5.18), and *Patient Counseling Information* (17.3)].

In olanzapine placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

Cerebrovascular Adverse Events (CVAE), Including Stroke — Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine and SYMBYAX are not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning and Patient Counseling Information* (17.3)].

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If after recovering from NMS, a patient requires treatment with an antipsychotic, the patient should be carefully monitored, since recurrences of NMS have been reported [see *Warnings and Precautions* (5.7) and *Patient Counseling Information* (17.4, 17.8)].

5.4 Hyperglycemia

Physicians should consider the risks and benefits when prescribing SYMBYAX to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100-126 mg/dL, nonfasting 140-200 mg/dL). Patients taking SYMBYAX should be monitored regularly for worsening of glucose control. Patients starting treatment with SYMBYAX

should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug [see *Patient Counseling Information* (17.5.)].

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the 2 highest serum concentrations was 15.0 mg/dL.

In a study of healthy volunteers, subjects who received olanzapine (N=22) for 3 weeks had a mean increase compared to baseline in fasting blood glucose of 2.3 mg/dL. Placebo-treated subjects (N=19) had a mean increase in fasting blood glucose compared to baseline of 0.34 mg/dL.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, SYMBYAX was associated with a greater mean change in random glucose compared to placebo (8.65 mg/dL vs -3.86 mg/dL). The difference in mean changes between SYMBYAX and placebo was greater in patients with evidence of glucose dysregulation at baseline (including those patients diagnosed with diabetes mellitus or related adverse reactions, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥ 200 mg/dL, or a baseline fasting glucose level ≥ 126 mg/dL). SYMBYAX-treated patients had a greater mean HbA_{1c} increase from baseline of 0.15% (median exposure 63 days), compared to a mean HbA_{1c} decrease of 0.04% in fluoxetine-treated subjects (median exposure 57 days) and a mean HbA_{1c} increase of 0.12% in olanzapine-treated patients (median exposure 56 days).

In an analysis of 6 controlled clinical studies, a larger proportion of SYMBYAX-treated subjects had glycosuria (4.4%) compared to placebo-treated subjects (1.4%).

The mean change in nonfasting glucose in patients exposed at least 48 weeks was 5.9 mg/dL (N=425).

Table 2 shows short-term and long-term changes in random glucose levels from adult SYMBYAX studies.

Table 2: Changes in Random Glucose Levels from Adult SYMBYAX Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure		At least 48 weeks exposure	
			N	Patients	N	Patients
Random Glucose	Normal to High (<140 mg/dL to ≥ 200 mg/dL)	Symbyax	609	2.3%	382	3.1%
		Placebo	346	0.3%	NA ^a	NA ^a
	Borderline to High (≥ 140 mg/dL and <200 mg/dL to ≥ 200 mg/dL)	Symbyax	44	34.1%	27	37.0%
		Placebo	28	3.6%	NA ^a	NA ^a

^a Not Applicable.

Controlled fasting glucose data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL vs 0.17 mg/dL).

The mean change in fasting glucose for olanzapine-treated patients exposed at least 48 weeks was 4.2 mg/dL (N=487). In analyses of patients who completed 9-12 months of olanzapine therapy, mean change in fasting and nonfasting glucose levels continued to increase over time.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with Schizophrenia (6 weeks) or Bipolar I Disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a greater mean change from baseline in fasting glucose levels compared to placebo (2.68 mg/dL vs -2.59 mg/dL). The mean change in fasting glucose for adolescents exposed at least 24 weeks was 3.1 mg/dL (N=121). Table 3 shows short-term and long-term changes in fasting blood glucose from adolescent olanzapine monotherapy studies.

Table 3: Changes in Fasting Glucose Levels from Adolescent Olanzapine Monotherapy Studies

			Up to 12 weeks	At least 24 weeks
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Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	exposure		exposure	
			N	Patients	N	Patients
Fasting Glucose	Normal to High (<100 mg/dL to ≥ 126 mg/dL)	Olanzapine	124	0%	108	0.9%
		Placebo	53	1.9%	NA ^a	NA ^a
	Borderline to High (≥ 100 mg/dL and <126 mg/dL to ≥ 126 mg/dL)	Olanzapine	14	14.3%	13	23.1%
		Placebo	13	0%	NA ^a	NA ^a

^a Not Applicable.

5.5 Hyperlipidemia

Undesirable alterations in lipids have been observed with SYMBYAX use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using SYMBYAX, is recommended [see *Patient Counseling Information* (17.6.)].

Clinically meaningful, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with SYMBYAX use. Clinically meaningful increases in total cholesterol have also been seen with SYMBYAX use.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, SYMBYAX-treated patients had an increase from baseline in mean random total cholesterol of 12.1 mg/dL compared to an increase from baseline in mean random total cholesterol of 4.8 mg/dL for olanzapine-treated patients and a decrease in mean random total cholesterol of 5.5 mg/dL for placebo-treated patients. Table 4 shows categorical changes in nonfasting lipid values.

In long-term olanzapine and fluoxetine in combination studies (at least 48 weeks), changes (at least once) in nonfasting total cholesterol from normal at baseline to high occurred in 12% (N=150) and changes from borderline to high occurred in 56.6% (N=143) of patients. The mean change in nonfasting total cholesterol was 11.3 mg/dL (N= 426).

Table 4: Changes in Nonfasting Lipids Values from Controlled Clinical Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	Patients
Nonfasting Triglycerides	Increase by ≥ 50 mg/dL	OFC	174	67.8%
		Olanzapine	172	72.7%
	Normal to High (<150 mg/dL to ≥ 500 mg/dL)	OFC	57	0%
		Olanzapine	58	0%
	Borderline to High (≥ 150 mg/dL and <500 mg/dL to ≥ 500 mg/dL)	OFC	106	15.1%
		Olanzapine	103	8.7%
Nonfasting Total Cholesterol	Increase by ≥ 40 mg/dL	OFC	685	35%
		Olanzapine	749	22.7%
		Placebo	390	9%
	Normal to High (<200 mg/dL to ≥ 240 mg/dL)	OFC	256	8.2%
		Olanzapine	279	2.9%
		Placebo	175	1.7%
	Borderline to High (≥ 200 mg/dL and <240 mg/dL to ≥ 240 mg/dL)	OFC	213	36.2%
		Olanzapine	261	27.6%
		Placebo	111	9.9%

Fasting lipid data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse reactions, patients treated with lipid lowering agents, patients with high baseline lipid levels.

In long-term olanzapine studies (at least 48 weeks), patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.6 mg/dL, 2.5 mg/dL, and 18.7 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 0.16 mg/dL. In an analysis of patients who completed 12 months of therapy, the mean nonfasting total cholesterol did not increase further after approximately 4-6 months.

The proportion of olanzapine-treated patients who had changes (at least once) in total cholesterol, LDL cholesterol or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low, was greater in long-term studies (at least 48 weeks) as compared with short-term studies. Table 5 shows categorical changes in fasting lipids values.

Table 5: Changes in Fasting Lipids Values from Adult Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure		At least 48 weeks exposure	
			N	Patients	N	Patients
	Increase by ≥ 50 mg/dL	Olanzapine	745	39.6%	487	61.4%
		Placebo	402	26.1%	NA ^a	NA ^a
Fasting Triglycerides	Normal to High (<150 mg/dL to ≥ 200 mg/dL)	Olanzapine	457	9.2%	293	32.4%
		Placebo	251	4.4%	NA ^a	NA ^a
	Borderline to High (≥ 150 mg/dL and <200 mg/dL to ≥ 200 mg/dL)	Olanzapine	135	39.3%	75	70.7%
		Placebo	65	20.0%	NA ^a	NA ^a
	Increase by ≥ 40 mg/dL	Olanzapine	745	21.6%	489	32.9%
		Placebo	402	9.5%	NA ^a	NA ^a
Fasting Total Cholesterol	Normal to High (<200 mg/dL to ≥ 240 mg/dL)	Olanzapine	392	2.8%	283	14.8%
		Placebo	207	2.4%	NA ^a	NA ^a
	Borderline to High (≥ 200 mg/dL and <240 mg/dL to ≥ 240 mg/dL)	Olanzapine	222	23.0%	125	55.2%
		Placebo	112	12.5%	NA ^a	NA ^a
	Increase by ≥ 30 mg/dL	Olanzapine	536	23.7%	483	39.8%
		Placebo	304	14.1%	NA ^a	NA ^a
Fasting LDL Cholesterol	Normal to High (<100 mg/dL to ≥ 160 mg/dL)	Olanzapine	154	0%	123	7.3%
		Placebo	82	1.2%	NA ^a	NA ^a
	Borderline to High (≥ 100 mg/dL and <160 mg/dL to ≥ 160 mg/dL)	Olanzapine	302	10.6%	284	31.0%
		Placebo	173	8.1%	NA ^a	NA ^a

^a Not Applicable.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the median increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. The safety and efficacy of olanzapine have not been established in patients under the age of 18 years.

In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescents, including those with Schizophrenia (6 weeks) or Bipolar I Disorder (manic or mixed episodes) (3 weeks), olanzapine-treated adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 12.9 mg/dL, 6.5 mg/dL, and 28.4 mg/dL, respectively, compared to increases from baseline in mean fasting total cholesterol and LDL cholesterol of 1.3 mg/dL and 1.0 mg/dL, and a decrease in triglycerides of 1.1 mg/dL for placebo-treated adolescents. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated adolescents and placebo-treated adolescents.

In long-term olanzapine studies (at least 24 weeks), adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.5 mg/dL, 5.4 mg/dL, and 20.5 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 4.5 mg/dL. Table 6 shows categorical changes in fasting lipids values in adolescents.

Table 6: Changes in Fasting Lipids Values from Adolescent Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 6 weeks exposure		At least 24 weeks exposure	
			N	Patients	N	Patients
Fasting Triglycerides	Increase by ≥ 50 mg/dL	Olanzapine	138	37.0%	122	45.9%
		Placebo	66	15.2%	NA ^a	NA ^a
	Normal to High (<90 mg/dL to >130 mg/dL)	Olanzapine	67	26.9%	66	36.4%
		Placebo	28	10.7%	NA ^a	NA ^a
	Borderline to High	Olanzapine	37	59.5%	31	64.5%
		Placebo				

(≥90 mg/dL and ≤130 mg/dL to >130 mg/dL)		Placebo	17	35.3%	NA ^a	NA ^a
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%	122	14.8%
		Placebo	66	4.5%	NA ^a	NA ^a
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%	78	7.7%
		Placebo	43	2.3%	NA ^a	NA ^a
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	36	38.9%	33	57.6%
		Placebo	13	7.7%	NA ^a	NA ^a
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%	121	22.3%
		Placebo	63	11.1%	NA ^a	NA ^a
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%	92	10.9%
		Placebo	44	4.5%	NA ^a	NA ^a
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%	21	47.6%
		Placebo	9	0%	NA ^a	NA ^a

^a Not Applicable.

5.6 Weight Gain

Potential consequences of weight gain should be considered prior to starting SYMBYAX. Patients receiving SYMBYAX should receive regular monitoring of weight [see *Patient Counseling Information* (17.7.)].

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, the mean weight increase for SYMBYAX-treated patients was greater than placebo-treated patients [4 kg (8.8 lb) vs -0.3 kg (-0.7 lb)]. Twenty-two percent of SYMBYAX-treated patients gained at least 7% of their baseline weight, with a median exposure of 6 weeks. This was greater than in placebo-treated patients (1.8%). Approximately 3% of SYMBYAX-treated patients gained at least 15% of their baseline weight, with a median exposure of 8 weeks. This was greater than in placebo-treated patients (0%). Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 2.5% of SYMBYAX-treated patients and 0% of placebo-treated patients.

In long-term olanzapine and fluoxetine in combination studies (at least 48 weeks), the mean weight gain was 6.7 kg (14.7 lb) (median exposure of 448 days, N=431). The percentages of patients who gained at least 7%, 15% or 25% of their baseline body weight with long-term exposure were 66%, 33%, and 10%, respectively. Discontinuation due to weight gain occurred in 1.2% of patients treated with olanzapine and fluoxetine in combination following at least 48 weeks of exposure.

In long-term olanzapine studies (at least 48 weeks), the mean weight gain was 5.6 kg (12.3 lb) (median exposure of 573 days, N=2021). The percentages of patients who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 64%, 32%, and 12%, respectively. Discontinuation due to weight gain occurred in 0.4% of olanzapine-treated patients following at least 48 weeks of exposure.

Table 7 includes data on adult weight gain with olanzapine pooled from 86 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 7: Weight Gain with Olanzapine Use in Adults

Amount Gained kg (lb)	6 Weeks (N=7465) (%)	6 Months (N=4162) (%)	12 Months (N=1345) (%)	24 Months (N=474) (%)	36 Months (N=147) (%)
≤0	26.2	24.3	20.8	23.2	17.0
0 to <5 (0-11 lb)	57.0	36.0	26.0	23.4	25.2
>5 to ≤10 (11-22 lb)	14.9	24.6	24.2	24.1	18.4
>10 to ≤15 (22-33 lb)	1.8	10.9	14.9	11.4	17.0
>15 to ≤20 (33-44 lb)	0.1	3.1	8.6	9.3	11.6
>20 to ≤25 (44-55 lb)	0	0.9	3.3	5.1	4.1
>25 to ≤30 (55-66 lb)	0	0.2	1.4	2.3	4.8
>30 (>66 lb)	0	0.1	0.8	1.2	2

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. Mean increase in weight in adolescents was greater than in adults. In 4 placebo-controlled trials, discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to 0% of placebo-treated patients.

Table 8: Weight Gain with Olanzapine Use in Adolescents from 4 Placebo-Controlled Trials

	Olanzapine-treated patients	Placebo-treated patients
Mean change in body weight from baseline (median exposure = 3 weeks)	4.6 kg (10.1 lb)	0.3 kg (0.7 lb)
Percentage of patients who gained at least 7% of baseline body weight	40.6% (median exposure to 7% = 4 weeks)	9.8% (median exposure to 7% = 8 weeks)
Percentage of patients who gained at least 15% of baseline body weight	7.1% (median exposure to 15% = 19 weeks)	2.7% (median exposure to 15% = 8 weeks)

In long-term olanzapine studies (at least 24 weeks), the mean weight gain was 11.2 kg (24.6 lb) (median exposure of 201 days, N=179). The percentages of adolescents who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 89%, 55%, and 29%, respectively. Among adolescent patients, mean weight gain by baseline BMI category was 11.5 kg (25.3 lb), 12.1 kg (26.6 lb), and 12.7 kg (27.9 lb), respectively, for normal (N=106), overweight (N=26) and obese (N=17). Discontinuation due to weight gain occurred in 2.2% of olanzapine-treated patients following at least 24 weeks of exposure.

Table 9 shows data on adolescent weight gain with olanzapine pooled from 6 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified. Little clinical trial data is available on weight gain in adolescents with olanzapine beyond 6 months of treatment.

Table 9: Weight Gain with Olanzapine Use in Adolescents

Amount Gained kg (lb)	6 Weeks (N=243) (%)	6 Months (N=191) (%)
≤0	2.9	2.1
0 to ≤5 (0-11 lb)	47.3	24.6
>5 to ≤10 (11-22 lb)	42.4	26.7
>10 to ≤15 (22-33 lb)	5.8	22.0
>15 to ≤20 (33-44 lb)	0.8	12.6
>20 to ≤25 (44-55 lb)	0.8	9.4
>25 to ≤30 (55-66 lb)	0	2.1
>30 to ≤35 (66-77 lb)	0	0
>35 to ≤40 (77-88 lb)	0	0
>40 (>88 lb)	0	0.5

5.7 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions

The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of SYMBYAX with MAOIs intended to treat depression is contraindicated [see *Contraindications (4) and Drug Interactions (7.1)*].

If concomitant treatment of SYMBYAX with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [see *Drug Interactions (7.4)*].

The concomitant use of SYMBYAX with serotonin precursors (such as tryptophan) is not recommended [see *Drug Interactions (7.5)*].

Treatment with SYMBYAX and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately, if the above reactions occur, and supportive symptomatic treatment should be initiated [see *Warnings and Precautions (5.3) and Patient Counseling Information (17.4, 17.8)*].

5.8 Allergic Reactions and Rash

In SYMBYAX premarketing controlled clinical studies, the overall incidence of rash or allergic reactions in SYMBYAX-treated patients [4.6% (26/571)] was similar to that of placebo [5.2% (25/477)]. The majority of the cases of rash and/or urticaria were mild; however, 3 patients discontinued (1 due to rash, which was moderate in severity and 2 due to allergic reactions, 1 of which included face edema).

In fluoxetine US clinical studies, 7% of 10,782 fluoxetine-treated patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical studies, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash

include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these reactions were reported to recover completely.

In fluoxetine premarketing clinical studies, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of fluoxetine, systemic reactions, possibly related to vasculitis, have developed in patients with rash. Although these reactions are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic reactions.

Anaphylactoid reactions, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary reactions, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These reactions have occurred with dyspnea as the only preceding symptom.

Whether these systemic reactions and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these reactions has not been identified. Upon the appearance of rash or of other possible allergic phenomena for which an alternative etiology cannot be identified, SYMBYAX should be discontinued.

5.9 Activation of Mania/Hypomania

A major depressive episode may be the initial presentation of Bipolar Disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a manic episode in patients at risk for Bipolar Disorder. Whether any of the symptoms described for clinical worsening and suicide risk represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for Bipolar Disorder; such screening should include a detailed psychiatric history, including a family history of suicide, Bipolar Disorder, and depression. It should be noted that SYMBYAX is approved for the acute treatment of depressive episodes associated with Bipolar I Disorder.

In the 2 controlled bipolar depression studies there was no statistically significant difference in the incidence of manic reactions (manic reaction or manic depressive reaction) between SYMBYAX- and placebo-treated patients. In 1 of the studies, the incidence of manic reactions was (7% [3/43]) in SYMBYAX-treated patients compared to (3% [5/184]) in placebo-treated patients. In the other study, the incidence of manic reactions was (2% [1/43]) in SYMBYAX-treated patients compared to (8% [15/193]) in placebo-treated patients. This limited controlled trial experience of SYMBYAX in the acute treatment of depressive episodes associated with Bipolar I Disorder makes it difficult to interpret these findings until additional data is obtained. Because of this and the cyclical nature of Bipolar I Disorder, patients should be monitored closely for the development of symptoms of mania/hypomania during treatment with SYMBYAX.

5.10 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

The incidence of dyskinetic movement in SYMBYAX-treated patients was infrequent. The mean score on the Abnormal Involuntary Movement Scale (AIMS) in the SYMBYAX-controlled database across clinical studies involving SYMBYAX-treated patients decreased from baseline. Nonetheless, SYMBYAX should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on SYMBYAX, drug discontinuation should be considered. However, some patients may require treatment with SYMBYAX despite the presence of the syndrome. The need for continued treatment should be reassessed periodically.

5.11 Orthostatic Hypotension

SYMBYAX may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, especially during the initial dose-titration period [see *Patient Counseling Information* (17.10)].

In the SYMBYAX-controlled clinical trials across all indications, there were no significant differences between SYMBYAX-treated patients and olanzapine, fluoxetine- or placebo-treated patients in exposure-adjusted rates of orthostatic systolic blood pressure decreases of at least 30 mm Hg. Orthostatic systolic blood pressure decreases of at least 30 mm Hg occurred in 4.0% (28/705), 2.3% (19/831), 4.5% (18/399), and 1.8% (8/442) of the SYMBYAX, olanzapine, fluoxetine, and placebo groups, respectively. In this group

of studies, the incidence of syncope-related adverse reactions (i.e., syncope and/or loss of consciousness) in SYMBYAX-treated patients was 0.4% (3/771) compared to placebo 0.2% (1/477).

In a clinical pharmacology study of SYMBYAX, 3 healthy subjects were discontinued from the trial after experiencing severe, but self-limited, hypotension and bradycardia that occurred 2 to 9 hours following a single 12-mg/50-mg dose of SYMBYAX. Reactions consisting of this combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in at least three other healthy subjects treated with various formulations of olanzapine (one oral, two intramuscular). In controlled clinical studies, the incidence of patients with a ≥ 20 bpm decrease in orthostatic pulse concomitantly with a ≥ 20 mm Hg decrease in orthostatic systolic blood pressure was 0.3% (2/706) in the SYMBYAX group, 0.2% (1/445) in the placebo group, 0.7% (6/837) in the olanzapine group, and 0% (0/404) in the fluoxetine group.

SYMBYAX should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

5.12 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. SYMBYAX is not approved for the treatment of patients with Alzheimer's disease.

5.13 Seizures

Seizures occurred in 0.2% (4/2547) of SYMBYAX-treated patients during open-label clinical studies. No seizures occurred in the controlled SYMBYAX studies. Seizures have also been reported with both olanzapine and fluoxetine monotherapy. SYMBYAX should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. SYMBYAX is not approved for the treatment of patients with Alzheimer's disease. Conditions that lower the seizure threshold may be more prevalent in a population of ≥ 65 years of age.

5.14 Abnormal Bleeding

SNRIs and SSRIs, including fluoxetine, may increase the risk of bleeding reactions. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding reactions related to SNRIs and SSRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of SYMBYAX and NSAIDs, aspirin, or other drugs that affect coagulation [*see Drug Interactions (7.6) and Patient Counseling Information (17.11)*].

5.15 Hyponatremia

Hyponatremia has been reported during treatment with SNRIs and SSRIs, including fluoxetine and SYMBYAX. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when SYMBYAX was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SNRIs and SSRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk [*see Use in Specific Populations (8.5)*]. Discontinuation of SYMBYAX should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death. [*See Patient Counseling Information (17.12)*].

5.16 Potential for Cognitive and Motor Impairment

Sedation-related adverse reactions were commonly reported with SYMBYAX treatment occurring at an incidence of 26.6% in SYMBYAX-treated patients compared with 10.9% in placebo-treated patients. Sedation-related adverse reactions (sedation, somnolence, hypersomnia, and lethargy) led to discontinuation in 2% (15/771) of patients in the controlled clinical studies. As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them adversely [*see Patient Counseling Information (17.13)*].

5.17 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic drugs. Appropriate care is advised when prescribing SYMBYAX for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration). [*See Patient Counseling Information (17.13)*].

5.18 Use in Patients with Concomitant Illness

Clinical experience with SYMBYAX in patients with concomitant systemic illnesses is limited [*see Clinical Pharmacology (12.4)*]. The following precautions for the individual components may be applicable to SYMBYAX.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical studies, SYMBYAX was associated with constipation, dry mouth, and tachycardia, all adverse reactions possibly related to cholinergic antagonism. Such adverse reactions

were not often the basis for study discontinuations; SYMBYAX should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, a history of paralytic ileus, or related conditions.

In 5 placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse reactions were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth, and visual hallucinations. The rate of discontinuation due to adverse reactions was significantly greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning, Warnings and Precautions (5.2), and Patient Counseling Information (17.3)*].

As with other CNS-active drugs, SYMBYAX should be used with caution in elderly patients with dementia. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised [see *Boxed Warning and Warnings and Precautions (5.2), and Patient Counseling Information (17.3)*].

SYMBYAX has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the premarket testing.

Caution is advised when using SYMBYAX in cardiac patients and in patients with diseases or conditions that could affect hemodynamic responses [see *Warnings and Precautions (5.11)*].

5.19 Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ receptors, SYMBYAX elevates prolactin levels, and a modest elevation persists during administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. As is common with compounds that increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats [see *Nonclinical Toxicology (13.1)*]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

In clinical studies of SYMBYAX, plasma prolactin concentrations were elevated in 27.6% of adults treated with SYMBYAX compared to 4.8% of placebo-treated patients and modest elevations persisted during administration; possibly associated clinical manifestations, such as galactorrhea and breast enlargement, were observed.

In clinical studies, elevated plasma prolactin concentrations were observed in 34% of adults treated with olanzapine compared to 13.1% of placebo-treated patients. In a pooled analysis from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestations such as galactorrhea (14/8136; 0.2%), gynecomastia (8/4896; 0.2% of males), and breast enlargement (2/3240; 0.06% of females) were reported.

In placebo-controlled olanzapine monotherapy studies in adolescent patients with Schizophrenia or Bipolar I Disorder (manic or mixed episodes), elevated prolactin concentrations compared to baseline occurred in 47.4% of olanzapine-treated patients compared to 6.8% of placebo-treated patients. In long-term clinical trials of olanzapine in adolescents, gynecomastia occurred in 2.4% of males (7/286) and galactorrhea occurred in 1.8% of females (3/168) [see *Use in Specific Populations (8.4)*].

5.20 Concomitant Use of Olanzapine and Fluoxetine Products

SYMBYAX contains the same active ingredients that are in Zyprexa[®], Zyprexa[®] Zydis[®] (olanzapine), and in Prozac[®], Prozac[®] Weekly[™], and Sarafem[®] (fluoxetine HCl). Caution should be exercised when prescribing these medications concomitantly with SYMBYAX [see *Overdosage (10)*].

5.21 Long Elimination Half-Life of Fluoxetine

Because of the long elimination half-lives of fluoxetine and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment. This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine [see *Clinical Pharmacology (12.3)*].

5.22 Discontinuation of Treatment with SYMBYAX

During marketing of fluoxetine, a component of SYMBYAX, SNRIs, and SSRIs, there have been spontaneous reports of adverse reactions occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these reactions are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with fluoxetine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and

norfluoxetine concentration decrease gradually at the conclusion of therapy, which may minimize the risk of discontinuation symptoms with this drug [see *Dosage and Administration (2.4)* and *Patient Counseling Information (17.16)*].

5.23 Laboratory Tests

Fasting blood glucose testing and lipid profile at the beginning of, and periodically during, treatment is recommended [see *Warnings and Precautions (5.4, 5.5)* and *Patient Counseling Information (17.5, 17.6)*].

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect or predict the rates observed in practice.

6.1 Clinical Trials Experience

The information below is derived from a clinical study database for SYMBYAX consisting of 2547 patients with treatment resistant depression, depressive episodes associated with Bipolar I Disorder, Major Depressive Disorder with psychosis, or sexual dysfunction with approximately 1085 patient-years of exposure. The conditions and duration of treatment with SYMBYAX varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or long-term exposure.

Adverse reactions were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a limited (i.e., reduced) number of standardized reaction categories.

In the tables and tabulations that follow, MedDRA or COSTART Dictionary terminology has been used to classify reported adverse reactions. The data in the tables represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is possible that reactions reported during therapy were not necessarily related to drug exposure.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing clinician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Controlled Studies Including Depressive Episodes Associated with Bipolar I Disorder and Treatment Resistant Depression — Overall, 11.3% of the 771 patients in the SYMBYAX group discontinued due to adverse reactions compared with 4.4% of the 477 patients for placebo. Adverse reactions leading to discontinuation associated with the use of SYMBYAX (incidence of at least 1% for SYMBYAX and greater than that for placebo) using MedDRA Dictionary coding were weight increased (2%) and sedation (1%) versus placebo patients which had 0% incidence of weight increased and sedation.

Commonly Observed Adverse Reactions in Short-Term, Controlled Studies Including Depressive Episodes Associated with Bipolar I Disorder and Treatment Resistant Depression — The most commonly observed adverse reactions associated with the use of SYMBYAX (incidence $\geq 5\%$ and at least twice that for placebo in the SYMBYAX-controlled database) using MedDRA Dictionary coding were: disturbance in attention, dry mouth, fatigue, hypersomnia, increased appetite, peripheral edema, sedation, somnolence, tremor, vision blurred and weight increased. Adverse reactions reported in clinical trials of olanzapine/fluoxetine in combination are generally consistent with treatment-emergent adverse reactions during olanzapine or fluoxetine monotherapy.

Adverse Reactions Occurring at an Incidence of 2% or More in Short-Term Controlled Studies Including Depressive Episodes Associated with Bipolar I Disorder and Treatment Resistant Depression — Table 10 enumerates the treatment-emergent adverse reactions associated with the use of SYMBYAX (incidence of at least 2% for SYMBYAX and twice or more than for placebo). The SYMBYAX-controlled column includes patients with various diagnoses while the placebo column includes only patients with bipolar depression and major depression with psychotic features.

**Table 10: Treatment-Emergent Adverse Reactions:
Incidence in Controlled Clinical Studies**

System Organ Class	Adverse Reaction	Percentage of Patients Reporting Event	
		SYMBYAX- Controlled (N=771)	Placebo (N=477)
Eye disorders	Vision blurred	5	2
Gastrointestinal disorders	Dry mouth	15	6
	Flatulence	3	1
	Abdominal distension	2	0
General disorders and administration site conditions	Fatigue	12	2
	Edema peripheral	9	0

	Edema	3	0
	Asthenia	3	1
	Pain	2	1
	Pyrexia	2	1
Infections and infestations	Sinusitis	2	1
Investigations	Weight increased	25	3
Metabolism and nutrition disorders	Increased appetite	20	4
Musculoskeletal and connective tissue disorders	Arthralgia	4	1
	Pain in extremity	3	1
	Musculoskeletal stiffness	2	1
Nervous system disorders	Somnolence	14	6
	Tremor	9	3
	Sedation	8	4
	Hypersomnia	5	1
	Disturbance in attention	5	1
	Lethargy	3	1
Psychiatric disorders	Restlessness	4	1
	Thinking abnormal	2	1
	Nervousness	2	1
Reproductive system and breast disorders	Erectile dysfunction	2	1

Extrapyramidal Symptoms

Dystonia, Class Effect for Antipsychotics — Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, the frequency and severity are greater with high potency and at higher doses of first generation antipsychotic drugs. In general, an elevated risk of acute dystonia may be observed in males and younger age groups receiving antipsychotics; however, events of dystonia have been reported infrequently (<1%) with the olanzapine and fluoxetine combination.

Additional Findings Observed in Clinical Studies

Sexual Dysfunction — In the pool of controlled SYMBYAX studies in patients with bipolar depression, there were higher rates of the treatment-emergent adverse reactions decreased libido, anorgasmia, impotence and abnormal ejaculation in the SYMBYAX group than in the placebo group. One case of decreased libido led to discontinuation in the SYMBYAX group. In the controlled studies that contained a fluoxetine arm, the rates of decreased libido and abnormal ejaculation in the SYMBYAX group were less than the rates in the fluoxetine group. None of the differences were statistically significant.

Sexual dysfunction, including priapism, has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Difference Among Dose Levels Observed in Other Olanzapine Clinical Trials

In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of olanzapine in patients with Schizophrenia or Schizoaffective Disorder, statistically significant differences among 3 dose groups were observed for the following safety outcomes: weight gain, prolactin elevation, fatigue and dizziness. Mean baseline to endpoint increase in weight (10 mg/day: 1.9 kg; 20 mg/day: 2.3 kg; 40 mg/day: 3 kg) was observed with significant differences between 10 vs 40 mg/day. Incidence of treatment-emergent prolactin elevation >24.2 ng per mL (female) or >18.77 ng per mL (male) at any time during the trial (10 mg/day: 31.2%; 20 mg/day: 42.7%; 40 mg/day: 61.1%) with significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day; fatigue (10 mg/day: 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%) with significant differences between 10 vs 40 and 20 vs 40 mg/day; and dizziness (10 mg/day: 2.6%; 20 mg/day: 1.6%; 40 mg/day: 6.6%) with significant differences between 20 vs 40 mg, was observed.

Other Adverse Reactions Observed in Clinical Studies

Following is a list of treatment-emergent adverse reactions reported by patients treated with SYMBYAX in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo.

Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; and rare reactions are those occurring in fewer than 1/1000 patients.

Body as a Whole — *Frequent*: chills, neck rigidity, photosensitivity reaction; *Rare*: death¹.

Cardiovascular System — *Frequent*: vasodilatation; *Infrequent*: QT-interval prolonged.

Digestive System — *Frequent*: diarrhea; *Infrequent*: gastritis, gastroenteritis, nausea and vomiting, peptic ulcer; *Rare*: gastrointestinal hemorrhage, intestinal obstruction, liver fatty deposit, pancreatitis.

Hemic and Lymphatic System — *Frequent*: ecchymosis; *Infrequent*: anemia, thrombocytopenia; *Rare*: leukopenia, purpura.

Metabolic and Nutritional — *Frequent*: generalized edema, weight loss; *Rare*: bilirubinemia, creatinine increased, gout.

Musculoskeletal System — *Rare*: osteoporosis.

Nervous System — *Frequent*: amnesia; *Infrequent*: ataxia, buccoglossal syndrome, coma, dysarthria, emotional lability, euphoria, hypokinesia, movement disorder, myoclonus; *Rare*: hyperkinesia, libido increased, withdrawal syndrome.

Respiratory System — *Infrequent*: epistaxis, yawn; *Rare*: laryngismus.

Skin and Appendages — *Infrequent*: alopecia, dry skin, pruritis; *Rare*: exfoliative dermatitis.

Special Senses — *Frequent*: taste perversion; *Infrequent*: abnormality of accommodation, dry eyes.

Urogenital System — *Frequent*: breast pain, menorrhagia², urinary frequency, urinary incontinence; *Infrequent*: amenorrhea², female lactation², hypomenorrhea², metrorrhagia², urinary retention, urinary urgency, urination impaired; *Rare*: breast engorgement².

¹ This term represents a serious adverse event but does not meet the definition for adverse drug reactions. It is included here because of its seriousness.

² Adjusted for gender.

Other Adverse Reactions Observed with Olanzapine or Fluoxetine Monotherapy

The following adverse reactions were not observed in SYMBYAX-treated patients during premarketing clinical studies but have been reported with olanzapine or fluoxetine monotherapy: aplastic anemia, cholestatic jaundice, diabetic coma, dyskinesia, eosinophilic pneumonia³, erythema multiforme, jaundice, neutropenia, sudden unexpected death³, violent behaviors³. Random triglyceride levels of ≥ 1000 mg/dL have been reported.

³ These terms represent serious adverse events but do not meet the definition for adverse drug reactions. They are included here because of their seriousness.

6.2 Vital Signs and Laboratory Studies

Vital Signs — Tachycardia, bradycardia, and orthostatic hypotension have occurred in SYMBYAX-treated patients [see *Warnings and Precautions* (5.12)]. The mean standing pulse rate of SYMBYAX-treated patients was reduced by 0.7 beats/min.

Laboratory Changes — In SYMBYAX clinical studies, (including treatment resistant depression, depressive episodes associated with Bipolar I Disorder, Major Depressive Disorder with psychosis, or sexual dysfunction) SYMBYAX was associated with statistically significantly greater frequencies for the following treatment-emergent findings in laboratory analytes (normal at baseline to abnormal at any time during the trial) compared to placebo: elevated prolactin (27.6% vs 4.8%); elevated urea nitrogen (2.8% vs 0.8%); elevated uric acid (2.9% vs 0.5%); low albumin (2.7% vs 0.3%); low bicarbonate (14.1% vs 8.8%); low hemoglobin (2.6% vs 0%); low inorganic phosphorus (1.9% vs 0.3%); low lymphocytes (1.9% vs 0%); and low total bilirubin (15.3% vs 3.9%).

As with olanzapine, asymptomatic elevations of hepatic transaminases [ALT, AST, and GGT] and alkaline phosphatase have been observed with SYMBYAX. In the SYMBYAX-controlled database, ALT elevations (normal baseline and ≥ 3 times the upper limit of the normal range post-baseline) were observed in 3.4% (20/586) of patients exposed to SYMBYAX compared with none of the 342 placebo patients and 3.5% (23/665) of olanzapine-treated patients. The difference between SYMBYAX and placebo was statistically significant. Of the SYMBYAX patients who started normal at baseline and had increases in ALT ≥ 5 times the upper limit of normal range, none experienced jaundice and four had transient elevations > 200 IU/L [see *Adverse Reactions* (6.1)].

In olanzapine placebo-controlled studies, clinically significant ALT elevations (≥ 3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared with 0% (0/115) of the placebo patients. None of these patients experienced jaundice. In 2 of these patients, liver enzymes decreased toward normal despite continued treatment, and in 2 others, enzymes decreased upon discontinuation of olanzapine. In the remaining 2 patients, 1, seropositive for hepatitis C, had persistent enzyme elevations for 4 months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger olanzapine premarketing database of about 2400 patients with baseline ALT ≤ 90 IU/L, the incidence of ALT elevation to > 200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

Among all 2500 patients in olanzapine clinical studies, approximately 1% (23/2500) discontinued treatment due to transaminase increases.

Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs.

Effect on Cardiac Repolarization — The mean increase in QT_c interval for SYMBYAX-treated patients (4.4 msec) in clinical studies was significantly greater than that for placebo-treated (-0.8 msec), olanzapine-treated (-0.3 msec) patients, and fluoxetine-treated (1.7 msec) patients. There were no significant differences between patients treated with SYMBYAX, placebo, olanzapine, or fluoxetine in the incidence of QT_c outliers (> 500 msec).

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SYMBYAX. Because these reactions are reported voluntarily from a population of uncertain size, it is difficult to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally (but not necessarily causally) related to SYMBYAX therapy include the following: rhabdomyolysis and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis).

7 DRUG INTERACTIONS

The risks of using SYMBYAX in combination with other drugs have not been extensively evaluated in systematic studies. The drug-drug interactions sections of fluoxetine and olanzapine are applicable to SYMBYAX. As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status [see *Clinical Pharmacology* (12.3)].

7.1 Monoamine Oxidase Inhibitors (MAOI)

SYMBYAX should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. There have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with an MAOI, and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome [see *Warnings and Precautions* (5.3)]. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) should be allowed after stopping SYMBYAX before starting an MAOI. [See *Contraindications* (4), *Warnings and Precautions* (5.21), and *Clinical Pharmacology* (12.3)].

7.2 CNS Acting Drugs

Caution is advised if the concomitant administration of SYMBYAX and other CNS-active drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status [see *Clinical Pharmacology* (12.3)].

7.3 Serotonergic Drugs

Based on the mechanism of action of SNRIs and SSRIs, including SYMBYAX, and the potential for serotonin syndrome, caution is advised when SYMBYAX is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort [see *Warnings and Precautions* (5.7)]. The concomitant use of SYMBYAX with SNRIs, SSRIs, or tryptophan is not recommended [see *Drug Interactions* (7.5)].

7.4 Triptans

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of SYMBYAX with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [see *Warnings and Precautions* (5.7)].

7.5 Tryptophan

Five patients receiving fluoxetine in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress. Concomitant use with tryptophan is not recommended [see *Warnings and Precautions* (5.7)].

7.6 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, Warfarin)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SNRIs or SSRIs are coadministered with warfarin [see *Warnings and Precautions* (5.14)]. Warfarin (20-mg single dose) did not affect olanzapine pharmacokinetics. Single doses of olanzapine did not affect the pharmacokinetics of warfarin. Patients receiving warfarin therapy should be carefully monitored when SYMBYAX is initiated or discontinued.

7.7 Electroconvulsive Therapy (ECT)

There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment [see *Warnings and Precautions* (5.13)].

7.8 Potential for Other Drugs to Affect SYMBYAX

Benzodiazepines — Co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine [see *Drug Interactions* (7.9)].

Inducers of 1A2 — Carbamazepine therapy (200 mg BID) causes an approximate 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance [see *Drug Interactions* (7.9)].

Alcohol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics [see *Drug Interactions* (7.9)].

Inhibitors of CYP1A2 — Fluvoxamine, decreases the clearance of olanzapine. This results in a mean increase in olanzapine C_{max} following fluvoxamine administration of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of the olanzapine component of SYMBYAX should be considered in patients receiving concomitant treatment with fluvoxamine.

The Effect of Other Drugs on Olanzapine — Fluoxetine, an inhibitor of CYP2D6, decreases olanzapine clearance a small amount [see *Clinical Pharmacology* (12.3)]. Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. The effect of CYP1A2 inhibitors, such as fluvoxamine and some fluoroquinolone antibiotics, on SYMBYAX has not been evaluated. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

7.9 Potential for SYMBYAX to Affect Other Drugs

Pimozide — Concomitant use of fluoxetine and pimozide is contraindicated. Clinical studies of pimozide with other antidepressants demonstrate an increase in drug interaction or QT_c prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QT_c prolongation warrants restricting the concurrent use of pimozide and fluoxetine. [See *Contraindications* (4)].

Carbamazepine — Patients on stable doses of carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Alcohol — The coadministration of ethanol with SYMBYAX may potentiate sedation and orthostatic hypotension [see *Drug Interactions* (7.8)].

Thioridazine — Thioridazine should not be administered with SYMBYAX or administered within a minimum of 5 weeks after discontinuation of SYMBYAX.

In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs that inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine [see *Contraindications* (4)].

Thioridazine administration produces a dose-related prolongation of the QT_c interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism [see *Contraindications* (4)].

Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated thioridazine plasma levels, thioridazine should not be administered with fluoxetine or within a minimum of five weeks after fluoxetine has been discontinued [see *Contraindications* (4)].

Tricyclic Antidepressants (TCAs) — Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

In two fluoxetine studies, previously stable plasma levels of imipramine and desipramine have increased >2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for 3 weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when SYMBYAX is coadministered or has been recently discontinued [see *Clinical Pharmacology* (12.3)].

Antihypertensive Agents — Because of the potential for olanzapine to induce hypotension, SYMBYAX may enhance the effects of certain antihypertensive agents [see *Warnings and Precautions* (5.11)].

Levodopa and Dopamine Agonists — The olanzapine component of SYMBYAX may antagonize the effects of levodopa and dopamine agonists.

Benzodiazepines — Multiple doses of olanzapine did not influence the pharmacokinetics of diazepam and its active metabolite N-desmethyldiazepam.

When concurrently administered with fluoxetine, the half-life of diazepam may be prolonged in some patients [see *Clinical Pharmacology* (12.3)]. Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

Clozapine — Elevation of blood levels of clozapine has been observed in patients receiving concomitant fluoxetine.

Haloperidol — Elevation of blood levels of haloperidol has been observed in patients receiving concomitant fluoxetine.

Phenytoin — Patients on stable doses of phenytoin have developed elevated plasma levels of phenytoin with clinical phenytoin toxicity following initiation of concomitant fluoxetine.

Drugs Metabolized by CYP2D6 — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP2D6. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by this enzyme.

Fluoxetine inhibits the activity of CYP2D6 and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving fluoxetine

concurrently or has taken it in the previous five weeks. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for a decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (including but not limited to, flecainide, propafenone, vinblastine, and TCAs).

Drugs Metabolized by CYP3A — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

In an in vivo interaction study involving the coadministration of fluoxetine with single doses of terfenadine (a CYP3A substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A activity is not likely to be of clinical significance.

Effect of Olanzapine on Drugs Metabolized by Other CYP Enzymes — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, and CYP2C19. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Lithium — Multiple doses of olanzapine did not influence the pharmacokinetics of lithium.

There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored in patients taking SYMBYAX concomitantly with lithium.

Drugs Tightly Bound to Plasma Proteins — The in vitro binding of SYMBYAX to human plasma proteins is similar to the individual components. The interaction between SYMBYAX and other highly protein-bound drugs has not been fully evaluated. Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs [see *Clinical Pharmacology* (12.3)].

Valproate — In vitro studies using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. Thus, a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

Biperiden — Multiple doses of olanzapine did not influence the pharmacokinetics of biperiden.

Theophylline — Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects — Pregnancy Category C

SYMBYAX — Embryo fetal development studies were conducted in rats and rabbits with olanzapine and fluoxetine in low-dose and high-dose combinations. In rats, the doses were: 2 and 4 mg/kg/day (low-dose) [1 and 0.5 times the maximum recommended human dose (MRHD) on a mg/m² basis, respectively], and 4 and 8 mg/kg/day (high-dose) [2 and 1 times the MRHD on a mg/m² basis, respectively]. In rabbits, the doses were 4 and 4 mg/kg/day (low-dose) [4 and 1 times the MRHD on a mg/m² basis, respectively], and 8 and 8 mg/kg/day (high-dose) [9 and 2 times the MRHD on a mg/m² basis, respectively]. In these studies, olanzapine and fluoxetine were also administered alone at the high-doses (4 and 8 mg/kg/day, respectively, in the rat; 8 and 8 mg/kg/day, respectively, in the rabbit). In the rabbit, there was no evidence of teratogenicity; however, the high-dose combination produced decreases in fetal weight and retarded skeletal ossification in conjunction with maternal toxicity. Similarly, in the rat there was no evidence of teratogenicity; however, a decrease in fetal weight was observed with the high-dose combination.

In a pre- and postnatal study conducted in rats, olanzapine and fluoxetine were administered during pregnancy and throughout lactation in combination (low-dose: 2 and 4 mg/kg/day [1 and 0.5 times the MRHD on a mg/m² basis], respectively, high-dose: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m² basis], respectively, and alone: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m² basis], respectively). Administration of the high-dose combination resulted in a marked elevation in offspring mortality and growth retardation in comparison to the same doses of olanzapine and fluoxetine administered alone. These effects were not observed with the low-dose combination; however, there were a few cases of testicular degeneration and atrophy, depletion of epididymal sperm and infertility in the male progeny. The effects of the high-dose combination on postnatal endpoints could not be assessed due to high progeny mortality.

There are no adequate and well-controlled studies with SYMBYAX in pregnant women.

SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Olanzapine — In oral reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the MRHD on a mg/m² basis, respectively), no evidence of teratogenicity was observed. In a rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD on a mg/m² basis). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD on a mg/m² basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the MRHD on a mg/m² basis). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled clinical studies with olanzapine in pregnant women. Seven pregnancies were observed during premarketing clinical studies with olanzapine, including two resulting in normal births, one resulting in neonatal death due to a cardiovascular defect, three therapeutic abortions, and one spontaneous abortion.

Fluoxetine — In oral embryo fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times the MRHD on a mg/m² basis, respectively) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m² basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m² basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m² basis).

Treatment of Pregnant Women During the Third Trimester — Neonates exposed to fluoxetine, a component of SYMBYAX, SNRIs, or SSRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SNRIs and SSRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see *Dosage and Administration* (2.3), *Contraindications* (4), *Warnings and Precautions* (5.7), and *Drug Interactions* (7.3)].

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1–2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

When treating pregnant women with fluoxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment. Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication. The physician may consider tapering fluoxetine in the third trimester.

8.2 Labor and Delivery

SYMBYAX — The effect of SYMBYAX on labor and delivery in humans is unknown. Parturition in rats was not affected by SYMBYAX. SYMBYAX should be used during labor and delivery only if the potential benefit justifies the potential risk.

Olanzapine — The effect of olanzapine on labor and delivery in humans is unknown. Parturition in rats was not affected by olanzapine.

Fluoxetine — The effect of fluoxetine on labor and delivery in humans is unknown. Fluoxetine crosses the placenta; therefore, there is a possibility that fluoxetine may be associated with adverse effects on the newborn.

8.3 Nursing Mothers

SYMBYAX — Studies evaluating the individual components of SYMBYAX (olanzapine and fluoxetine) in nursing mothers are described below. Because of the potential for serious adverse reactions in nursing infants from SYMBYAX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is recommended that women not breast-feed when receiving SYMBYAX.

Olanzapine — In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving olanzapine should not breast-feed.

Fluoxetine — Fluoxetine is excreted in human breast milk. In 1 breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng per mL. The concentration in the mother's plasma was 295.0 ng per mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on fluoxetine developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng per mL of fluoxetine and 208 ng per mL of norfluoxetine on the 2nd day of feeding.

8.4 Pediatric Use

SYMBYAX — Safety and effectiveness in children and adolescent patients have not been established [see *Boxed Warning and Warnings and Precautions* (5.1)]. Anyone considering the use of SYMBYAX in a child or adolescent must balance the potential risks with the clinical need.

Safety and effectiveness of olanzapine and fluoxetine in combination in children and adolescent patients have not been established.

Fluoxetine — Significant toxicity, including myotoxicity, long-term neurobehavioral and reproductive toxicity, and impaired bone development, has been observed following exposure of juvenile animals to fluoxetine. Some of these effects occurred at clinically relevant exposures.

In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from weaning (Postnatal Day 21) through adulthood (Day 90), male and female sexual development was delayed at all doses, and growth (body weight gain, femur length) was decreased during the dosing period in animals receiving the highest dose. At the end of the treatment period, serum levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and hypospermia) was observed at the high dose. When animals were evaluated after a recovery period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased reactivity at all doses and learning deficit at the high dose) and reproductive functional impairment (decreased mating at all doses and impaired fertility at the high dose) were seen; in addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were found in the high dose group, indicating that the reproductive organ effects seen at the end of treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dose in this study were approximately 0.1-0.2, 1-2, and 5-10 times, respectively, the average exposure in pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat exposures to the major metabolite, norfluoxetine, were approximately 0.3-0.8, 1-8, and 3-20 times, respectively, pediatric exposure at the MRD.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg, intraperitoneal) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These doses did not affect overall growth (body weight gain or femoral length). The doses administered to juvenile mice in this study are approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area (mg/m²) basis.

In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric MRD on a mg/m² basis. Because of the early dosing period in this study, the significance of these findings to the approved pediatric use in humans is uncertain.

8.5 Geriatric Use

SYMBYAX — Clinical studies of SYMBYAX did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see *Dosage and Administration* (2.3)].

Olanzapine — Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263 patients) were ≥65 years of age. In patients with Schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared with younger patients. Studies in patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared with younger patients with Schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning*, *Dosage and Administration* (2.3), and *Warnings and Precautions* (5.2)].

Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient.

Fluoxetine — US fluoxetine clinical studies included 687 patients ≥65 years of age and 93 patients ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SNRIs and SSRIs, including SYMBYAX, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse reaction [see *Warnings and Precautions* (5.15)].

8.6 Hepatic Impairment

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose of the fluoxetine-component of SYMBYAX should be used in patients with cirrhosis. Caution is advised when using SYMBYAX in patients with diseases or conditions that could affect its metabolism [see *Dosage and Administration* (2.3) and *Clinical Pharmacology* (12.4)].

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

SYMBYAX, as with fluoxetine and olanzapine, has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical studies did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of SYMBYAX (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

In studies in rats and rhesus monkeys designed to assess abuse and dependence potential, olanzapine alone was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence at oral doses up to 15 (rat) and 8 (monkey) times the MRHD (20 mg) on a mg/m² basis.

10 OVERDOSAGE

SYMBYAX — During premarketing clinical studies of the olanzapine/fluoxetine combination, overdose of both fluoxetine and olanzapine were reported in five study subjects. Four of the five subjects experienced loss of consciousness (3) or coma (1). No fatalities occurred.

Adverse reactions involving overdose of fluoxetine and olanzapine in combination, and SYMBYAX, have been reported spontaneously to Eli Lilly and Company. An overdose of combination therapy is defined as confirmed or suspected ingestion of a dose of >20 mg olanzapine in combination with a dose of >80 mg fluoxetine. Adverse reactions associated with these reports included somnolence (sedation), impaired consciousness (coma), impaired neurologic function (ataxia, confusion, convulsions, dysarthria), arrhythmias, lethargy, essential tremor, agitation, acute psychosis, hypotension, hypertension, and aggression. Fatalities have been confounded by exposure to additional substances including alcohol, thioridazine, oxycodone, and propoxyphene.

Olanzapine — In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious reactions: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia as well as a patient that experienced sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg of oral olanzapine; however, in another case, a patient was reported to survive an acute olanzapine ingestion of approximately 2 g of oral olanzapine.

Fluoxetine — Worldwide exposure to fluoxetine is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdose, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdose were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown outcome. One of the 6 fatalities was a 9-year-old boy who had a history of OCD, Tourette's Syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams, which was non-lethal.

Other important adverse reactions reported with fluoxetine overdose (single or multiple drugs) included coma, delirium, ECG abnormalities (such as QT-interval prolongation and ventricular tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like reactions, pyrexia, stupor, and syncope.

10.1 Management of Overdose

In managing overdose, the possibility of multiple drug involvement should be considered. In case of acute overdose, establish and maintain an airway and ensure adequate ventilation, which may include intubation. Induction of emesis is not recommended as the possibility of obtundation, seizures, or dystonic reactions of the head and neck following overdose may create a risk for aspiration. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

A specific precaution involves patients who are taking or have recently taken SYMBYAX and may have ingested excessive quantities of a TCA (tricyclic antidepressant). In such cases, accumulation of the parent TCA and/or an active metabolite may increase the possibility of serious sequelae and extend the time needed for close medical observation.

Due to the large volume of distribution of olanzapine and fluoxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidote for either fluoxetine or olanzapine overdose is known. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Do not use epinephrine, dopamine, or other sympathomimetics with β-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.

The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*.

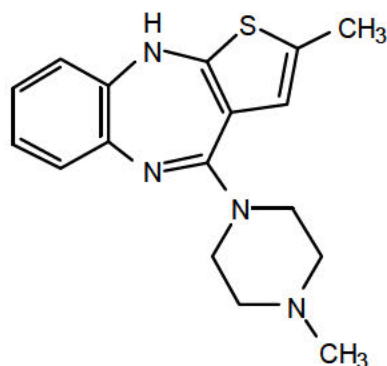
11 DESCRIPTION

SYMBYAX (olanzapine and fluoxetine HCl capsules) combines an atypical antipsychotic and a selective serotonin reuptake inhibitor, olanzapine (the active ingredient in Zyprexa, and Zyprexa Zydis) and fluoxetine hydrochloride (the active ingredient in Prozac, Prozac Weekly, and Sarafem).

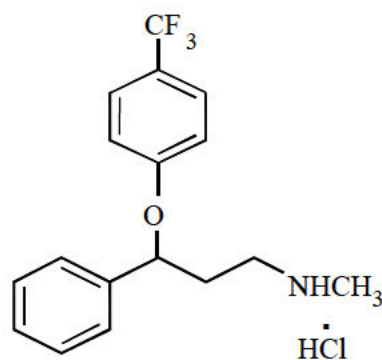
Olanzapine belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44.

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI). The chemical designation is (+)-N-methyl-3-phenyl-3-[(α,α,α -trifluoro-*p*-tolyl)oxy]propylamine hydrochloride. The molecular formula is $C_{17}H_{18}F_3NO \cdot HCl$, which corresponds to a molecular weight of 345.79.

The chemical structures are:



Olanzapine



fluoxetine hydrochloride

Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg per mL in water.

SYMBYAX capsules are available for oral administration in the following strength combinations:

	3 mg/25 mg	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
olanzapine equivalent	3	6	6	12	12
fluoxetine base equivalent	25	25	50	25	50

Each capsule also contains pregelatinized starch, gelatin, dimethicone, titanium dioxide, sodium lauryl sulfate, edible black ink, red iron oxide, yellow iron oxide, and/or black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Although the exact mechanism of SYMBYAX is unknown, it has been proposed that the activation of 3 monoaminergic neural systems (serotonin, norepinephrine, and dopamine) is responsible for its enhanced antidepressant effect. In animal studies, ZYPREXA and fluoxetine in combination has been shown to produce synergistic increases in norepinephrine and dopamine release in the prefrontal cortex compared with either component alone, as well as increases in serotonin.

12.2 Pharmacodynamics

Olanzapine binds with high affinity to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$ ($K_i=4, 11, \text{ and } 5 \text{ nM}$, respectively), dopamine D_{1-4} ($K_i=11 \text{ to } 31 \text{ nM}$), histamine H_1 ($K_i=7 \text{ nM}$), and adrenergic α_1 receptors ($K_i=19 \text{ nM}$). Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ ($K_i=57 \text{ nM}$) and muscarinic M_{1-5} ($K_i=73, 96, 132, 32, \text{ and } 48 \text{ nM}$, respectively). Olanzapine binds weakly to $GABA_A$, BZD, and β -adrenergic receptors ($K_i>10 \mu\text{M}$). Fluoxetine is an inhibitor of the serotonin transporter and is a weak inhibitor of the norepinephrine and dopamine transporters.

Antagonism at receptors other than dopamine and $5HT_2$ may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic-like effects. The antagonism of histamine H_1 receptors by olanzapine may explain the somnolence observed with this drug. The antagonism of α_1 -adrenergic receptors by olanzapine may explain the orthostatic hypotension observed with this drug. Fluoxetine has relatively low affinity for muscarinic, α_1 -adrenergic, and histamine H_1 receptors.

12.3 Pharmacokinetics

SYMBYAX — Fluoxetine (administered as a 60-mg single dose or 60 mg daily for 8 days) caused a small increase in the mean maximum concentration of olanzapine (16%) following a 5-mg dose, an increase in the mean area under the curve (17%) and a

small decrease in mean apparent clearance of olanzapine (16%). In another study, a similar decrease in apparent clearance of olanzapine of 14% was observed following olanzapine doses of 6 or 12 mg with concomitant fluoxetine doses of 25 mg or more. The decrease in clearance reflects an increase in bioavailability. The terminal half-life is not affected, and therefore the time to reach steady state should not be altered. The overall steady-state plasma concentrations of olanzapine and fluoxetine when given as the combination in the therapeutic dose ranges were comparable with those typically attained with each of the monotherapies. The small change in olanzapine clearance, observed in both studies, likely reflects the inhibition of a minor metabolic pathway for olanzapine via CYP2D6 by fluoxetine, a potent CYP2D6 inhibitor, and was not deemed clinically significant. Therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination.

Absorption and Bioavailability

SYMBYAX — Following a single oral 12-mg/50-mg dose of SYMBYAX, peak plasma concentrations of olanzapine and fluoxetine occur at approximately 4 and 6 hours, respectively. The effect of food on the absorption and bioavailability of SYMBYAX has not been evaluated. The bioavailability of olanzapine given as Zyprexa, and the bioavailability of fluoxetine given as Prozac were not affected by food. It is unlikely that there would be a significant food effect on the bioavailability of SYMBYAX.

Olanzapine — Olanzapine is well absorbed and reaches peak concentration approximately 6 hours following an oral dose. Food does not affect the rate or extent of olanzapine absorption when olanzapine is given as Zyprexa. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation.

Fluoxetine — Following a single oral 40-mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng per mL are observed after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine given as Prozac, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant.

Distribution

SYMBYAX — The in vitro binding to human plasma proteins of the olanzapine/fluoxetine combination is similar to the binding of the individual components.

Olanzapine — Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng per mL, binding primarily to albumin and α_1 -acid glycoprotein.

Fluoxetine — Over the concentration range from 200 to 1000 ng per mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α_1 -glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated [see *Drug Interactions* (7.9)].

Metabolism and Elimination

SYMBYAX — SYMBYAX therapy yielded steady-state concentrations of norfluoxetine similar to those seen with fluoxetine in the therapeutic dose range.

Olanzapine — Olanzapine displays linear pharmacokinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr). Administration of olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age [see *Dosage and Administration* (2.3) and *Clinical Pharmacology* (12.4)].

Following a single oral dose of 14 C-labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and CYP450-mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYP1A2, CYP2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6-mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Fluoxetine — Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Fluoxetine is extensively metabolized in the liver to its only identified active metabolite, norfluoxetine, via the CYP2D6 pathway. A number of unidentified metabolites exist.

In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical Issues Related to Metabolism and Elimination

The complexity of the metabolism of fluoxetine has several consequences that may potentially affect the clinical use of SYMBYAX.

Variability in metabolism — A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme CYP2D6. Such individuals are referred to as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants (TCAs). In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative nonsaturable pathways (non-CYP2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because the metabolism of fluoxetine, like that of a number of other compounds including TCAs and other selective serotonin antidepressants, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions [see *Drug Interactions* (7.9)].

Accumulation and slow elimination — The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng per mL and norfluoxetine in the range of 72 to 258 ng per mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because the metabolism of fluoxetine is not proportional to dose. However, norfluoxetine appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine.

12.4 Specific Populations

Geriatric — Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in geriatric patients. Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity.

In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly subjects (≥ 65 years of age) than in non-elderly subjects (< 65 years of age).

The disposition of single doses of fluoxetine in healthy elderly subjects (> 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥ 60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng per mL at the end of 6 weeks. No unusual age-associated pattern of adverse reactions was observed in those elderly patients.

Renal Impairment — The pharmacokinetics of SYMBYAX has not been studied in patients with renal impairment. However, olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not routinely required.

Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on olanzapine metabolite elimination has not been studied.

In depressed patients on dialysis ($N=12$), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.

Hepatic Impairment — Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in patients with hepatic impairment. The lowest starting dose should be considered for patients with hepatic impairment [see *Dosage and Administration* (2.3) and *Warnings and Precautions* (5.18)].

Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects ($N=6$) with clinically significant cirrhosis (Childs-Pugh Classification A and B) revealed little effect on the pharmacokinetics of olanzapine.

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of

2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects.

Gender — Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status — Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely required.

Race — No SYMBYAX pharmacokinetic study was conducted to investigate the effects of race. In vivo studies have shown that exposures to olanzapine are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race, therefore, are not routinely required.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance of olanzapine in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. SYMBYAX dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of the olanzapine component [see *Dosage and Administration* (2.3)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity, or fertility studies were conducted with SYMBYAX. The following data are based on findings in studies performed with the individual components.

Carcinogenesis

Olanzapine — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, and 30/20 mg/kg/day [equivalent to 0.8 to 5 times the maximum recommended human daily dose (MRHD) on a mg/m² basis] and 0.25, 2, and 8 mg/kg/day (equivalent to 0.06 to 2 times the MRHD on a mg/m² basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, and 4 mg/kg/day (males) and 0.25, 1, 4, and 8 mg/kg/day (females) (equivalent to 0.1 to 2 and 0.1 to 4 times the MRHD on a mg/m² basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in females dosed at 8 mg/kg/day (2 times the MRHD on a mg/m² basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2 to 5 times the MRHD on a mg/m² basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the MRHD on a mg/m² basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the finding of prolactin-mediated endocrine tumors in rodents is unknown [see *Warnings and Precautions* (5.19)].

Fluoxetine — The dietary administration of fluoxetine to rats and mice for two years at doses of up to 10 and 12 mg/kg/day, respectively (approximately 1.2 and 0.7 times, respectively, the MRHD on a mg/m² basis), produced no evidence of carcinogenicity.

Mutagenesis

Olanzapine — No evidence of genotoxic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Fluoxetine — Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of Fertility

SYMBYAX — Fertility studies were not conducted with SYMBYAX. However, in a repeat-dose rat toxicology study of three months duration, ovary weight was decreased in females treated with the low-dose [2 and 4 mg/kg/day (1 and 0.5 times the MRHD on a mg/m² basis), respectively] and high-dose [4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m² basis), respectively] combinations of olanzapine and fluoxetine. Decreased ovary weight, and corpora luteal depletion and uterine atrophy were observed to a greater extent in the females receiving the high-dose combination than in females receiving either olanzapine or fluoxetine alone. In a 3-month repeat-dose dog toxicology study, reduced epididymal sperm and reduced testicular and prostate weights were observed with the high-dose combination of olanzapine and fluoxetine [5 and 5 mg/kg/day (9 and 2 times the MRHD on a mg/m² basis), respectively] and with olanzapine alone (5 mg/kg/day or 9 times the MRHD on a mg/m² basis).

Olanzapine — In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the MRHD on a mg/m² basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male-mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the MRHD on a mg/m² basis). Diestrous

was prolonged and estrous was delayed at 1.1 mg/kg/day (0.6 times the MRHD on a mg/m² basis); therefore, olanzapine may produce a delay in ovulation.

Fluoxetine — Two fertility studies conducted in adult rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m² basis) indicated that fluoxetine had no adverse effects on fertility. However, adverse effects on fertility were seen when juvenile rats were treated with fluoxetine at a high dose (30 mg/kg) associated with significant toxicity [see *Use in Specific Populations* (8.4)].

14 CLINICAL STUDIES

14.1 Depressive Episodes Associated with Bipolar I Disorder

The efficacy of SYMBYAX for the acute treatment of depressive episodes associated with Bipolar I Disorder was established in 2 identically designed, 8-week, randomized, double-blind, controlled studies of patients who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for Bipolar I Disorder, Depressed utilizing flexible dosing of SYMBYAX (6/25, 6/50, or 12/50 mg/day), olanzapine (5 to 20 mg/day), and placebo. These studies included patients (≥18 years of age [n=788]) with or without psychotic symptoms and with or without a rapid cycling course.

The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 to 60. The primary outcome measure of these studies was the change from baseline to endpoint in the MADRS total score. In both studies, SYMBYAX was statistically significantly superior to both olanzapine monotherapy and placebo in reduction of the MADRS total score.

14.2 Treatment Resistant Depression

The efficacy of SYMBYAX in acute treatment resistant depression was demonstrated with data from 3 clinical studies (n=579). Doses evaluated in these studies ranged from 6 to 18 mg for olanzapine and 25 to 50 mg for fluoxetine.

An 8-week randomized, double-blind controlled study was conducted to evaluate the efficacy of SYMBYAX in patients (n=300) who met DSM-IV criteria for Major Depressive Disorder and did not respond to 2 antidepressants of adequate dose and duration in their current episode. Patients who were not responding to an antidepressant in their current episode entered an 8-week open-label fluoxetine lead-in; non-responders were randomized (1:1:1) to receive SYMBYAX, olanzapine, or fluoxetine, and were treated for 8 weeks. SYMBYAX was flexibly dosed between 6/50 mg, 12/50 mg, and 18/50 mg. Results from this study yielded statistically significant greater reduction in mean total MADRS scores from baseline to endpoint for SYMBYAX versus fluoxetine and olanzapine. A second study with the same treatment-resistant patient population (n=28), when analyzed with change in MADRS as the outcome measure, demonstrated statistically significantly greater reduction in MADRS scores for SYMBYAX versus fluoxetine and olanzapine. A third study demonstrated statistically significantly greater reduction in total MADRS scores for SYMBYAX versus fluoxetine or olanzapine alone, when analyzed in a subpopulation of depressed patients (n=251) who met the definition of treatment resistance (patients who had not responded to 2 antidepressants of adequate dose and duration in the current episode).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SYMBYAX capsules are supplied in 3/25-, 6/25-, 6/50-, 12/25-, and 12/50-mg (mg equivalent olanzapine/mg equivalent fluoxetine^a) strengths.

SYMBYAX	CAPSULE STRENGTH				
	3 mg/25 mg	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
Color	Peach	Mustard Yellow	Mustard Yellow	Red & Light	Red & Light
	& Light Yellow	& Light Yellow	& Light Grey	Yellow	Grey
Capsule No.	PU3230	PU3231	PU3233	PU3232	PU3234
Identification	Lilly 3230	Lilly 3231	Lilly 3233	Lilly 3232	Lilly 3234
	3/25	6/25	6/50	12/25	12/50
NDC Codes					
Bottles 30	0002-3230-30	0002-3231-30	0002-3233-30	0002-3232-30	0002-3234-30
Bottles 100		0002-3231-02	0002-3233-02	0002-3232-02	0002-3234-02

Bottles 1000		0002-3231-04	0002-3233-04	0002-3232-04	0002-3234-04
Blisters ID ^b 100		0002-3231-33	0002-3233-33	0002-3232-33	0002-3234-33

^a Fluoxetine base equivalent.

^b IDENTI-DOSE[®], Unit Dose Medication, Lilly.

16.2 Storage and Handling

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Keep tightly closed and protect from moisture.

17 PATIENT COUNSELING INFORMATION

See the *FDA-approved Medication Guide*.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SYMBYAX.

17.1 Information on Medication Guide

Prescribers or other health professionals should inform patients, their families, and their caregivers about the potential benefits and potential risks associated with treatment with SYMBYAX and should counsel them in its appropriate use. A patient Medication Guide is available for SYMBYAX. The prescribers or other health professionals should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

17.2 Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication [see *Boxed Warning and Warnings and Precautions* (5.1)].

17.3 Elderly Patients with Dementia-Related Psychosis: Increased Mortality and Cerebrovascular Adverse Events (CVAE), Including Stroke

Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with olanzapine had a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) compared with placebo. SYMBYAX is not approved for elderly patients with dementia-related psychosis [see *Boxed Warning and Warnings and Precautions* (5.2)].

17.4 Neuroleptic Malignant Syndrome (NMS)

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including olanzapine, a component of SYMBYAX. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) [see *Warnings and Precautions* (5.3)].

17.5 Hyperglycemia

Patients should be advised of the potential risk of hyperglycemia-related adverse reactions. Patients should be monitored regularly for worsening of glucose control. Patients and caregivers should be counseled that metabolic changes have occurred during treatment with SYMBYAX. Patients who have diabetes should follow their doctor's instructions about how often to check their blood sugar while taking SYMBYAX [see *Warnings and Precautions* (5.4)].

17.6 Hyperlipidemia

Patients should be counseled that hyperlipidemia has occurred during treatment with SYMBYAX. Patients should have their lipid profile monitored regularly [see *Warnings and Precautions* (5.5)].

17.7 Weight gain

Patients should be counseled that weight gain has occurred during treatment with SYMBYAX. Patients should have their weight monitored regularly [see *Warnings and Precautions* (5.6)].

17.8 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions

Patients should be cautioned about the risk of serotonin syndrome or NMS-like reactions with the concomitant use of SYMBYAX and triptans, tryptophan, tramadol, or other serotonergic agents [see *Warnings and Precautions* (5.7) and *Drug Interactions* (7.3)]. Patients should be advised of the signs and symptoms associated with serotonin syndrome or NMS-like reactions that may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, in which the

symptoms may include hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be cautioned to seek medical care immediately if they experience these symptoms.

17.9 Allergic Reactions and Rash

Patients should be advised to notify their physician if they develop a rash or hives [see *Warnings and Precautions* (5.8)]. Patients should also be advised of the signs and symptoms associated with a severe allergic reaction, including swelling of the face, eyes, or mouth, or have trouble breathing. Patients should be cautioned to seek medical care immediately if they experience these symptoms.

17.10 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol [see *Warnings and Precautions* (5.11) and *Drug Interactions* (7.8, 7.9)]. Patients should be advised to change positions carefully to help prevent orthostatic hypotension, and to lie down if they feel dizzy or faint, until they feel better. Patients should be advised to call their doctor if they experience any of the following signs and symptoms associated with orthostatic hypotension: dizziness, fast or slow heart beat, or fainting.

17.11 Abnormal Bleeding

Patients should be cautioned about the concomitant use of SYMBYAX and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents have been associated with an increased risk of bleeding [see *Warnings and Precautions* (5.14)]. Patients should be advised to call their doctor if they experience any increased or unusual bruising or bleeding while taking Symbyax.

17.12 Hyponatremia

Patients should be advised that hyponatremia has been reported during treatment with SNRIs and SSRIs, including SYMBYAX. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death [see *Warnings and Precautions* (5.15)].

17.13 Potential for Cognitive and Motor Impairment

As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them adversely [see *Warnings and Precautions* (5.16)].

17.14 Body Temperature Regulation

Patients should be advised regarding appropriate care in avoiding overheating and dehydration. Patients should be advised to call their doctor right away if they become severely ill and have some or all of these symptoms of dehydration: sweating too much or not at all, dry mouth, feeling very hot, feeling thirsty, not able to produce urine [see *Warnings and Precautions* (5.17)].

17.15 Concomitant Medication

Patients should be advised to inform their physician if they are taking Prozac®, Prozac Weekly™, Sarafem®, fluoxetine, Zyprexa®, or Zyprexa® Zydis®. Patients should be advised to inform their physicians if they are taking, plan to take, or have stopped taking any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions. Patients should also be advised to inform their physicians if they plan to discontinue any medications they are taking while taking SYMBYAX, as stopping a medication may also impact the overall blood level of SYMBYAX [see *Warnings and Precautions* (5.20)].

17.16 Discontinuation of Treatment with SYMBYAX

Patients should be advised to take SYMBYAX exactly as prescribed, and to continue taking SYMBYAX as prescribed even after their mood symptoms improve. Patients should be advised that they should not alter their dosing regimen, or stop taking SYMBYAX, without consulting their physician [see *Warnings and Precautions* (5.22)].

17.17 Alcohol

Patients should be advised to avoid alcohol while taking SYMBYAX [see *Drug Interactions* (7.8, 7.9)].

17.18 Use in Specific Populations

Pregnancy — Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during SYMBYAX therapy [see *Use in Specific Populations* (8.1)].

Nursing Mothers — Patients, if taking SYMBYAX, should be advised not to breast-feed [see *Use in Specific Populations* (8.3)].

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Medication Guide

SYMBYAX® (SIM-be-ax)
(olanzapine and fluoxetine hydrochloride)
Capsule

Read the Medication Guide that comes with SYMBYAX before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment. Talk with your doctor or pharmacist if there is something you do not understand or you want to learn more about SYMBYAX.

What is the most important information I should know about SYMBYAX?

Antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions:

Talk to your, or your family member's, healthcare provider about:

- all risks and benefits of treatment with antidepressant medicines.
- all treatment choices for depression or other serious mental illness.

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.

2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- or other unusual changes in behavior or mood.

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

SYMBYAX may be associated with the following serious risks:

High blood sugar (hyperglycemia): High blood sugar can occur if you have diabetes already or even if you have never had diabetes. In rare cases, this could lead to ketoacidosis (build up of acid in the blood due to ketones), coma, or death. Your doctor should do lab tests to check your blood sugar before you start taking SYMBYAX and during treatment. In people who do not have diabetes, sometimes high blood sugar goes away when SYMBYAX is stopped. People with diabetes and some people who did not have diabetes before taking SYMBYAX need to take medicine for high blood sugar even after they stop taking SYMBYAX.

If you have diabetes, follow your doctor's instructions about how often to check your blood sugar while taking SYMBYAX.

Call your doctor if you have any of these symptoms of high blood sugar (hyperglycemia) while taking SYMBYAX:

- feel very thirsty
- need to urinate more than usual
- feel very hungry
- feel weak or tired
- feel sick to your stomach
- feel confused, or your breath smells fruity.

High cholesterol and triglyceride levels in the blood (fat in the blood): These have been observed in patients treated with SYMBYAX, especially in teenagers (13-17 years old) who received olanzapine, one of the components of SYMBYAX. SYMBYAX is not approved for use in patients less than 18 years old. You may not have any symptoms, so your doctor should do blood tests to check your cholesterol and triglyceride levels before you start taking SYMBYAX and during treatment.

Increase in weight (weight gain): Weight gain is very commonly seen in patients who take SYMBYAX. Teenagers (13-17 years old) who received olanzapine, one of the components of SYMBYAX, are more likely to gain weight and to gain more weight than adults. SYMBYAX is not approved for use in patients less than 18 years old. Some patients may gain a lot of weight while taking SYMBYAX, so you and your doctor should check your weight regularly. Talk to your doctor about ways to control weight gain, such as eating a healthy, balanced diet, and exercising.

What is SYMBYAX?

SYMBYAX is a prescription medicine approved for use in adults:

- for short-term treatment of episodes of depression that happen with Bipolar I Disorder.
- for short-term treatment of episodes of depression that do not respond to 2 other medicines, also called treatment resistant depression.

SYMBYAX contains two medicines, olanzapine and fluoxetine hydrochloride.

It is not known if olanzapine is safe and works in children under 18 years of age.

It is not known if olanzapine and fluoxetine hydrochloride taken together, or as SYMBYAX, is safe and works in children under 18 years of age.

The symptoms of Bipolar I Disorder include alternating periods of depression and high or irritable mood, increased activity and restlessness, racing thoughts, talking fast, impulsive behavior, and a decreased need for sleep. With treatment, some of your symptoms of Bipolar I Disorder may improve.

The symptoms of treatment resistant depression include decreased mood, decreased interest, increased guilty feelings, decreased energy, decreased concentration, changes in appetite, and suicidal thoughts or behavior. With treatment, some of your symptoms of treatment resistant depression may improve.

If you do not think you are getting better, call your doctor.

Who should not take SYMBYAX?

- Do not take SYMBYAX if you take a Monoamine Oxidase Inhibitor (MAOI) or if you stopped taking an MAOI in the last 2 weeks.

- Do not take an MAOI **within 5 weeks of stopping SYMBYAX**. People who take SYMBYAX close in time to an MAOI can have serious and life-threatening side effects, with symptoms including:
 - high fever
 - continued muscle spasms that you cannot control
 - rigid muscles
 - changes in heart rate and blood pressure that happen fast
 - confusion
 - unconsciousness.
- Ask your doctor or pharmacist if you are not sure if your medicine is an MAOI.
- Do not take SYMBYAX if you take Mellaril[®] (thioridazine). Do not take Mellaril **within 5 weeks of stopping SYMBYAX**. **Mellaril can cause serious heart rhythm problems and you could die suddenly.**
- Do not take SYMBYAX if you take the antipsychotic medicine pimozide (Orap[®]).

What should I tell my doctor before taking SYMBYAX?

SYMBYAX may not be right for you. Before starting SYMBYAX, tell your doctor about all your medical conditions, including if you have or had any of the following:

- heart problems
- seizures (convulsions)
- diabetes or high blood sugar levels (hyperglycemia)
- high cholesterol or triglyceride levels in your blood
- liver problems
- low or high blood pressure
- strokes or “mini-strokes” also called transient ischemic attacks (TIAs)
- bleeding problems
- Alzheimer’s disease
- narrow-angle glaucoma
- enlarged prostate in men
- bowel obstruction
- breast cancer
- are pregnant or plan to become pregnant. It is not known if SYMBYAX will harm your unborn baby.
- are breast-feeding or plan to breast-feed. Olanzapine and fluoxetine can pass into your breast milk and may harm your baby. You should not breast-feed while taking SYMBYAX. Talk to your doctor about the best way to feed your baby if you take SYMBYAX.

Tell your doctor about all the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. SYMBYAX and some medicines may interact with each other and may not work as well, or cause possible serious side effects. Your doctor can tell you if it is safe to take SYMBYAX with your other medicines. Do not start or stop any medicine while taking SYMBYAX without talking to your doctor first.

If you take SYMBYAX, you should not take any other medicines that contain:

- olanzapine (the active ingredient in Zyprexa[®] and Zyprexa[®] Zydis[®]) or
- fluoxetine hydrochloride (the active ingredient in Prozac[®], Prozac[®] Weekly[™], and Sarafem[®]).

You could take too much medicine (overdose).

How should I take SYMBYAX?

- Take SYMBYAX exactly as prescribed. Your doctor may need to change (adjust) the dose of SYMBYAX until it is right for you.
- If you miss a dose of SYMBYAX, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of SYMBYAX at the same time.
- **To prevent serious side effects, do not stop taking SYMBYAX suddenly. If you need to stop taking SYMBYAX, your doctor can tell you how to safely stop taking it.**
- **If you take too much SYMBYAX, call your doctor or poison control center right away, or get emergency treatment.**
- SYMBYAX can be taken with or without food.
- SYMBYAX is usually taken one time each day, in the evening.
- If you do not think you are getting better or have any concerns about your condition while taking SYMBAX, call your doctor.

What should I avoid while taking SYMBYAX?

- SYMBYAX can cause sleepiness and may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how SYMBYAX affects you.
- Avoid drinking alcohol while taking SYMBYAX. Drinking alcohol while you take SYMBYAX may make you sleepier than if you take SYMBYAX alone.

What are the possible side effects of SYMBYAX?

Other possible serious risks:

- **Increased risk of death and increased incidence of stroke or “mini-strokes” called transient ischemic attacks (TIAs) in elderly people with psychosis related to dementia** (a brain disorder that lessens the ability to remember, think, and reason). SYMBYAX is not approved for these patients.
- **Severe allergic reactions:** Tell your doctor right away if you get red itchy welts (hives) or, a rash alone or with fever and joint pain, while taking SYMBYAX. Call your doctor right away if you become severely ill and have some or all of these symptoms:
 - swelling of your face, eyes, or mouth
 - trouble breathing
- **Neuroleptic malignant syndrome (NMS):** NMS is a rare but very serious condition that can happen in people who take antipsychotic medicines, including SYMBYAX. NMS can cause death and must be treated in a hospital. Call your doctor right away if you become severely ill and have some or all of these symptoms:
 - high fever
 - excessive sweating
 - rigid muscles
 - confusion
 - changes in your breathing, heartbeat, and blood pressure
- **Tardive Dyskinesia:** This condition causes body movements that keep happening and that you cannot control. These movements usually affect the face and tongue. Tardive dyskinesia may not go away, even if you stop taking SYMBYAX. It may also start after you stop taking SYMBYAX. Tell your doctor if you get any body movements that you cannot control.
- **Serotonin Syndrome:** This is a condition that can be life threatening. Call your doctor right away if you become severely ill and have some or all of these symptoms:
 - agitation
 - hallucinations
 - problems with coordination
 - racing heart beat
 - over-active reflexes
 - fever
 - nausea, vomiting, and diarrhea
- **Abnormal bleeding:** Tell your doctor if you notice any increased or unusual bruising or bleeding while taking SYMBYAX, especially if you take one of these medicines:
 - the blood thinner warfarin (Coumadin, Jantoven)
 - a non-steroidal anti-inflammatory drug (NSAID)
 - aspirin
- **Low salt (sodium) levels in the blood (hyponatremia):** Call your doctor right away if you become severely ill and have some or all of these symptoms:
 - headache
 - feel weak
 - confusion
 - problems concentrating
 - memory problems
 - feel unsteady
- **Decreased blood pressure when you change positions, with symptoms of dizziness, fast or slow heart beat, or fainting**
- **Difficulty swallowing**
- **Seizures**
- **Problems with control of body temperature:** You could become very hot, for instance when you exercise a lot or stay in an area that is very hot. It is important for you to drink water to avoid dehydration. Call your doctor right away if you become severely ill and have some or all of these symptoms of dehydration:
 - sweating too much or not at all
 - dry mouth
 - feeling very hot
 - feeling thirsty
 - not able to produce urine

Common possible side effects of SYMBYAX include: dry mouth, tiredness, sleeping for long period of time, increased appetite, swelling of your hands and feet, drowsiness, tremors (shakes), or blurred vision.

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the possible side effects with SYMBYAX. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SYMBYAX?

- Store SYMBYAX at room temperature, between 59°F to 86°F (15°C to 30°C).
- Keep SYMBYAX away from light.
- Keep SYMBYAX dry and away from moisture. Keep the bottle closed tightly.

Keep SYMBYAX and all medicines out of the reach of children.

General information about SYMBYAX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SYMBYAX for a condition for which it was not prescribed. Do not give SYMBYAX to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about SYMBYAX. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about SYMBYAX that was written for healthcare professionals. For more information about SYMBYAX call 1-800-Lilly-Rx (1-800-545-5979) or visit www.symbyax.com.

What are the ingredients in SYMBYAX?

Active ingredients: olanzapine and fluoxetine hydrochloride

Inactive ingredients: pregelatinized starch, gelatin, dimethicone, titanium dioxide, sodium lauryl sulfate, edible black ink, red iron oxide, yellow iron oxide, and/or black iron oxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide revised Month DD, YYYY

Eli Lilly and Company

Indianapolis, IN 46285, USA

www.symbyax.com

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-520/S-012

MEDICAL REVIEW(S)

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

DATE: March 7, 2009

FROM: Gwen L. Zornberg, M.D., Sc.D.
Medical Team Leader
Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation of Complete Response action
Complete Response by Lilly (19 September 2008) to
Approvable letter issued 1 August 2008 for
Olanzapine and Fluoxetine in combination (Symbyax®) in
acute treatment of Treatment Resistant Depression (TRD) in
& supplements NDA 21-520: (b) (4) S-012, (b) (4)

DOSAGE FORMS: 3/25, 6/25, 12/25, 6/50, 12/50 mg (olanzapine/fluoxetine) capsules

TO: File NDA 21-520/SE1-012
Complete Response (1 August 2008)
Original 28 September 2006 TRD submission

REVIEWERS: Jing Zhang, M.D., Ph.D., Clinical; Sharon Mills, BSN, RN,
CCRP, Patient labeling and Education Team, Division of Risk
Management.

1.0 BACKGROUND

Symbyax®, olanzapine and fluoxetine hydrochloride in combination (OFC) is approved for acute treatment of depressive episodes associated with Bipolar I Disorder in adults. The original NDA was submitted 4 November 2002 by Eli Lilly & Co. Since approval of Symbyax on 24 December 2003, the division has become aware of new safety information from analyses of data related to increased risks of hyperglycemia, hyperlipidemia, and weight gain associated with olanzapine, and therefore, with Symbyax (OFC) treatment.

On 28 March 2007, FDA issued an Approvable Letter regarding the Symbyax sNDA for TRD.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended FDCA to provide the agency with new authorities to require sponsors of approved drugs to develop and comply with Risk Evaluation Mitigation Strategy (REMS) section 505-1 of the FDCA if FDA finds that a REMS is necessary to ensure that FDA has determined that Symbyax use poses a serious and significant public health concern and that Symbyax is a product for which information in patient labeling could help prevent serious adverse events. FDA has determined that Symbyax meets two of three criteria for a Medication Guide (MG) as set forth in 21 CFR 208.1.

- Symbyax is a product that has been found to pose serious risks relative to benefit of which patients should be made aware because information concerning risks could affect patients' decisions to use or continue to use the medication.
- Symbyax is a product for which patient labeling could help prevent serious adverse events.

The MG is the salient component of the REMS for Symbyax to facilitate and enhance appropriate use and provide important information about the medication in an understandable format.

A meeting was held 24 May 2007 with Lilly to discuss the approach to update safety information on hyperglycemia, hyperlipidemia, and increase in weight. Agreement was reached regarding a rolling timetable for submission of safety data. These risks had been identified in addition to the increased risk of suicidality associated with SSRI antidepressant use (e.g., fluoxetine) in Symbyax. This information was not available in 2002 and 2003 when Symbyax was granted approval for depressive episodes associated with Bipolar I Disorder.

FDA issued an Approvable action letter dated 1 August 2008 for the TRD claim and the following outstanding labeling supplements for Symbyax NDA 21-520: (b) (4), S-012, S-(b) (4). FDA concluded that NDA 21-520/S-012 would not be considered complete until the outstanding information on hyperglycemia, hyperlipidemia, and increase in weight were received for review. The 19 September 2008 submission by Lilly was found to be a complete response to the 1 August 2008 AE letter.

2.0 CHEMISTRY

There were no CMC issues requiring review as part of this application.

3.0 PHARMACOLOGY

There were no Pharmacology/Toxicology issues requiring review as part of this application.

4.0 BIOPHARMACEUTICS

There were no further biopharmaceutics issues requiring review as part of this application.

5.0 CLINICAL DATA

5.1 Clinical Sections of Labeling

REVISED MEDICATION GUIDE

The division requested consultation from the Division of Risk Management (DRISK) to review draft Symbyax prescribing information (PI); the draft Symbyax MG; and the proposed Symbyax REMS, that were submitted 19 September 2008. Sharon Mills conducted the primary DRISK review. The principle changes to Symbyax labeling in PLR format reflect the findings that SSRI antidepressant use is associated with elevated risk of suicidal thinking and behavior and with increased exposure and over time, olanzapine use (including when used with fluoxetine), is associated with elevated risks of weight gain, blood glucose and hyperlipidemia.

The DRISK review is informed by research to improve risk communication to a broad patient population, including those with lower literacy and clinical risk/benefit related discussions with DPP. In the DRISK revisions to the applicant's draft MG, the changes comprised: simplified wording with efforts to clarify concepts; enhance consistency with the PI; rearrange information as necessary to conform to the format and regulations specified in 21 CFR 208.20; remove unnecessary information; and meets criteria as specified in the agency's "Guidance for Useful Written Consumer Medication Information" (published July 2006).

The following conclusions and recommendations were provided to DPP by DRISK with respect to the proposed REMS:

In the absence of the new REMS template prior to submission of the REMS as part of Lilly's Complete Response, the applicant was not able to follow the recommended format, which has been sent.

DRISK recommends revising the REMS goal as follows:

[REDACTED] (b) (4)

DRISK found the applicant's proposed timetable for assessments annually after approval of the REMS is acceptable. The assessments, however, must be submitted separately and not as part of a Periodic Safety Update Report (PSUR).

DRISK noted that the applicant should submit for review a detailed plan to evaluate patients' understanding about the safe use of Symbyax at least 2 months before they plan to conduct the evaluation and should include in the submission:

All methodology and instruments that are used to evaluate the patients' understanding about the safe use of Symbyax including: sample size and confidence; selection criteria; recruitment methods; expected number of patients to be surveyed; how often the surveys will be administered; use of controls to minimize bias; and explain the methods to be used to compensate for the limitations associated with the methodology; the questionnaires and moderator's guide for use in the survey; any background information on testing survey questions and correlation to the messages in the MG. Finally, background information on testing survey questions and correlation to the messages in the MG should also be included.

DRISK recommends including in the approval letter a reminder of the sponsor's responsibility to provide the methodological information needed to assess the effectiveness of the REMS as stated above, including an evaluation of:

- Patients' understanding of the serious risks of Symbyax
- A report on periodic assessments of the distribution and dispensing of the MG in accordance with 21 CFR 208.24
- A report on failures to adhere to distribution and dispensing requirements, and corrective action taken to address noncompliance.

The first and most prominent section of the Med Guide is entitled:

"What is the most important information I should know about SYMBYAX?"

that appropriately focuses on suicidal thinking or behavior and then other aspects of antidepressant use.

In the next section entitled:

(b) (4)

Increase in weight is third side effect highlighted after hyperglycemia **"High blood sugar (hyperglycemia)"** and hyperlipidemia **"High cholesterol and triglyceride levels (fat in the blood)"** sections.

In a teleconference with Lilly on 5 March 2009, the applicant noted

(b) (4)

This statement is at odds with the two provisos from approved labeling in the following **"What is Symbyax?"** section below:

“It is not known if olanzapine is safe and works in children under 18 years of age.

It is not known if olanzapine and fluoxetine hydrochloride taken together, or as SYMBYAX, is safe and works in children under 18 years of age.”

DRISK also provided recommendations and reminders to convey to the applicant prior to completion of a full review of the MG and REMS for Symbyax:

Question 2: Does the Division agree that the Medication Guide for Zyprexa only applies to the tablet and Zydis formulations?

Response: At the 25 August 2008 meeting with Lilly, the Division agreed.

3.2 Clarify the wording of the suicidality Medication Guides for Symbyax and Prozac

Question 3: Does the Division agree that we should use the 2007 template for the suicidality Medication Guide for Symbyax and Prozac?

Response: At the 25 August 2008 meeting with Lilly, the Division agreed.

Lilly included within their Complete Response Document a section “Discussion of Approvable Letters received 1 August 2008 for Zyprexa (olanzapine), Symbyax (OFC), and Prozac (fluoxetine hydrochloride),” beginning on page 19. Section 3 poses questions regarding the REMS on pages 22 and 23 of the Complete Response document.

Question 4: Does the Division agree with the REMS proposal for Zyprexa and Symbyax?

Response: DRISK recommends that Lilly revise and resubmit the proposed REMS to follow the template that the review division provides and revise the goal of the REMS and submit the methodology for a survey to evaluate the methodology for the assessments to evaluate patients understanding about the safe use of Symbyax as outlined above.

DRISK Comments on the proposed Medication Guide:

The antidepressant related information about suicidal thoughts and behavior is set off from the other risks by listing it first in the most important information section (and in a box) for emphasis.

DRISK noted also that Lilly inquired about use of the 2007 template for suicidality. DRISK defers to DPP.

Reviewer's Comment on the DRISK Proposals for the Symbyax Medication Guide:

It was agreed to consider revision of the statement that is not based on data: (b) (4)

I think that this statement provided in the DRISK consultation does not appear to be evidence-based and is inconsistent with approved prescribing information. Otherwise, I am in general agreement with the proposals by DRISK including the recommendation for a survey to evaluate patients' understanding of the Medication Guide.

Clinical Labeling Review

(b) (4)

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

6.0 POSTMARKETING COMMITMENT

With respect to the Post Marketing Commitment AE letter (1 August 2008) agreed to by Lilly, the Division asked Lilly to commit to submitting the results of the long-term study of the effectiveness and safety of OFC in TRD employing (b) (4) H6P-MC-HDAY no later than 3 years after the date of approval. The sponsor agreed with the Divisions continued recommendation that the stabilization phase of HDAY be (b) (4). A full protocol is expected to be submitted in the first quarter of 2009. The separate statistical plan will be submitted later, as requested by FDA. Lilly intends to submit the results of this study during the first quarter of 2015, which is acceptable as noted in the meeting minutes (25 August 2008).

7.0 CONCLUSIONS AND RECOMMENDATIONS

Once final agreement is reached with the applicant on Symbyax labeling and the REMS including the Symbyax Medication Guide (including the sections from Zyprexa and Prozac), I am not aware of any additional issues that would preclude an approval action being taken on the claim for treatment of TRD. The Division review of the DRISK consultation on the Medication Guides is ongoing and will inform further discussions with Lilly. Dr. Zhang and I concur on recommending to the Division Director that a complete response action letter be issued if final agreement cannot be reached by the action date of 19 March 2009.

cc: Original NDA 21-520/000 and S-012

NDA 21-520/ S- (b) (4) S-012 S- (b) (4) S- (b) (4)

HFD-130

/RGrewal/JZhang/GZornberg/MMathis/TLaughren/3_7_09.doc

DOC: Symbyax_TRD_CompleteResponse_Zornberg_Memo.doc

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

/s/

Gwen Zornberg
3/7/2009 07:46:45 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
NDA #21,520

NDA#:	21,520/S-012
Sponsor:	Eli Lilly and Company
Drug:	Olanzapine/fluoxetine Combination (SYMBYAX®)
Material Submitted:	Complete Response to Approvable Letter on August 1, 2008
Proposed Indication:	Treatment Resistant Depression
Dosage Forms:	3/25, 6/25, 12/25, 6/50, 12/50 mg
Administration:	Oral tablet
Intended Population:	Adults
Related Supplements:	NDA 21-520: (b) (4) S-012, (b) (4)
Medical Reviewer:	Jing Zhang, MD. PhD.

I. Background

This submission includes a complete response document that addresses the issues raised in FDA's Approvable Letter of 1 August 2008, as well as discussion with the division that occurred at a face to face meeting held 25 August 2008. Please refer to pertinent FDA documents for detailed information. In this submission, the sponsor proposed a revised labeling and a Symbyax medication guide (MG) for FDA review.

II. Review of Clinical Data

Medication Guide

The Symbyax MG review was performed in consultation with the Office of Surveillance and Epidemiology (OSE). Sharon Mills from the Division of Risk Management (DRISK) is the primary reviewer for the Symbyax medication guide. Please refer to her review for detailed information.

Summary of DRISK's key Recommendations

1. Recommend placing the antidepressant class information about suicidality and actions into a box to set off the suicidality text from the other serious adverse effects.

2. In the section "[REDACTED]" (b) (4)
[REDACTED]:"

Change the order of [REDACTED] (b) (4) so that it follows [REDACTED] (b) (4)
[REDACTED]

Under "high blood sugar (hyperglycemia), following language was added: *If you have diabetes, follow your doctor's instructions about how often to check your blood sugar while taking Symbyax.*

3. In the section "What is Symbyax?" information about the onset of feeling better and instruction to call your doctor if you do not think you are getting better was revised. [REDACTED] (b) (4)
[REDACTED]

4. A new section "What should I avoid while taking Symbyax?" was created. This section includes following information: a) Symbyax may affect patients' ability to make decisions, think clearly or react quickly [REDACTED] (b) (4)
[REDACTED]; b) Patients should avoid drinking alcohol.

5. In the section "What Are the Possible Side Effects of SYMBYAX?"

Recommend [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

Recommend all serious side effects should be listed in the MG because MG should be consistent with the Warnings and Precautions section of the Product Insert (PI).

6. A new section "How should I store Symbyax?" was added to MG.

Reviewer's Comments

In section "[REDACTED]" (b) (4)
[REDACTED], the DRISK added following

language (b) (4)

Since safety and efficacy information of Symbyax in patients who are under 18 years of age have not been established, this statement should be revised.

Safety data on weight gain with olanzapine monotherapy in teenagers (13 to 17 year old) had been established. I recommend change the statement to " (b) (4)

I agree with the rest recommendations in DRISK's review.

Labeling Review

5 WARNINGS AND PRECAUTIONS

All recommended changes in this section also apply to the section of WARNINGS AND PRECAUTIONS in HIGHLIGHTS OF PRESCRIBING INFORMATION.

In section 5.4 Hyperglycemia, the division recommends adding following information from the healthy volunteer study to be consistent with the Zyprexa labeling.

In a study of healthy volunteers, subjects who received olanzapine (N=22) for 3 weeks had a mean increase compared to baseline in fasting blood glucose of 2.3 mg/dL. Placebo-treated subjects (N=19) had a mean increase in fasting blood glucose compared to baseline of 0.34 mg/dL.

The section 5.7 Serotonin Syndrome should be revised. We recommend replacing this section with new class labeling language regarding serotonin syndrome or neuroleptic malignant syndrome (NMS) like reaction to be consistent with the Prozac labeling.

In section 5.11 Hemodynamic Effects, the sponsor replaced old title "Orthostatic hypotension" with new title (b) (4). We think the old title "Orthostatic hypotension" presents the cardiovascular AEs of Symbyax more accurately than (b) (4). We recommend keeping the old title "Orthostatic hypotension" in this section.

(b) (4)
[Redacted text block]

(b) (4)
[Redacted text block]

(b) (4)
[Redacted text block]

6 ADVERSE REACTIONS

Under section 6.1 Clinical Trial Experience/Other Events Observed in Clinical Studies, the sponsor added following adverse events (AEs) into the list:

(b) (4)
[Redacted text block]

These AEs has been discussed in the section WARNING AND PRECAUTIONS. We consider them redundant here and these AEs should be removed from the list.

In addition, all (b) (4) regarding safety data should be deleted in all applicable sections because these comparisons (safety analyses) are not based on hypothesis testing.

The rest labeling revisions proposed by the sponsor were reviewed and were considered acceptable.

Jing Zhang, MD. PhD.
March 6, 2009

cc: NDA 21-520
HFD-130 (Div. File)
HFD-130/J Zhang
 /G Zornberg
 /M Mathis
 /T Laughren
 /R Grewal

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

/s/

Jing Zhang
3/6/2009 08:17:51 PM
MEDICAL OFFICER

Gwen Zornberg
3/6/2009 08:50:39 PM
MEDICAL OFFICER

I find the evidence-based changes to labeling [REDACTED] (b) (4)
[REDACTED] to be satisfactory. Please refer
to today's TL review for further discussion, including
of DRISK recommendations.

**COMPLETE
RESPONSE**

MEMORANDUM

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

DATE: July 25, 2008

FROM: Gwen L. Zornberg, M.D., Sc.D.
Medical Team Leader
Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation of Approvable action for olanzapine and
fluoxetine in combination (Symbyax®)

TO: File NDA 21-520/SE012
Complete Response to Approvable Letter
SN 000 (Original 28 September 2006 submission)

REVIEWERS: Clinical, Dr. Jing Zhang. Safety issues pertaining to weight gain
and metabolic labeling changes and MedGuide, Dr. Evelyn
Mentari.

1.0 BACKGROUND

Symbyax®, olanzapine and fluoxetine in combination (OFC), is approved for Depressive Episodes associated with Bipolar Disorder. Approval has been contingent upon completion of changes to labeling regarding metabolic changes and weight gain, satisfactory post-marketing commitments regarding long-term data and a request for a foreign regulatory update.

2.0 CHEMISTRY

There were no CMC issues requiring review as part of this application.

3.0 PHARMACOLOGY

There were no Pharmacology/Toxicology issues requiring review as part of this application.

4.0 BIOPHARMACEUTICS

5.0

There were no further biopharmaceutics issues requiring review as part of this application.

6.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Conclusions Regarding the Efficacy Data

In the memorandum recommending an approvable action by Dr. Thomas Laughren dated 23 March 2007, Dr. Laughren found that Lilly has submitted sufficient data to support the conclusion that Symbyax is effective and acceptably safe in the treatment of TRD.

5.2 Safety Data

5.2.1 Clinical Safety Issues and Findings of Particular Interest

Common and Drug-Related Adverse Events

OFC treated patients exhibited an overall AE rate of approximately 83%. This is minimally higher than placebo-treated patients (74%), but similar to olanzapine-treated (82.7%) and fluoxetine-treated (82.3%) patients. The most frequently reported adverse events in the OFC treatment group (reported by $\geq 5\%$ of OFC-treated patients) were: increased weight, increased appetite, dry mouth, somnolence, fatigue, headache, peripheral edema, tremor, dizziness, sedation, diarrhea, nausea, and anxiety.

Serious Adverse Events (SAEs) in Clinical Trials

Serious adverse events (SAEs) were reported by 4.0% of OFC-treated, 2.8% of fluoxetine-treated, 3.4% of olanzapine-treated, and 5.9% of placebo-treated patients. SAEs that were reported by two or more of the 771 OFC-treated patients were depression (8), suicidal ideation (6), chest pain (2), dyspnea (2), and peripheral edema (2). Depression was statistically significantly more common in OFC-treated than in fluoxetine-treated patients, but the majority of these events occurred in Studies HGGY and HGGA, which were studies in bipolar and psychotic depression and did not have fluoxetine treatment arms. Given the smaller sample size for fluoxetine compared to OFC and the lack of fluoxetine arms in the studies with the highest rates of serious depression events, it is difficult to assess the potential relationship to fluoxetine. There were no other statistically significant differences between OFC and other treatment groups with respect to rates of individual SAEs. There were no deaths among subjects in the clinical trials that were likely related to OFC.

Adverse Events Leading to Dropout

Most of the adverse events that led to discontinuation for OFC-treated patients were events that were common with OFC and olanzapine (weight gain, somnolence, sedation) or that were associated with the underlying disease (suicidal ideation). The only events

that led to discontinuation at a statistically significantly higher rate for OFC-treated patients than for another group were increased weight (2.1%) and sedation (1.3%). In general, rates of discontinuation due to adverse events, both overall and for individual events, were similar for OFC- and olanzapine-treated patients.

5.3 Clinical Sections of Labeling

The requirement for approval hinged on adequate analysis and presentation of safety information with updated data regarding changes in weight and serum glucose and lipid levels as confirmed by the Division and the Safety team. The principle changes in Symbyax labeling in PLR format are reflected in the following tables demonstrating that with increased exposure and over time, olanzapine use including when used with fluoxetine (as Symbyax), is associated with an elevated risk of weight gain, blood glucose and hyperlipidemia.

Table 7: Adult Weight Gain with Olanzapine Use

Amount Gained kg (lb)	6 Weeks (N=7465) (%)	6 Months (N=4162) (%)	12 Months (N=1345) (%)	24 Months (N=474) (%)	36 Months (N=147) (%)
≤0	26.2	24.3	20.8	23.2	17.0
0 to ≤5 (0-11 lb)	57.0	36.0	26.0	23.4	25.2
>5 to ≤10 (11-22 lb)	14.9	24.6	24.2	24.1	18.4
>10 to ≤15 (22-33 lb)	1.8	10.9	14.9	11.4	17.0
>15 to ≤20 (33-44 lb)	0.1	3.1	8.6	9.3	11.6
>20 to ≤25 (44-55 lb)	0	0.9	3.3	5.1	4.1
>25 to ≤30 (55-66 lb)	0	0.2	1.4	2.3	4.8
>30 (>66 lb)	0	0.1	0.8	1.2	2

Similarly, in adolescents, olanzapine use including when used with fluoxetine (as Symbyax) is associated with an elevated risk of weight gain, blood glucose and hyperlipidemia with increased exposure and over time.

Table ^(b)₍₄₎ Adolescent Weight Gain with Olanzapine Use

Amount Gained kg (lb)	6 Weeks (N=243) (%)	6 Months (N=191) (%)
≤0	2.9	2.1
0 to ≤5 (0-11 lb)	47.3	24.6
>5 to ≤10 (11-22 lb)	42.4	26.7
>10 to ≤15 (22-33 lb)	5.8	22.0
>15 to ≤20 (33-44 lb)	0.8	12.6
>20 to ≤25 (44-55 lb)	0.8	9.4
>25 to ≤30 (55-66 lb)	0	2.1
>30 to ≤35 (66-77 lb)	0	0
>35 to ≤40 (77-88 lb)	0	0
>40 (>88 lb)	0	0.5

As there was no data available on fasting glucose levels with Symbyax administration, random glucose levels are presented in labeling demonstrating elevated risk of hyperglycemia that increases with time on olanzapine and fluoxetine.

Table 2: Changes in Random Glucose Levels from Adult Symbyax Studies

			Up to 12 weeks exposure		At least 48 weeks exposure	
Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	Patients	N	Patients
Random Glucose	Normal to High (<140 mg/dL to ≥200 mg/dL)	Symbyax	609	2.3% ^a	382	3.1%
		Placebo	346	0.3	NA ^b	NA ^b
	Borderline to High (≥140 mg/dL and <200 mg/dL to ≥200 mg/dL)	Symbyax	44	34.1% ^a	27	37.0%
		Placebo	28	3.6%	NA ^b	NA ^b

^a Statistically significant compared to placebo.

^b Not Applicable.

The elevations found in lipid levels are consistent with previous reports and are now updated.

Changes in Non-fasting Lipids Values from Controlled Clinical Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	Patients
Nonfasting Triglycerides	Increase by ≥ 50 mg/dL	OFC	174	67.8%
		Olanzapine	172	72.7%
	Normal to High (<150 mg/dL to ≥ 500 mg/dL)	OFC	57	0%
		Olanzapine	58	0%
	Borderline to High (≥ 150 mg/dL and <500 mg/dL to ≥ 500 mg/dL)	OFC	106	15.1%
		Olanzapine	103	8.7%
Nonfasting Total Cholesterol	Increase by ≥ 40 mg/dL	OFC	685	35% ^{a,b}
		Olanzapine	749	22.7%
		Placebo	390	9%
	Normal to High (<200 mg/dL to ≥ 240 mg/dL)	OFC	256	8.2% ^{a,b}
		Olanzapine	279	2.9%
		Placebo	175	1.7%
	Borderline to High (≥ 200 mg/dL and <240 mg/dL to ≥ 240 mg/dL)	OFC	213	36.2% ^{a,b}
		Olanzapine	261	27.6%
		Placebo	111	9.9%

(b) (4)

Table 5: Changes in Fasting Lipids Values from Adult Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure		At least 48 weeks exposure	
			N	Patients	N	Patients
Fasting Triglycerides	Increase by ≥ 50 mg/dL	Olanzapine	745	39.6% ^a	487	61.4%
		Placebo	402	26.1%	NA ^b	NA ^b
	Normal to High (<150 mg/dL to ≥ 200 mg/dL)	Olanzapine	457	9.2% ^a	293	32.4%
		Placebo	251	4.4%	NA ^b	NA ^b
	Borderline to High (≥ 150 mg/dL and <200 mg/dL to ≥ 200 mg/dL)	Olanzapine	135	39.3% ^a	75	70.7%
		Placebo	65	20.0%	NA ^b	NA ^b
Fasting Total Cholesterol	Increase by ≥ 40 mg/dL	Olanzapine	745	21.6% ^a	489	32.9%
		Placebo	402	9.5%	NA ^b	NA ^b
	Normal to High (<200 mg/dL to ≥ 240 mg/dL)	Olanzapine	392	2.8%	283	14.8%
		Placebo	207	2.4%	NA ^b	NA ^b
	Borderline to High (≥ 200 mg/dL and <240 mg/dL to ≥ 240 mg/dL)	Olanzapine	222	23.0% ^a	125	55.2%
		Placebo	112	12.5%	NA ^b	NA ^b
Fasting LDL Cholesterol	Increase by ≥ 30 mg/dL	Olanzapine	536	23.7% ^a	483	39.8%
		Placebo	304	14.1%	NA ^b	NA ^b
	Normal to High (<100 mg/dL to ≥ 160 mg/dL)	Olanzapine	154	0%	123	7.3%
		Placebo	82	1.2%	NA ^b	NA ^b
	Borderline to High (≥ 100 mg/dL and <160 mg/dL to ≥ 160 mg/dL)	Olanzapine	302	10.6%	284	31.0%
		Placebo	173	8.1%	NA ^b	NA ^b

(b) (4)

(b) (4) Not Applicable.

6.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

This NDA was not presented to the PDAC.

7.0 POSTMARKETING COMMITMENT

The sponsor submitted a proposed synopsis in response to the Division's requirement in the approvable letter outlining the design of a long-term effectiveness relapse prevention study, which was reviewed by Dr. Zhang (24 July 2008).

Primary Objective and Measure

The primary objective of Study HDAY is to test the hypothesis that among patients who have responded to treatment with OFC, time to relapse for those randomized to continue treatment with OFC will be longer than time to relapse for those randomized to switch from OFC to fluoxetine.

(b) (4)

Inclusion Criteria:

- Be male or female, 18 to 65 years of age.
- Must fulfill the criteria for recurrent MDD without psychotic features

as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), based on clinical assessment and confirmed by the Structured Clinical Interview for DSM-IV Axis I

(b) (4)

- Must have demonstrated failure to achieve satisfactory antidepressant response to adequate trials of 2 different antidepressants within the current episode of MDD.

(b) (4)

The Antidepressant Treatment History Form (ATHF) will be used to obtain standardized information about past treatment trials.

-

(b) (4)

Secondary Objectives: no key secondary parameters were identified, though numerous secondary endpoints were proposed.

Flexible Dosing

The dosing will be flexible in the OFC group. This study will include 5 possible OFC doses (6/25, 12/25, 6/50, 12/50, and 18/50 mg/day, where the first number indicates the olanzapine dosage and the second number indicates the fluoxetine dosage) and 2 possible fluoxetine doses (25 and 50 mg/day).

Statistical Analysis

The hypothesis of principal interest is that OFC is superior to fluoxetine in time to relapse of depression in patients with acute depression who have responded to OFC.

(b) (4)

Determination of Sample Size

Up to approximately (b) (4) subjects will be entered into the stabilization/maintenance period (SPII) of this study. In order to test the primary hypothesis that time to relapse for acute OFC responders randomized to continued treatment with OFC will be greater than that of acute OFC responders randomized to switch from OFC to fluoxetine-only treatment,

(b) (4)

Safety Measures and Subgroup analyses: The safety measures will include weight, certain treatment-emergent adverse events, QTc measurements, and EPS scales.

Comments on Relapse Prevention Study Design:

We will convey to the sponsor, the following recommendations.

1. The stabilization period prior to randomization must be (b) (4) weeks long.
2. If claims are sought in labeling, key secondary endpoints must be pre-specified in the protocol that the sponsor will submit.
3. Fasting glucose and lipid levels, as well as weight and BMI should be measured prior to the minimum of (b) (4) weeks long stabilization period and at Baseline prior to randomization to double-blind treatment for assessment of time to relapse.

8.0 FOREIGN REGULATORY UPDATE

Lilly warrants that they have reviewed the world literature and found no evidence contrary to the presented conclusions about the safety of OFC in the general population.

8.0 CONCLUSIONS AND RECOMMENDATIONS

Dr. Zhang has thoroughly reviewed the response to the approvable letter. Dr. Mentari has reviewed the laboratory and clinical data and tables for labeling related to weight gain and metabolic changes. I have found the responses by the sponsor on face to be non-objectable.

With respect to the post-marketing long-term study, we will convey to the sponsor that in order to support a long-term claim in labeling for the proposed relapse prevention study to require (b) (4) week stabilization period prior to randomization to double blind treatment. Any key secondary endpoints must be pre-specified. It would be informative to measure changes in weight, as well as serum glucose and lipids before and after the (b) (4) week stabilization period (prior to randomization).

I recommend that an approvable action be taken based on resolution of the Division requirements that Lilly integrate information provided by the sponsor in response to requests by the Safety Team to describe the effects of olanzapine on weight as well as serum glucose and lipid levels.

The Symbyax product will need to carry a *MedGuide*. Consequently, I recommend to the Division Director an approvable action until agreement is reached with Lilly on the *MedGuide* and final labeling.

Post Marketing Commitments will include the long-term study (relapse prevention proposed by Lilly) and continued post-marketing surveillance for symptoms of metabolic

syndrome and clinical and laboratory changes associated with these and related conditions, [REDACTED]

(b) (4)

We have provided draft labeling for Symbyax finalized by the Deputy Director, Dr. Mitchell Mathis, to be provided with an approvable action letter along with the labeling for Zyprexa and Prozac as an integrated process.

cc: Original NDA 21-520/000 and S-012

HFD-130

HFD-130/JZhang/GZornberg/MMathis/TLaughren /RGrewal/SHardeman/PDavid

DOC: Symbyax_TRDCompleteResponse_Zornberg_AP_Memo.doc

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

/s/

Gwen Zornberg
7/25/2008 03:47:52 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
NDA #21,520

NDA#:	21,520/S-012
Sponsor:	Eli Lilly and Company
Drug:	Olanzapine/fluoxetine Combination (SYMBYAX®)
Material Submitted:	Complete Response to Approvable Letter on August 30, 2007 Resubmission in Response to Approvable letter on Feb. 1, 2008
Proposed Indication:	Treatment Resistant Depression
Dosage Forms:	3/25, 6/25, 12/25, 6/50, 12/50 mg
Administration:	Oral tablet
Intended Population:	Adults
Related Supplements:	N20,592/039, N21,086/021, N18936/077
Medical Reviewer:	Jing Zhang, MD. PhD.

I. Background

In the Approvable Action Letter for NDA 21,520/S-012, olanzapine/fluoxetine combination (OFC) for treatment resistant depression (TRD) in adults, dated 28 March 2007. The agency requested that the sponsor address following issues before the application may be approved.

- Updated information on risks of weight gain, hyperglycemia, and hyperlipidemia
- Post marketing commitments
- Labeling
- Foreign regulatory update/labeling
- Request for safety update and world literature update

The sponsor submitted a Completed Response to the Approvable Action letter dated 30 August 2007, and addressed issues listed above. FDA sent a letter to Lilly on 13 September 2007 indicating that the 30 August 2007 submission did not constitute a Complete Response because of lack important safety information related to hyperglycemia, hyperlipidemia, and weight gain in order to adequately update the labeling with all relevant risk information. Lilly resubmitted their Complete Response to the Approvable Letter on Feb. 1, 2008. In the re-submission,

Lilly included a plan of rolling submissions to provide additional hyperglycemia, hyperlipidemia, and weight gain information. The rolling submissions regarding risks of weight gain, hyperglycemia, and hyperlipidemia were reviewed by the safety team and Evelyn Mentari, MD is the primary medical reviewer. The detailed information regarding weight gain, hyperglycemia, and hyperlipidemia associated with OFC can be found in her review. This review will address the remaining issues for regulatory processing.

II. Review of Clinical Data

1. Updated information on risks of weight gain, hyperglycemia, and hyperlipidemia

Please refer to the safety review by Evelyn Mentari, MD. and the Division Director's memorandum reviewing all data relevant to risks of weight gain, hyperglycemia, and hyperlipidemia.

2. Post marketing commitments

Lilly commits to conducting a phase IV study to evaluate the longer term effectiveness and safety of OFC in treatment-resistant depression. Lilly submitted a proposal for a phase IV commitment study (though not the protocol) that is designed to assess the ability of OFC to reduce the risk of relapse in patients with TRD who have responded to treatment with OFC.

2.1 Proposed Study

Overall Study design

The proposed study, Study H6P-MC-HDAY (HDAY), consists of 4 periods: a screening phase (phase I), an (b) (4) week stabilization/maintenance phase (phase II), a (b) (4)-week double-blind, randomized withdrawal phase (phase III) (b) (4)

Following a brief screening phase (phase I), approximately (b) (4) patients with TRD will enter Phase II, and receive open-label OFC for (b) (4) weeks. In order to move to the phase III, patients must have received OFC for a minimum of (b) (4) weeks and meet detailed response criteria for the last (b) (4) (b) (4). In phase III, approximately (b) (4) patients will be randomly allocated to

either receiving OFC or to receive fluoxetine alone in a (b) (4) for 27 weeks. Patients who relapse during this phase will be discontinued from the study. (b) (4)

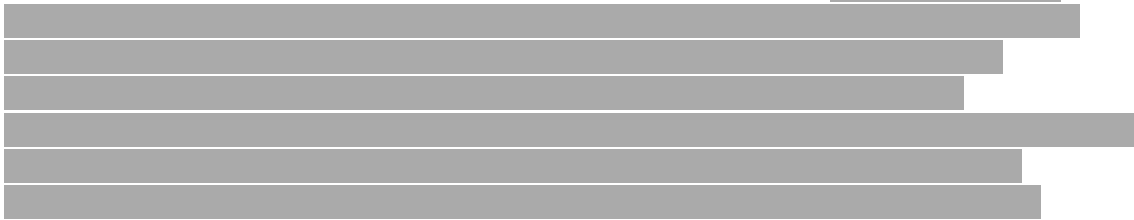


Figure 1 illustrates the study design.



Figure 1 Proposed design for long-term study of OFC in TRD

Study Measures

Efficacy Assessments:

MADRS, CGI-Severity, (b) (4)

(b) (4) In addition, rates of response and remission will be assessed during all phases of the study, and rates of relapse will be assessed after randomization.

During the stabilization phase, the following definitions of response and remission will apply:



During the randomization phase, the definitions of response and remission will remain the same. Relapse will be defined as follows:

Relapse. Relapse will be defined as meeting any of the following criteria:

- (b) (4) MADRS improvement on MADRS score combined with concomitant CGI (b) (4)
- Hospitalization for depression or suicidality
- Discontinuation due to lack of efficacy/worsening of depression
- (b) (4) worsening on suicidality scale or suicide-related adverse event rated (b) (4)

Safety Assessments

Standard safety measures, including treatment-emergent adverse events, (b) (4), and changes in vital signs and weight, laboratory analytes, and ECGs will be included. In addition, important safety measures relevant to the evaluation of OFC will include fasting serum levels of lipids and glucose.

Dosing

This study will include 5 possible OFC doses (6/25, 12/25, 6/50, 12/50, and 18/50 mg/day. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2.2 Reviewer's Comments

The study design is non-objectionable except for one limitation—the length of stabilization period (phase II) is too short. The sponsor proposed an (b) (4) week open-label stabilization period and patients had to be stabilized for at least (b) (4) to move to next phase. Based on the division's current practice, a (b) (4) stabilization period design (patients have to be fully stabilized for (b) (4)) is required for a relapse prevention trial. If the sponsor considers using the results from this study to support a claim for a long-term indication of OFC in the future, it is

recommended that the sponsor increase the length of the stabilization phase to ensure that patients will be stabilized for (b) (4) before they move to the phase III.

The sponsor needs to provide a protocol for Study HDAY after this supplement NDA is approved.

3. Labeling

The sponsor submitted revised draft labeling. Numerous changes were recommended by the division, especially in the section of Warnings and Precautions regarding risks of hyperglycemia, hyperlipidemia and weight gain associated with OFC. Please refer to approval letter for NDA 21520/S-012 for detailed labeling change recommendations.

4. Foreign Regulatory Update/Labeling

As of 1 July 2006, Lilly had received regulatory approval to market Symbyax (olanzapine/fluoxetine combination) for the treatment of depressive episodes associated with bipolar depression in 8 countries. There have been no additional approvals since that time.

In addition, neither OFC nor the coadministration of olanzapine and fluoxetine are approved anywhere in the world for the treatment-resistant depression indication.

Despite these approvals, OFC is only marketed in 2 countries: the United States and Mexico. It was marketed briefly in Argentina (from October 2004 through March 2006), but marketing was discontinued because marketing expectations were not met.

5. Request for Safety Update and World Literature Update

Safety Update

There are no ongoing Lilly-sponsored nonclinical or clinical studies of Symbyax. Therefore a safety update is not applicable.

World Literature Update

The original worldwide literature update provided with the submission was conducted for the time period 1966 through 2 May 2006. The revised update covers an additional year

through 31 May 2007. For both time periods, searches were conducted using Ovid Embase and Ovid Medline, with specific time parameters given as follows:

- OVID EMBASE 2006 Week 17 to 2007 Week 22
- Ovid MEDLINE April Week 3 2006 to May Week 4 2007
- Ovid MEDLINE In Process & Other Non-Indexed Citations May 2, 2006 to May 31, 2007

Four separate searches (Fluoxetine monotherapy and TRD, Olanzapine monotherapy and TRD, Olanzapine and fluoxetine combination (OFC) and TRD, and TRD alone) were performed by a Pharm D Global Medical Information associate. The searches were designed to provide information about OFC and its component monotherapies in relation to treatment-resistant depression (TRD).

Lilly warrants that they have reviewed the literature systematically and in detail. They have discovered no findings contrary to previously presented conclusions about the safety of Symbyax.

III. Conclusions and Recommendations

Lilly's submissions constituted a completed responses to the Approvable Letter on 28 March 28 2007. It is recommended that these supplements (NDA 21,520/012) be approved.

Jing Zhang, MD. PhD.
July 23, 2008

cc: NDA 21-520
HFD-130 (Div. File)
HFD-130/JZhang
/GZornberg
/MMathis
/TLaughren
/RGrewal

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/s/

Jing Zhang
7/24/2008 11:29:39 AM
MEDICAL OFFICER

Gwen Zornberg
7/24/2008 03:37:55 PM
MEDICAL OFFICER

I concur with Dr. Zhang's recommendation to the Division
Director that a letter with an Approval action
be issued for the Treatment Resistant Depression indication
in labeling.

**CLINICAL REVIEW: CHANGES IN WEIGHT, LIPIDS, AND
GLUCOSE WITH OLANZAPINE AND
OLANZAPINE/FLUOXETINE COMBINATION**

Application Type	NDA
Submission Number	Zyprexa (olanzapine) 20-592 Symbyax (olanzapine/fluoxetine) 21-520
Reviewer Name	Evelyn Mentari, MD, MS
Review Completion Date	July 15, 2008
Therapeutic Class	Second Generation Antipsychotic (olanzapine) Second Generation Antipsychotic/Selective Serotonin Reuptake Inhibitor (olanzapine/fluoxetine)
Subject	Hyperglycemia, Hyperlipidemia, and Weight Gain
Applicant	Eli Lilly and Company
Formulation	Oral
Dosing Regimen	Multiple
Indication	Multiple

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I. Background

I.1. FDA Information Request

FDA requested additional data analyses related to weight gain, hyperlipidemia, and hyperglycemia in an approvable letter, received by Lilly on March 28, 2007, for a supplemental New Drug Application (sNDA) for Symbyax® [olanzapine/fluoxetine combination (OFC)] for the treatment of treatment-resistant depression (TRD). FDA included similar requests in the approvable letter for two sNDAs for olanzapine for the treatment of schizophrenia and bipolar disorder (acute manic or mixed episodes) in adolescent patients, received by Lilly on April 30, 2007.

FDA and Lilly established a plan for specific analyses to be submitted; this plan was discussed in a meeting between FDA and Lilly on May 24, 2007. Lilly provided the requested data in a series of 4 rolling submissions.

I.2. Timeline of Actions Related to FDA's Request for Analyses Related to Weight Gain, Hyperlipidemia, and Hyperglycemia

The following is a timeline of actions related to FDA's request for analyses related to weight gain, hyperlipidemia, and hyperglycemia:

- August 30, 2007: Lilly submitted analyses of adult and adolescent data for olanzapine and adult data for OFC from placebo-controlled trials (Data Package #1).
- September 10, 2007: Lilly submitted revised and updated placebo-controlled databases (Data Package #1).
- September 13, 2007: FDA sent Lilly a letter indicating that the August 30 2007 submissions did not constitute complete responses.
- October 4, 2007: Lilly submitted Changes Being Effected labeling supplements for Zyprexa and Symbyax and final Dear Health Care Practitioner Letter; this submission also included a revision of Data Package #1 (originally submitted August 30, 2007, revised September 10, 2007 and revised again October 3, 2007).
- November 1, 2007: Lilly submitted analyses of weight, lipids, and glucose data from its active comparator-controlled trials, CATIE, and CAFE (Data Package #2).
- December 19, 2007: Lilly submitted Data Package #3, which included overall/long-term integrated analyses of weight, lipids, and glucose from the olanzapine adult integrated, olanzapine adolescent integrated, and OFC adult integrated databases (to NDAs 20-592/s040 and s041 and 21-520/s012).

- February 1, 2008: Lilly sent the Resubmission/Complete Response for Symbyax sNDA for TRD (NDA 21-520/s012).
- February 4, 2008: Lilly sent the Resubmission/Complete Response for olanzapine plus fluoxetine sNDAs for TRD (NDA 20-592/s039, NDA 21-086/s021, and NDA 18-936/s077).
- February 5, 2008: Lilly sent the Resubmission/Complete Response for Zyprexa adolescent sNDAs for schizophrenia and bipolar disorder (acute manic or mixed episodes) (NDA 20-592/s040 and s041).
- March 5, 2008: Lilly sent corrections related to a programming error that affected 59 tables across the first 2 data packages submitted: Data Package #1 (placebo-controlled data) and Data Package #2 (active-comparator-controlled data). This error affected the calculation of median exposure in affected tables; it did not affect calculation of variables of greatest interest in each table. Sponsor Table 3.1 below lists the original and revised tables involved in correcting the programming error.

Table 3.1. List of Tables Presenting Categorical Analyses for Lipids-Related Analytes, with Links to Original and Revised Versions

Submission Database Topic	Table	
	Original	Revised
First Submission (Placebo-Controlled Olanzapine and OFC Databases)		
Olanzapine Adult Placebo-Controlled Database		
TE Clin Sig Changes: All Patients	Table 5.6	Table 11.1
TE Clin Sig Changes: By Baseline Dyslipidemia Status	Table 5.7	Table 11.2
TE Absolute Changes: By Baseline Category	Table 5.8	Table 11.3
TE Clin Sig Changes: All Patients with 12 Weeks of Exposure	Table 8.6	Table 11.4
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 12 Weeks of Exposure	Table 8.7	Table 11.5
TE Clin Sig Changes: All Patients with 24 Weeks of Exposure	Table 8.38	Table 11.6
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 24 Weeks of Exposure	Table 8.39	Table 11.7
Olanzapine Adolescent Placebo-Controlled Database		
TE Clin Sig Changes: All Patients	Table 5.15	Table 12.1
TE Clin Sig Changes: By Baseline Dyslipidemia Status	Table 5.16	Table 12.2
TE Absolute Changes: By Baseline Category	Table 5.17	Table 12.3
TE Clin Sig Changes: All Patients with 12 Weeks of Exposure	Table 8.14	Table 12.4
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 12 Weeks of Exposure	Table 8.15	Table 12.5
TE Clin Sig Changes: All Patients with 24 Weeks of Exposure	Table 8.46	Table 12.6
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 24 Weeks of Exposure	Table 8.47	Table 12.7
OFC Adult Controlled Database		
TE Clin Sig Changes: All Patients	Table 5.24	Table 13.1
TE Clin Sig Changes: By Baseline Dyslipidemia Status	Table 5.25	Table 13.2
TE Absolute Changes: By Baseline Category	Table 5.26	Table 13.3
TE Clin Sig Changes: All Patients with 12 Weeks of Exposure	Table 8.22	Table 13.4
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 12 Weeks of Exposure	Table 8.23	Table 13.5

Abbreviations: TE Clin Sig = Treatment-Emergent Clinically Significant

Table 3.1. List of Tables Presenting Categorical Analyses for Lipids-Related Analytes, with Links to Original and Revised Versions (continued)

Submission Database Topic	Links to Tables	
	Original	Revised
First Submission (Placebo-Controlled Olanzapine and OFC Databases), concluded		
OFC Adult Placebo-Controlled Database		
TE Clin Sig Changes: All Patients	Table 5.33	Table 14.1
TE Clin Sig Changes: By Baseline Dyslipidemia Status	Table 5.34	Table 14.2
TE Absolute Changes: By Baseline Category	Table 5.35	Table 14.3
TE Clin Sig Changes: All Patients with 12 Weeks of Exposure	Table 8.30	Table 14.4
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 12 Weeks of Exposure	Table 8.31	Table 14.5
Second Submission (Comparator-Controlled Databases)		
Clozapine-Controlled Database		
TE Clin Sig Changes: All Patients	Table 6.6	Table 15.1
TE Clin Sig Changes: By Baseline Dyslipidemia Status	Table 6.7	Table 15.2
TE Absolute Changes: By Baseline Category	Table 6.8	Table 15.3
TE Clin Sig Changes: All Patients with 12 Weeks of Exposure	Table 8.6	Table 15.4
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 12 Weeks of Exposure	Table 8.7	Table 15.5
TE Clin Sig Changes: All Patients with 24 Weeks of Exposure	Table 8.46	Table 15.6
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 24 Weeks of Exposure	Table 8.47	Table 15.7
Quetiapine-Controlled Database		
TE Clin Sig Changes: All Patients	Table 6.15	Table 16.1
TE Clin Sig Changes: By Baseline Dyslipidemia Status	Table 6.16	Table 16.2
TE Absolute Changes: By Baseline Category	Table 6.17	Table 16.3
TE Clin Sig Changes: All Patients with 12 Weeks of Exposure	Table 8.14	Table 16.4
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 12 Weeks of Exposure	Table 8.15	Table 16.5
TE Clin Sig Changes: All Patients with 24 Weeks of Exposure	Table 8.54	Table 16.6
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 24 Weeks of Exposure	Table 8.55	Table 16.7
Second Submission (Comparator-Controlled Databases), concluded		
Risperidone-Controlled Database		
TE Clin Sig Changes: All Patients	Table 6.24	Table 17.1
TE Clin Sig Changes: By Baseline Dyslipidemia Status	Table 6.25	Table 17.2
TE Absolute Changes: By Baseline Category	Table 6.26	Table 17.3
TE Clin Sig Changes: All Patients with 12 Weeks of Exposure	Table 8.22	Table 17.4
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 12 Weeks of Exposure	Table 8.23	Table 17.5
TE Clin Sig Changes: All Patients with 24 Weeks of Exposure	Table 8.62	Table 17.6
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 24 Weeks of Exposure	Table 8.63	Table 17.7
Ziprasidone-Controlled Database		
TE Clin Sig Changes: All Patients	Table 6.33	Table 18.1
TE Clin Sig Changes: By Baseline Dyslipidemia Status	Table 6.34	Table 18.2
TE Absolute Changes: By Baseline Category	Table 6.46	Table 18.3
TE Clin Sig Changes: All Patients with 12 Weeks of Exposure	Table 8.30	Table 18.4
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 12 Weeks of Exposure	Table 8.31	Table 18.5
TE Clin Sig Changes: All Patients with 24 Weeks of Exposure	Table 8.70	Table 18.6
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 24 Weeks of Exposure	Table 8.71	Table 18.7
Haloperidol-Controlled Database		
TE Clin Sig Changes: All Patients	Table 6.42	Table 19.1
TE Clin Sig Changes: By Baseline Dyslipidemia Status	Table 6.43	Table 19.2
TE Absolute Changes: By Baseline Category	Table 6.44	Table 19.3
TE Clin Sig Changes: All Patients with 12 Weeks of Exposure	Table 8.38	Table 19.4
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 12 Weeks of Exposure	Table 8.39	Table 19.5
TE Clin Sig Changes: All Patients with 24 Weeks of Exposure	Table 8.78	Table 19.6
TE Clin Sig Changes: By Baseline Dyslipidemia Status for Patients with 24 Weeks of Exposure	Table 8.79	Table 19.7

Abbreviations: TE Clin Sig = Treatment-Emergent Clinically Significant

- May 12, 2008: The fourth requested data package regarding weight gain, hyperlipidemia, and hyperglycemia in special populations was entered to the Electronic Document Room.

- May 14, 2008: The sponsor submitted proposed labeling for Zyprexa and for Symbyax.
- June 4, 2008: Lilly submitted a response to an FDA request (dated May 27, 2008) for revised versions of tables assessing weight gain outliers in each subject group, stratifying by treatment exposure time. The request specified that revised tables should use the same methods as previously submitted tables, except that revised tables should assess weight gain at 6 weeks, 6 months, 12 months, 24 months, and 36 months.

These submissions as a group adequately addressed the requests for information, initiated by FDA in March 2007, regarding changes in weight, blood lipids, and blood glucose with use of olanzapine and olanzapine fluoxetine combination (OFC).

The sponsor's May 12, 2008 submission included analyses of changes in weight, blood lipids, and blood glucose in Elderly Alzheimer's/Parkinson's Databases and in Antipsychotic-Naïve Databases. Analyses of elderly subjects were reviewed but are not discussed in detail in this document. Changes in weight, blood lipids, and blood glucose in olanzapine-treated elderly Alzheimer's/Parkinson's patients were of smaller magnitude than changes for olanzapine-treated adult patients in general.

II. Weight Gain

II.1. Weight Gain: Olanzapine Adult Subjects

II. 1.1. Weight Gain: Olanzapine Adult Subjects in Placebo-Controlled Trials

Note: Tables describing analyses for Adult Placebo-Controlled subjects are from the 10/04/07 submission.

In a pooled analysis of adult subjects in placebo-controlled trials (trial duration ranged from 3 to 8 weeks), olanzapine-treated subjects had a mean weight gain of 2.64 kg (median exposure 47 days), compared to a mean weight loss of 0.26 kg in placebo-treated subjects (median exposure 35 days) ($P < 0.001$) (Sponsor Table 4.2 below). Rate of weight gain was 0.45 kg/week in olanzapine-treated subjects and -0.05 kg/week in placebo-treated subjects. In similar analyses stratified according to baseline BMI, mean differences in weight change between olanzapine-treated subjects and placebo-treated subjects were similar across baseline BMI groups.

Table 4.2. Weight
Mean Change from Baseline to Endpoint (LOCF): All Patients
Olanzapine Adult Placebo-Controlled Database

Therapy	Mean Modal Dose	Days of Exposure (Min,Q1,Q2,Q3,Max)	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value	Rate of Weight Gain (kg per Week)	
				Mean	Std	Mean	Std				Mean	Std
OLZ	10.9	Trt: (1,22,47,63,964) Wgt: (1,21,42,59,964)	1983	78.78	20.11	2.64	4.73	2.62	2.85	<.001	0.45	1.19
PLA	0.0	Trt: (1,21,35,57,604) Wgt: (1,20,30,57,604)	1278	78.72	19.70	-0.26	2.91	-0.23			-0.05	0.80

OLZ = olanzapine, PLA = placebo, Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
N = Number of patients having both baseline and post-baseline measurements.
Exposure: Trt: total days of exposure to therapy.
Wgt: total days of exposure from start of therapy to last available weight.
Included studies: HBED, HGAD, HGAP, HGBH, HGEH, HGGA, HGGF, HGGW, HGGY, HGJZ, HGKK, HGKL, HGKQ.

* P-values are from Type III Sum of Squares from the ANOVA model: Weight_Change = Protocol Therapy.
Least Square mean differences are from the same ANOVA model.

The sponsor also reported observed case mean changes in weight from baseline to 6 endpoints (2, 4, 8, 12, 24, and 48 weeks) (see Sponsor Table 4.4 below). With each successive endpoint, the mean weight gain in olanzapine-treated subjects increased, while the mean weight loss in placebo-treated subjects also was successively greater.

Table 4.4. Weight
Mean Change from Baseline to Endpoint (Observed Case): By Duration of Exposure
Olanzapine Adult Placebo-Controlled Database

		Baseline	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
OLZ	N	2052	1791	1367	835	347	37	24
	Change from Baseline	Mean	78.73	1.27	2.21	3.58	8.82	9.64
		Std	20.12	3.04	2.90	4.49	6.85	7.83
	t-Test *	p-Value		<.001	<.001	<.001	<.001	<.001
PLA	N	1345	1115	844	489	207	7	4
	Change from Baseline	Mean	78.69	0.04	0.06	-0.20	-1.62	-1.86
		Std	19.89	1.83	2.34	3.10	2.79	3.85
	t-Test *	p-Value		.523	.471	.162	.276	.405
Treatment Comparison **		p-Value		<.001	<.001	<.001	.001	.012

OLZ = olanzapine, PLA = placebo.
N = Number of patients having measurements at both baseline and the week shown.
Included studies: HBED, HGAD, HGAP, HGBH, HGEH, HGGA, HGGF, HGGW, HGGY, HGJZ, HGKK, HGKL, HGKQ.

* Within group p-values are from a t-test on the mean change.

** P-values are from Type III Sum of Squares from the ANOVA model: Weight_Change = Protocol Therapy.

Sponsor Table 4.5 below summarizes the proportions of patients with treatment-emergent significant weight gain of at least 7%, 15%, and 25%. Olanzapine-treated subjects had significantly greater weight gain than placebo-treated subjects at each level of weight gain evaluated. The incidence of treatment-emergent weight gain of at least 7% was 22.2% for olanzapine and 3.0% for placebo (median exposure time of about 8 weeks in both treatment groups).

Table 4.5. Weight Treatment-Emergent Significant Changes: All Patients Olanzapine Adult Placebo-Controlled Database

PCS Category	Therapy	Mean Modal Dose	Days of Exposure to PCS (Min,Q1,Q2,Q3,Max)	Total Days of Exposure (Min,Q1,Q2,Q3,Max)	N	PCS Flag	n	%	*P-value
PCS Weight Gain (7%)	OLE	10.9	(6,40,56,84,742)	(6,54,57,88,964) (1,21,30,56,847)	1983	Yes	441	22.2	<.001
						No	1542	77.8	
	PLA	0.0	(14,28,55,70,210)	(20,37,56,84,329) (1,20,30,57,604)	1278	Yes	38	3.0	
						No	1240	97.0	
PCS Weight Gain (15%)	OLE	10.9	(20,56,86,262,742)	(20,56,100,443,860) (1,21,42,57,964)	1983	Yes	84	4.2	<.001
						No	1899	95.8	
	PLA	0.0	(37,37,43,56,134)	(37,37,56,84,196) (1,20,30,57,604)	1278	Yes	4	0.3	
						No	1274	99.7	
PCS Weight Gain (25%)	OLE	10.9	(56,185,294,477,742)	(56,223,443,540,860) (1,21,42,59,964)	1983	Yes	16	0.8	<.001
						No	1967	99.2	
	PLA	0.0		(1,20,30,57,604)	1278	Yes	0	0.0	
						No	1278	100.0	

OLE = olanzapine, PLA = placebo.

N = Number of patients having both baseline and post-baseline measurements.

n = Number of patients having the indicated PCS flag.

Total days of exposure is the number of days from the start of therapy until the last available weight.

Days of exposure to PCS is the number of days from the start of therapy until PCS weight gain.

Included studies: HBBD, HGAD, HGAP, HGBH, HGBH, HGBA, HGGF, HGGW, HGGY, HGJZ, HGKK, HGKL, HGKQ.

* Frequencies analyzed using two-tailed Fisher's Exact Test.

In the database of adult placebo-controlled olanzapine trials, 0.2% of olanzapine-treated and no placebo-treated subjects discontinued due to weight gain-related adverse events (increased appetite and increased weight) (P=0.16).

II.1.2. Weight Gain: Olanzapine Adult Subjects in Comparator-Controlled Trials

Table 1 summarizes weight results across the 5 databases that compare olanzapine to other antipsychotics (clozapine, quetiapine, risperidone, ziprasidone, and haloperidol).

Clozapine

Patients treated with olanzapine or clozapine experienced comparable weight in head-to-head studies in the Lilly clozapine-controlled database. Similar proportions of clozapine-treated and olanzapine-treated patients had upward shifts in body mass index (BMI). Similar proportions of clozapine-treated and olanzapine-treated patients gained at least 7% or 15% of their baseline weight. Mean weight gain was non-statistically significantly higher for clozapine-treated than olanzapine-treated patients.

Quetiapine

Patients treated with olanzapine or quetiapine experienced comparable weight gain in head-to-head studies in the Lilly quetiapine-controlled database, with no statistically significant differences observed. Olanzapine-treated patients had numerically higher mean weight changes, but olanzapine-treated patients had longer median treatment exposure durations. Similar proportions of quetiapine-treated patients and olanzapine-treated patients had shifts in BMI from normal to above normal or upward in general, but non-statistically significantly higher proportions of olanzapine-treated patients than quetiapine-treated patients gained at least 7% or 15% of baseline weight. It is important to note that the majority of patients in this

database were overweight or obese at baseline; thus these results may have limited generalizability beyond this population.

Risperidone

Patients treated with olanzapine experienced greater weight gain compared to risperidone in head-to-head studies in the Lilly risperidone-controlled database. Analyses of both mean change and treatment-emergent significant changes demonstrated statistically significantly greater changes in weight for olanzapine-treated patients compared to risperidone-treated patients. Statistically significantly more olanzapine-treated patients than risperidone-treated patients gained at least 7% of baseline weight, and significantly higher proportions of olanzapine-treated patients than risperidone-treated patients had shifts in BMI from normal to above normal or upward in general.

Ziprasidone

Patients treated with olanzapine experienced greater weight gain compared to ziprasidone in head-to-head studies in the Lilly ziprasidone-controlled database. Analyses of both mean change and treatment-emergent significant changes demonstrated statistically significantly greater changes in olanzapine-treated patients compared to ziprasidone-treated patients, but olanzapine-treated patients had longer median treatment exposure durations. Statistically significantly more olanzapine-treated patients than ziprasidone-treated patients had treatment-emergent weight gain of 7%, 15%, or 25%, and higher proportions of olanzapine-treated patients than ziprasidone-treated patients had shifts in BMI from normal to above normal or upward in general.

Haloperidol

Patients treated with olanzapine experienced greater weight gain compared to haloperidol in head-to-head studies in the Lilly haloperidol-controlled database. Analyses of both mean change and treatment-emergent significant changes demonstrated statistically significant differences between olanzapine and haloperidol in favor of haloperidol; duration of treatment exposure was similar in the two treatment groups. Higher proportions of olanzapine-treated patients than haloperidol-treated patients had shifts in BMI from normal to above normal or upward in general.

Table 1. Summary of Weight Data from Lilly Comparator-Controlled Databases

	olanzapine clozapine		olanzapine quetiapine		olanzapine risperidone		olanzapine ziprasidone		olanzapine haloperidol	
LS mean change in weight (kg)	2.46	3.36	0.90	-0.07	3.68	2.18 a	2.79	-1.38 a	3.73	0.50 a
N	228	224	235	228	713	697	463	443	2604	1461
Median Exposure	125 days	124 days	167 days	132 days	70 days	70 days	168 days	102 days	60 days	42 days
Patients with PCS Weight Gain										
N	228	224	235	228	713	697	463	443	2604	1461
≥7% (%)	28.9%	34.8%	16.6%	11.8%	30.6%	20.2% a	30.0%	6.5% a	35.2%	12.8% a
Median Exposure	126 days	126 days	140 days	131 days	196 days	50 days	187 days	173 days	209 days	209 days
≥15% (%)	8.8%	12.5%	2.1%	0.4%	9.4%	5.0% b	8.0%	0.9% a	11.8%	4.0% a
Median Exposure	126 days	126 days	137 days	56 days	336 days	198 days	196 days	168 days	322 days	328 days
≥25% (%)	1.8%	2.2%	0.4%	0.4%	2.2%	1.1%	2.2%	0.5% b	3.6%	0.9% a
Median Exposure	125 days	171 days	175 days	56 days	363 days	298 days	196 days	195 days	366 days	378 days
Proportion with upward shift in BMI category										
N _c	25.7%	28.2%	15.2%	16.8%	29.6%	20.1% b	30.3%	11.7% a	30.0%	14.1% a
	70	71	99	95	114	77	92	34	603	152

Abbreviations: BL = baseline; BMI = body mass index; LS = least squares; N = number of patients in analysis; PCS = potentially clinically significant; pts = patients.

P values are for the within baseline BMI category based on the Type III Sum of Squares from the ANOVA model: Weight Change = Protocol therapy. Least Square Mean differences are from the same ANOVA model.

a Statistically significantly different; $p < .001$.

b Statistically significantly different at $p < .05$.

c N excludes patients who were obese at baseline and could not experience upward shift.

II.1.3. Weight Gain: Olanzapine Adult Subjects: Long Term Controlled and Uncontrolled Data

Sponsor Table 2.1 from the 12/19/07 submission below compared changes in weight for all patients and patients with at least 48 weeks of exposure. In patients with at least 48 weeks of exposure, the mean weight gain was 5.6 kg (median exposure of 573 days, N=2021).

Table 2.1. Weight Data from the Olanzapine Adult Integrated Database All Patients and Patients with at Least 48 weeks of Exposure

OLANZAPINE ADULT Weight	All patients		With ≥48 weeks' exposure	
	N	estimate (95% CI)	N	estimate (95% CI)
LOCF mean change in weight (kg):				
—For all patients	12020	3.15 (3.0, 3.3)	2021	5.61 (5.2, 6.0)
Median exposure; mean rate of change		84 d; 0.26 kg/wk		573 d; 0.07 kg/wk
—For pts underweight at BL	329	4.15 (3.6, 4.7)	49	7.37 (5.4, 9.3)
Median exposure; mean rate of change		83 d; 0.34 kg/wk		648 d; 0.10 kg/wk
—For pts with normal BMI at BL	4046	3.78 (3.6, 4.0)	765	6.84 (6.2, 7.5)
Median exposure; mean rate of change		94 d; 0.27 kg/wk		627 d; 0.08 kg/wk
—For pts with overweight BMI at BL	3313	3.07 (2.9, 3.3)	642	5.37 (4.7, 6.1)
Median exposure; mean rate of change		90 d; 0.25 kg/wk		630 d; 0.07 kg/wk
—For pts with obese BMI at BL	2795	2.30 (2.1, 2.5)	388	3.11 (2.1, 4.1)
Median exposure; mean rate of change		64 d; 0.27 kg/wk		572 d; 0.04 kg/wk
Patients with PCS weight gain:				
≥7% (%)	12020	32.5% (31.7, 33.3)	2021	64.4% (62.2, 66.5)
Median exposure until PCS event		56 days		99 days
≥15% (%)	12020	10.5% (10.0, 11.1)	2021	31.7% (29.6, 33.7)
Median exposure until PCS event		139 days		210 days
≥25% (%)	12020	3.1% (2.8, 3.4)	2021	12.3% (10.9, 13.8)
Median exposure until PCS event		225 days		296 days
Upward shift in BMI category ^a	7698	31.2% (30.2, 32.3)	1456	53.6% (51.0, 56.2)
Discontinuations due to weight gain-related adverse events	12425	0.5% (0.4, 0.6)	2034	0.4% (0.2, 0.8)

Abbreviations: BL = baseline; BMI = body mass index; CI = confidence interval; d = days; kg/wk = kilograms per week; LOCF = last observation carried forward; N = number of patients in analysis; PCS = potentially clinically significant; pts = patients.

^a N excludes patients who were obese at baseline and could not experience upward shift.

The percentages of patients who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 64%, 32%, and 12%, respectively (Sponsor Table 5.4.2 from the 12/19/07 submission below).

Weight
Treatment-Emergent Significant Changes from Baseline to Anytime
Olanzapine Adult Integrated Database: Patients with at Least 48 Weeks of Exposure

OLZ = olanzapine, Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
N = Number of patients having both baseline and post-baseline measurements.
n = Number of patients having the indicated PCS flag.
Total days of exposure is the number of days of exposure to therapy.
Days of exposure to PCS is the number of days from the start of therapy until PCS weight gain.
Included studies: E003, E202, E204, E304, E305, HGAD, HGAF, HGAP, HGBA, HGBB, HGBI, HGBE, HGBD, HGBU, HGBX, HGCF, HGCL, HGCM, HGCG, HGCV, HGBD, HGDR, HGDI, HGDO, HGEC, HGEH, HGEJ, HGEF, HGGF, HGGN, HGHL, HGHO, HGJZ, HGKA, HGKB, P022.

Table 5.1.10. Weight
Shifts from Baseline to Various Time Points (Observed Case)
Olanzapine Adult Integrated Database: All Patients

OLZ = olanzapine.
N = Number of patients having measurements at both baseline and the time point shown.
After 6 weeks, the data in the table is from the last visit in a window +/- 2 weeks from the indicated time point.
Included studies: E003, E201, E202, E204, E301, E304, E305, HDAO, HGAD, HGAJ, HGAP, HGBA, HGBF, HGBG, HGBH, HGBI, HGBJ, HGKE, HGBM, HGBO, HGBQ, HGBU, HGBX, HGCF, HGCH, HGCK, HGCL, HGCM, HGCO, HGCO, HGCU, HGCV, HGCX, HGCV, HGCE, HGDB, HGDI, HGDI, HGDO, HGDT, HGDU, HGDV, HGDE, HGEE, HGEG, HGEJ, HGEP, HGEB, HGER, HGPH, HGFM, HGFT, HGGA, HGGO, HGGF, HGGI, HGGN, HGGY, HGHD, HGHN, HGJY, HGHL, HGHO, HGHR, HGIZ, HGIA, HGIE, HGII, HGJB, HGJU, HGJZ, HGKA, HGKB, HGKK, HGKL, HGLO, HGLF, HGLG, E022.

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The OFC Adult Controlled Database includes all 7 of the clinical studies designed to study the acute treatment of some form of depression that included both an OFC treatment group and at least an olanzapine treatment group or a fluoxetine treatment group. Sponsor analyses of this database present results for OFC, olanzapine, fluoxetine, and placebo, although only 2 studies contained an OFC group and a placebo group.

Separate analyses of pooled results from 2 studies that contain both a placebo treatment group and an OFC treatment group (Studies HGGA and HGGY) are presented later in the sponsor submission; data from these two studies pooled together are referred to as the “OFC Adult Placebo-Controlled Database”.

Reviewer Note: Because analyses of the OFC Adult Controlled Database include more subjects, the sponsor focuses on these results; the results of this database and the OFC Adult Placebo-Controlled Database are qualitatively similar.

OFC has not been systematically studied in adolescent subjects. The sponsor proposes using data from olanzapine monotherapy studies to provide information on adolescents in the OFC label.

Sponsor Table 4.22 below reports the last observation carried forward (LOCF) mean change from baseline to endpoint in weight. OFC-treated subjects had statistically significantly more weight gain than placebo-treated subjects and fluoxetine-treated subjects. There was no significant difference in weight gain between OFC-treated subjects and olanzapine-treated subjects.

**Table 4.22. Weight
Mean Change from Baseline to Endpoint (LOCF): All Patients
OFC Adult Controlled Database**

Therapy	Mean Modal Dose (mg)	Exposure (days) (min, Q1, Q2, Q3, max)	Baseline			Change to Endpoint			LSMean Diff. (vs OFC)	*P-values Overall	Rate of Weight Gain (kg/wk)		
			N	Mean	Std	Mean	Std	LSMean Change			OFC vs.	Mean	Std
OFC	8.5/39.0	Wgt: (1,49,56,69,112) Trt: (1,52,57,70,116)	742	83.02	22.36	3.97	3.68	4.00		<.001	0.57	0.73	
FLX	42.1	Wgt: (3,50,56,60,115) Trt: (4,53,56,60,130)	441	85.26	24.07	-0.21	2.60	-0.45	-4.45	<.001	-0.01	0.69	
OLZ	9.6	Wgt: (1,33,55,57,112) Trt: (1,35,56,57,112)	841	82.95	21.28	3.57	3.63	4.13	0.13	.472	0.61	0.78	
PLA	0.0	Wgt: (2,27,42,56,112) Trt: (2,28,43,56,113)	445	81.72	21.51	-0.29	2.70	1.02	-2.98	<.001	-0.06	0.71	

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
OFC = olanzapine + fluoxetine combination, FLX = fluoxetine, OLZ = olanzapine, PLA = placebo.
Exposure TRT: total days of exposure to therapy.
Exposure WGT: total days of exposure from start of therapy until last available weight.
N = number of patients having both baseline and post-baseline measurements.
*P-value is from Type III Sums of Squares from ANOVA model; change = protocol therapy.
Included studies: HCKB, HDAO, HGFR, HGGA, HGGY, HGHZ, HGIE.

In analyses of mean changes in weight stratified by baseline BMI, treatment by subgroup interaction was not significant.

Sponsor Table 4.24 below reports observed case analyses of mean changes in weight at weeks 2, 4, 8, and 12. Mean weight gain in OFC-treated subjects was 4.29 kg (9.4 lb) at 8 weeks compared with a mean weight loss of 0.54 kg (-1.2 lb) in placebo-treated subjects ($P < 0.001$).

The incidence of statistically significant changes in weight parameters in patients treated with OFC and olanzapine in the OFC databases tend to be greater than the incidence of such changes in patients treated with olanzapine in the olanzapine databases. This difference may be related to differences between the patient populations of olanzapine and OFC databases; patients in the OFC database were less likely to have been previously treated with antipsychotics.

Table 4.24. Weight Mean Change from Baseline to Endpoint (Observed Case): By Duration of Exposure OFC Adult Controlled Database

		Baseline	WEEK 2	WEEK 4	WEEK 8	WEEK 12
OFC	n	704	698	651	538	176
Change from Baseline	Mean	82.78	1.74	2.87	4.29	4.76
	std	22.31	2.00	2.65	3.50	4.27
t-test*	p-val		<.001	<.001	<.001	<.001
FLX	n	431	427	398	329	43
Change from Baseline	Mean	85.30	-0.22	-0.33	-0.24	-0.16
	std	24.11	1.63	2.65	2.55	2.85
t-test*	p-val		0.005	0.014	0.090	0.714
OLZ	n	778	774	696	535	41
Change from Baseline	Mean	82.94	1.94	3.06	4.11	4.07
	std	21.20	2.20	2.87	3.83	3.86
t-test*	p-val		<.001	<.001	<.001	<.001
PLA	n	403	400	353	196	
Change from Baseline	Mean	81.87	0.02	-0.03	-0.54	
	std	21.35	1.76	2.19	3.20	
t-test*	p-val		0.788	0.771	0.020	
Treatment Comparisons**						
Therapy	p-val		<.001	<.001	<.001	<.001
OFC vs. FLX	p-val		<.001	<.001	<.001	<.001
OFC vs. OLZ	p-val		<.001	0.001	0.313	0.324
OFC vs. PLA	p-val		<.001	<.001	<.001	

OFC = olanzapine + fluoxetine combination, FLX = fluoxetine, OLZ = olanzapine, PLA = placebo.

n = number of patients having measurements at both baseline and the week shown.

Imputed values: HCKB, HDAO, HGFZ, HGGG, HGGY, HGHZ, HGIE.

*Within group p-values are from a t-test on the mean change.

**p-value is from Type III Sums of Squares from the ANOVA model; change = protocol therapy.

Program Location: RMP.H6PSREG2.SASPGM (OCWGTUC1)

Sponsor Table 4.25 from the 10/04/07 submission reports that 22% of OFC-treated patients gained at least 7% of their baseline weight, with a median exposure of 6 weeks. This was statistically significantly greater than in placebo-treated patients (1.8%). Approximately three percent of OFC-treated patients gained at least 15% of their baseline weight, with a median exposure of 8 weeks. This was statistically significantly greater than in placebo-treated patients (0%). Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories.

Table 4.25. Weight Treatment-Emergent Significant Changes: All Patients OFC Adult Controlled Database

Categories	Therapy	Mean Modal Dose (mg)	Exposure to PCS (min,Q1,Q2,Q3,max)	Total Exposure (min,Q1,Q2,Q3,max)	PCS Flag	n	%	P-values	
								Overall	(OFC vs)
PCS Weight Gain (7%)	OFC	8.5/39.0	(6,29,42,54,100)	(11,55,59,84,100) (1,43,56,63,112)	742 Yes No	164 578	22.1 77.9	<.001	
	FLX	42.1	(34,34,35,59, 59)	(55,55,56,59, 59) (3,49,56,60,115)	441 Yes No	3 438	0.7 99.3		
	OLZ	9.6	(6,22,33,45,112)	(13,54,56,58,112) (1,28,55,57, 91)	841 Yes No	173 668	20.6 79.4	.461	
	PLA	0.0	(15,20,21,28, 57)	(20,21,56,57, 58) (2,27,42,56,112)	445 Yes No	8 437	1.8 98.2		
PCS Weight Gain (15%)	OFC	8.5/39.0	(34,50,56,69, 86)	(41,57,79,84, 95) (1,48,56,67,112)	742 Yes No	21 721	2.8 97.2	<.001	
	FLX	42.1		(3,50,56,60,115)	441 Yes No	0 441	0.0 100.0		
	OLZ	9.6	(21,34,45,50, 57)	(44,56,56,57, 62) (1,31,55,57,112)	841 Yes No	17 824	2.0 98.0	.326	
PCS Weight Gain (15%)	PLA	0.0		(2,27,42,56,112)	445 Yes No	0 445	0.0 100.0	<.001	

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
OFC = olanzapine + fluoxetine combination, FLX = fluoxetine, OLZ = olanzapine, PLA = placebo.
Frequencies analyzed using Fisher's exact test.
N = number of patients with baseline and at least one post-baseline weight.
n = number of patients having both baseline and post-baseline measures and meeting PCS flag criteria.
Total Exposure is number of days from randomization until last available weight.
Exposure to PCS is number of days from randomization until PCS weight change.
Included studies: HCKE, HDAO, HGFE, HGGA, HGGY, HGHZ, HGIE.

In this database, 2.5% of OFC-treated subjects and 1.9% of olanzapine-treated subjects discontinued due to weight gain-related adverse events, compared to no fluoxetine-treated subjects or placebo-treated subjects.

II.2.2. Weight Gain: Olanzapine Fluoxetine Combination Subjects (Adults): Placebo-Controlled Trials

The OFC Placebo-Controlled Adult Database contains data pooled from the two studies that contain both a placebo treatment group and an OFC treatment group (Studies HGGA and HGGY). OFC-treated subjects had a mean weight gain of 2.78 kg (median exposure time 56 days) compared to a mean weight loss of 0.29 kg in placebo-treated patients (median exposure time 43 days). The treatment-by-subgroup interaction was not significant.

The proportions of subjects with weight gain of at least 7% and at least 15% were statistically significantly higher for OFC-treated subjects compared with placebo-treated subjects in all baseline BMI subgroups. In this database, in which median exposure times did not exceed 6 weeks, no subjects in either treatment group experienced weight gain of at least 25%. Proportions of subjects with treatment-emergent clinically significant weight gain were highest for subjects in the normal baseline BMI category.

No subjects discontinued due to weight gain-related adverse effects in Studies HGGA and HGGY.

II.2.3. Weight Gain: Olanzapine Fluoxetine Combination Subjects (Adults): Long Term Controlled and Uncontrolled Data

Sponsor Table 2.3 from the 12/19/07 submission compares weight results for all OFC-treated subjects and OFC-treated subjects with at least 48 weeks of treatment exposure. In long-term olanzapine and fluoxetine in combination studies (at least 48 weeks), the mean weight gain was 6.7 kg (14.7 lb) (median exposure of 448 days, N=431).

**Table 2.3. Weight Data from the OFC Adult Integrated Database
All Patients and Patients with at Least 48 weeks of Exposure**

OFC ADULT Weight	All patients		With ≥48 weeks' exposure	
	N	estimate (95% CI)	N	estimate (95% CI)
LOCF mean change in weight (kg):				
—For all patients	2870	4.14 (3.9, 4.4)	431	6.70 (6.0, 7.5)
Median exposure; mean rate of change		115 d; 0.29 kg/wk		448 d; 0.11 kg/wk
—For pts underweight at BL	42	6.78 (4.8, 8.8)	10	9.91 (3.6, 16.2)
Median exposure; mean rate of change		121 d; 0.34 kg/wk		539 d (0.13 kg/wk)
—For pts with normal BMI at BL	784	4.81 (4.5, 5.2)	145	7.32 (6.2, 8.4)
Median exposure; mean rate of change		112 d; 0.34 kg/wk		434 d; 0.12 kg/wk
— For pts with overweight BMI at BL	874	4.13 (3.8, 4.5)	120	6.97 (5.7, 8.2)
Median exposure; mean rate of change		117 d; 0.30 kg/wk		448 d; 0.11 kg/wk
— For pts with obese BMI at BL	1159	3.60 (3.2, 4.0)	155	5.69 (4.2, 7.2)
Median exposure; mean rate of change		117 d; 0.24 kg/wk		450 d; 0.09 kg/wk
Patients with PCS weight gain:				
≥7% (%)	2870	40.4% (38.6, 42.2)	431	65.9% (61.2, 70.4)
Median exposure until PCS event		56 days		81 days
≥15% (%)	2870	12.4% (11.2, 13.6)	431	33.4% (29.0, 38.1)
Median exposure until PCS event		119 days		196 days
≥25% (%)	2870	2.7% (2.2, 3.4)	431	10.2% (7.5, 13.5)
Median exposure until PCS event		208 days		285 days
Upward shift in BMI category ^a	1700	39.2% (36.9, 41.6)	275	58.9% (52.8, 64.8)
Discontinuations due to weight gain-related adverse events	2929	4.1% (3.4, 4.9)	431	1.2% (0.4, 2.7)

Abbreviations: BL = baseline; BMI = body mass index; CI = confidence interval;

d = days; kg/wk = kilograms per week; LOCF = last observation carried forward; N = number of patients in analysis; PCS = potentially clinically significant; pts = patients.

^a N excludes patients who were obese at baseline and could not experience upward shift.

The percentages of patients with at least 48 weeks of treatment exposure who gained at least 7%, 15% or 25% of their baseline body weight with long-term exposure were 66%, 33%, 10%, respectively (Sponsor Table 5.12.2 from the 12/19/07 submission).

Table 5.12.2. Weight Treatment-Emergent Significant Changes from Baseline to Anytime OFC Adult Integrated Database: Patients with at Least 48 Weeks of Exposure

PCS Category	Therapy	Mean Modal Dose	Days of Exposure to PCS (Min,Q1,Q2,Q3,Max)	Total Days of Exposure (Min,Q1,Q2,Q3,Max)	PCS N Flag	n	95% Confidence Interval		
							%	Lower	Upper
PCS Weight Gain (7%)	OFC	8.4/49.6	(9,47,81,172,563)	(336,388,455,534,600) (336,364,421,529,669)	431 Yes No	284 147	65.9	61.2	70.4
PCS Weight Gain (15%)	OFC	8.4/49.6	(41,129,196,290,563)	(336,391,462,536,600) (336,371,445,532,669)	431 Yes No	144 287	33.4	29.0	38.1
PCS Weight Gain (25%)	OFC	8.4/49.6	(86,232,285,426,541)	(336,392,517,539,600) (336,376,448,532,669)	431 Yes No	44 387	10.2	7.5	13.5

OFC = olanzapine + fluoxetine combination, Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
N = Number of patients having both baseline and post-baseline measurements.
n = Number of patients having the indicated PCS flag.
Total days of exposure is the number of days of exposure to therapy.
Days of exposure to PCS is the number of days from the start of therapy until PCS weight gain.
Included studies: HGGG, HGIE, HGIP.

Sponsor Table 18 below contains categories of weight gain for patients from 10 trials who were included in the OFC adult integrated database. The proportion of patients with clinically significant weight gain increased with each successive time period.

Table 18. Categorical Weight Changes from Baseline to Various Timepoints Observed Case Analysis OFC Adult Overall Integrated Database

OFC Overall Integrated Database

Therapy	Weight Change (kg)	Time Point (OC)							
		6 wks		6 mos		12 mos		24 mos	
		N	%	N	%	N	%	N	%
OFC	wt chng <=0	292	17.1	157	17.0	65	14.3	0	0.0
	0< wt chng <=5	986	57.7	347	37.6	146	32.1	1	100.0
	5< wt chng <=10	393	23.0	280	30.4	124	27.3	0	0.0
	10< wt chng <=15	36	2.1	98	10.6	78	17.1	0	0.0
	15< wt chng <=20	3	0.2	31	3.4	25	5.5	0	0.0
	20< wt chng <=25	0	0.0	8	0.9	15	3.3	0	0.0
	25< wt chng <=30	0	0.0	0	0.0	1	0.2	0	0.0
	30< wt chng <=35	0	0.0	1	0.1	0	0.0	0	0.0
	35< wt chng <=40	0	0.0	0	0.0	1	0.2	0	0.0
	40< wt chng	0	0.0	0	0.0	0	0.0	0	0.0
	Total for Time Point (n)	1710	100.0	922	100.0	455	100.0	1	100.0

OFC = olanzapine + fluoxetine combination.
N = Number of patients having measurements at both baseline and the time point shown.
Timepoint Windows: 6 weeks = days 35 to 48; 6 months = 6 months +/- 2 weeks; 12 months = 12 months +/- 1 month; 24 months = 24 months +/- 2 months; 36 months = 36 months +/- 3 months.
Included studies: HCKB, HDAO, HDAQ, HGFR, HGGG, HGGY, HGHZ, HGIE, HGIP, HGMA.

II. 3. Weight Gain: Olanzapine Adolescent Subjects

Sponsor Table 4.11 below reports the LOCF mean weight change from baseline to endpoint for all subjects in the Olanzapine Adolescent Placebo-Controlled Database (subject ages 13-17 years). Mean weight increase was 4.6 kg (10.1 lb) in 3 weeks' median exposure time in olanzapine-treated adolescent subjects compared to 0.34 kg (0.7 lb) in 3 weeks' median exposure time in placebo-treated subjects (P<0.001).

**Table 4.11. Weight
Mean Change from Baseline to Endpoint (LOCF): All Patients
Olanzapine Adolescent Placebo-Controlled Database**

Therapy	Mean Modal Dose	Days of Exposure (Min,Q1,Q2,Q3,Max)	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value	Rate of Weight Gain (kg per Week)	
				Mean	Std	Mean	Std				Mean	Std
OLZ	11.2	Trt: (4,21,22,42,338) Wgt: (4,21,22,42,338)	197	66.32	18.14	4.61	4.48	5.72	4.66	<.001	1.07	0.85
PLA	0.0	Trt: (2,20,22,42,382) Wgt: (2,20,22,42,382)	112	67.98	17.19	0.34	2.78	1.06			0.06	0.59

OLZ = olanzapine, PLA = placebo, Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = Number of patients having both baseline and post-baseline measurements.

Exposure: Trt: total days of exposure to therapy.

Wgt: total days of exposure from start of therapy to last available weight.

Included studies: HGGF, HGIN, HGIU, HGKL.

* P-values are from Type III Sum of Squares from the ANOVA model: Weight_Change = Protocol Therapy.
Least Square mean differences are from the same ANOVA model.

Although no clinical trials designed to compare adolescents to adults were conducted, the data from adolescent trials were compared to those of adult trials. Mean increase in weight in adolescents (4.6 kg over 3 weeks' median exposure time) was greater than in adults (2.6 kg over 7 weeks' median exposure time). Mean weight gain was statistically significantly greater in olanzapine-treated adolescent subjects compared to placebo-treated subjects in all baseline BMI categories. The largest absolute mean weight gains were in patients who were overweight or obese at baseline. The treatment-by-subgroup interaction was significant.

The incidence of treatment-emergent weight gain of at least 7% (Sponsor Table 4.16 of the 10/04/2007 submission below) was 40.6% for adolescents (median exposure about 3.5 weeks) versus 9.8% of placebo-treated adolescent subjects (median exposure about 14 weeks); when compared to adult placebo-controlled categorical analysis, adolescents had a higher incidence of clinically significant weight gain of at least 7% in a shorter period of treatment exposure (22.2% incidence in about 8 weeks of median exposure). Mean modal doses of olanzapine were comparable in the adolescent (11.2 mg/day) versus adult (10.9 mg/day) placebo-controlled analyses. Compared to 6.8% of placebo-treated adolescent subjects, 19.2% of olanzapine-treated adolescent subjects shifted to a higher BMI category. 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 2.7% of placebo-treated patients, with a median exposure of 19 weeks.

Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories, but mean changes in weight were greater in adolescents with BMI categories above normal at baseline.

Table 4.16. Weight Treatment-Emergent Significant Changes: All Patients Olanzapine Adolescent Placebo-Controlled Database

PCS Category	Therapy	Mean Modal Dose	Days of Exposure to PCS (Min,Q1,Q2,Q3,Max)	Total Days of Exposure (Min,Q1,Q2,Q3,Max)	N	PCS Flag	n	%	*P-value
PCS Weight Gain (7%)	OLZ	11.2	(11,21,27,42,338)	(11,21,31,43,338) (4,20,21,34,336)	197	Yes	80	40.6	<.001
						No	117	59.4	
	PLA	0.0	(14,28,56,225,382)	(21,41,97,335,382) (2,19,21,40,339)	112	Yes	11	9.8	
						No	101	90.2	
PCS Weight Gain (15%)	OLZ	11.2	(19,41,132,308,338)	(19,41,132,330,338) (4,20,22,42,336)	197	Yes	14	7.1	.123
						No	183	92.9	
	PLA	0.0	(21,21,56,382,382)	(21,21,335,382,382) (2,20,22,42,339)	112	Yes	3	2.7	
						No	109	97.3	
PCS Weight Gain (25%)	OLZ	11.2	(139,265,303,330,338)	(265,277,329,330,338) (4,20,22,42,337)	197	Yes	5	2.5	.163
						No	192	97.5	
	PLA	0.0		(2,20,22,42,382)	112	Yes	0	0.0	
						No	112	100.0	

OLZ = olanzapine, PLA = placebo.
N = Number of patients having both baseline and post-baseline measurements.
n = Number of patients having the indicated PCS flag.
Total days of exposure is the number of days from the start of therapy until the last available weight.
Days of exposure to PCS is the number of days from the start of therapy until PCS weight gain.
Included studies: HGGF, HGIN, HGIU, HGKL.
* Frequencies analyzed using two-tailed Fisher's Exact Test.

Sponsor Table 13 below reports an observed case analysis of the distribution of patients in several categories of weight gain at the end points of 6 weeks, 6 months, and 12 months. The frequency of weight gain greater than 10 kg (22 lb) was 21/336 (6%) at 6 weeks, 89/191(47%) at 6 months, and 5/8 (63%) at 12 months.

Table 13. Categorical Weight Changes from Baseline to Various Timepoints Observed Case Analysis Olanzapine Adolescent Overall Integrated Database

		Time Point (OC)					
Therapy	Weight Change (kg)	6 wks		6 mos		12 mos	
		N	%	N	%	N	%
OLZ	wt chng <=0	8	2.4	4	2.1	0	0.0
	0< wt chng <=5	162	48.2	47	24.6	1	12.5
	5< wt chng <=10	145	43.2	51	26.7	2	25.0
	10< wt chng <=15	16	4.8	42	22.0	2	25.0
	15< wt chng <=20	3	0.9	24	12.6	1	12.5
	20< wt chng <=25	2	0.6	18	9.4	1	12.5
	25< wt chng <=30	0	0.0	4	2.1	1	12.5
	30< wt chng <=35	0	0.0	0	0.0	0	0.0
	35< wt chng <=40	0	0.0	0	0.0	0	0.0
	40< wt chng	0	0.0	1	0.5	0	0.0
Total for Time Point (n)		336	100.0	191	100.0	8	100.0

OLZ = olanzapine.
N = Number of patients having measurements at both baseline and the time point shown.
Timepoint Windows: 6 weeks = days 35 to 48; 6 months = 6 months +/- 2 weeks; 12 months = 12 months +/- 1 month; 24 months = 24 months +/- 2 months; 36 months = 36 months +/- 3 months.
Included studies: HGGF, HGIN, HGIU, HGKL, HGMF, LOAY.

In long-term studies (at least 24 weeks), the mean weight gain was 11.2 kg (24.6 lb) (median exposure of 201 days, N=179) (Sponsor Table 5.7.7 in 12/19/07 submission).

**Table 5.7.7. Weight
Mean Change from Baseline to Endpoint (LOCF) Overall
Olanzapine Adolescent Integrated Database: Patients with at Least 24 Weeks of Exposure**

Therapy	Mean Modal Dose	Days of Exposure (Min, Q1, Q2, Q3, Max)	N	Baseline		Change to Endpoint		95% Confidence Interval		Rate of Weight Gain (kg per Week)	
				Mean	Std	Mean	Std	Lower	Upper	Mean	Std
OLZ	12.2	Trt: (168,182,202,224,338) Wgt: (112,182,201,222,338)	179	65.98	17.73	11.24	7.70	10.10	12.37	0.39	0.28

OLZ = olanzapine, Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
N = Number of patients having both baseline and post-baseline measurements.
Exposure: Trt: total days of exposure to therapy.
Wgt: total days of exposure from start of therapy to last available weight.
Included studies: HGGF, HGIN, HGIU, LOAY.

The percentages of adolescents who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 89%, 55%, and 29%, respectively (Sponsor Table 5.7.2 from the 12/19/07 submission).

**Table 5.7.2. Weight
Treatment-Emergent Significant Changes from Baseline to Anytime
Olanzapine Adolescent Integrated Database: Patients with at Least 24 Weeks of Exposure**

PCS Category	Therapy	Mean Modal Dose	Days of Exposure to PCS (Min, Q1, Q2, Q3, Max)	Total Days of Exposure (Min, Q1, Q2, Q3, Max)	PCS N	Flag	n	95% Confidence Interval		
								%	Lower	Upper
PCS Weight Gain (7%)	OLZ	12.2	(4,21,31,70,197)	(168,182,201,222,338) (173,193,210,225,336)	179	Yes No	160 19	89.4	83.9	93.5
PCS Weight Gain (15%)	OLZ	12.2	(21,63,104,138,265)	(168,182,203,224,338) (168,183,196,221,336)	179	Yes No	99 80	55.3	47.7	62.7
PCS Weight Gain (25%)	OLZ	12.2	(41,111,139,175,247)	(168,182,203,222,338) (168,183,197,224,337)	179	Yes No	52 127	29.1	22.5	36.3

OLZ = olanzapine, Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
N = Number of patients having both baseline and post-baseline measurements.
n = Number of patients having the indicated PCS flag.
Total days of exposure is the number of days of exposure to therapy.
Days of exposure to PCS is the number of days from the start of therapy until PCS weight gain.
Included studies: HGGF, HGIN, HGIU, LOAY.

Among adolescent patients, mean weight gain by baseline BMI category was 11.5 kg (25.3 lb), 12.1 kg (26.6 lb), and 12.7 kg (27.9 lb), respectively, for normal (N=106), overweight (N=26) and obese (N=17) (Sponsor Table 5.7.8 from the 12/19/07 submission).

Table 5.7.8. Weight Mean Change from Baseline to Endpoint (LOCF): By Baseline Body Mass Index Status Olanzapine Adolescent Integrated Database: Patients with at Least 24 Weeks of Exposure

Therapy	Mean Modal Dose	Days of Exposure (Min,Q1,Q2,Q3,Max)	N	Baseline		Change to Endpoint		95% Confidence Interval		Rate of Weight Gain (kg per Week)	
				Mean	Std	Mean	Std	Lower	Upper	Mean	Std
BMI Category: Underweight											
OLZ	11.3	Trt: (168,182,202,217,239) Wgt: (168,182,202,217,239)	29	48.95	6.46	8.78	5.10	6.85	10.72	0.31	0.17
BMI Category: Normal Weight											
OLZ	12.4	Trt: (168,182,197,224,336) Wgt: (168,182,197,224,336)	106	61.84	9.13	11.49	7.91	9.97	13.01	0.40	0.29
BMI Category: Overweight											
OLZ	12.9	Trt: (168,191,201,234,338) Wgt: (112,189,197,221,338)	26	77.85	10.13	12.12	8.90	8.52	15.72	0.43	0.33
BMI Category: Obese											
OLZ	11.8	Trt: (169,183,203,220,320) Wgt: (169,183,203,220,320)	17	103.43	18.75	12.65	8.02	8.53	16.78	0.45	0.31

OLZ = olanzapine, Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
N = Number of patients having both baseline and post-baseline measurements.
Exposure: Trt: total days of exposure to therapy.
Wgt: total days of exposure from start of therapy to last available weight.
Underweight: 0 <= BMI < 18.5, Normal weight: 18.5 <= BMI < 25, Overweight: 25 <= BMI < 30, Obese: BMI >= 30.
Included studies: HGGF, HGIN, HGIU, LOAY.

Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to zero placebo-treated patients.

II.4. Weight Gain: Antipsychotic-Naïve Subjects

Sponsor Table 2.2.5 compares selected weight results from adult olanzapine antipsychotic-naïve databases versus comparable databases for overall populations (naïve and non-naïve combined). There were several statistically significant differences between olanzapine- and placebo-treated antipsychotic-naïve patients. Olanzapine-treated antipsychotic-naïve adults had mean increases in weight across all baseline BMI categories, as did olanzapine-treated adults overall. Mean increases in weight for patients with normal, overweight, and obese BMI were higher for antipsychotic-naïve patients than for olanzapine treated patients overall. In the subset of patients with at least 24 weeks of exposure, mean increases and proportions with potentially clinically significant increases in weight were generally greater for the antipsychotic-naïve population than for the adult population (except for mean change in the subset of patients who were underweight at baseline); proportions of subjects with upward shifts in BMI category were almost identical in the 2 databases.

Table 2.2.5. Comparison of Selected Weight Results: Adult Olanzapine Antipsychotic-Naïve Databases versus Comparable Databases for Overall Populations (Naïve and Non-Naïve Combined)

Weight (kg) ^a	Placebo-Controlled Databases				Haloperidol-Controlled Databases				Overall Integrated Databases			
	AP-naïve Adults		Adults		AP-naïve Adults		Adults		All Exposures		≥24 Wks Exposure	
	Olz	Pla	Olz	Pla	Olz	Hal	Olz	Hal	AP-nv	All	AP-nv	All
Mean change for all patients	2.90	-0.13	2.64	-0.26	6.60	3.99	3.45	0.39	4.02	3.15	6.25	4.81
N	344	239	1983	1278	71	58	2604	1461	902	12020	143	4280
—with underweight BMI at BL	2.04	1.11	3.26	0.54	8.71	5.85	4.23	1.69	3.12	4.15	3.70	6.24
N	26	11	51	34	3	3	97	58	37	329	13	118
—with normal BMI at BL	2.93	-0.07	2.90	-0.06	6.84	2.61	4.07	1.02	3.95	3.78	6.78	5.89
N	168	114	705	474	46	33	1158	626	355	4046	67	1564
—with overweight BMI at BL	3.19	-0.59	2.71	-0.21	6.74	7.33	3.36	-0.31	4.10	3.07	6.31	4.52
N	91	64	563	377	18	13	758	397	261	3313	47	1273
—with obese BMI at BL	2.72	0.28	2.25	-0.35	1.64	2.64	1.91	-0.76	4.19	2.30	5.89	2.90
N	58	45	518	350	4	7	461	266	248	2795	16	851
PCS weight gain:												
≥7%	29.7%	3.8%	22.2%	3.0%	57.7%	31.0%	35.2%	12.8%	31.6%	32.5%	63.6%	55.4%
≥15%	2.3%	0.4%	4.2%	0.3%	31.0%	17.2%	11.8%	4.0%	6.3%	10.5%	25.9%	24.1%
≥25%	0.3%	0.0%	0.8%	0.0%	12.7%	5.2%	3.6%	0.9%	1.6%	3.1%	9.8%	8.0%
N for all 3	344	239	1983	1278	71	58	2604	1461	902	12020	143	4280
Upward shift in BMI categ.	21.8%	7.4%	23.4%	8.9%	38.8%	24.5%	30.0%	14.1%	29.9%	31.2%	46.5%	46.1%
N ^b	285	189	1318	885	67	49	2013	1081	653	7698	127	2955
Discont. due to weight gain-related AEs	0.8%	0.0%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	1.8%	0.5%	0.0%	0.3%
N ^b	354	249	2056	1345	73	58	2701	154	927	12425	143	4303

Abbreviations: AE = adverse event; AP = antipsychotic; AP-nv = antipsychotic-naïve; BL = baseline; BMI = body mass index; categ. = category; Discont. = discontinued; Hal = haloperidol; N = number of patients in analysis; Olz = olanzapine; PCS = potentially clinically significant; Pla = placebo; wks = weeks.

^a Shaded cells indicate a statistically significant comparison at $p < .05$. There were no statistical comparisons made between databases.

^b Treatment groups in the Olz Adult Placebo-Controlled Database were not compared statistically. N is patients not in highest category at baseline.

Sources: Placebo-controlled—Outputs LOWGTQ11/21, FQWGTQ11/31/51; and Data Package 1 Tables 6.1, 6.8, 6.10, and 6.12; Haloperidol-controlled—

II.5. Weight Gain: Reviewer Comment

II.5.1. Weight Gain: Summary

An extensive body of published literature describes short-term and long-term significant weight gain as a common adverse event with use of olanzapine. Table 2 summarizes the mean weight gain with olanzapine reported in published studies reviewed.

Table 2. Mean Weight Gain with Olanzapine Use in Published Studies

Study	Study Type	Follow-up Time	Mean Δ Weight (kg)	Wt gain (kg)/month	>6 month
Kinon	RCT retro	#30 months	6.26 kg	0.2	x
Lieberman	RCT	9.2 months	0.9 kg/month	0.9	x
Stroup	RCT	6.3 months	0.6 kg/month	0.6	x
McEvoy	RCT	2.7 months	0.5 kg/month	0.5	
Mortimer	RCT	5.5 months	3.9 kg	0.7	
McGlashan	RCT	#12 months	8.79 kg	0.7	x
Breier	RCT	#6.5 months	3.06 kg	0.5	x
Kinon	RCT	#5.6 months	2.53 kg	0.5	
Tran	RCT	#6.5 months	4.1 kg	0.6	x
McQuade	RCT	#26 weeks	4.23 kg	0.7	x
Simpson	Pros Obs	# 6 months	4.97 kg	0.8	x
Lieberman	RCT	# 7 weeks	7.3 kg	4.9 *	
Atmaca	RCT	# 6 weeks	4.41 kg	6.4	
Allison	Meta-analysis	#10 weeks	4.15 kg	1.8	

RCT retro = Retrospective, secondary analysis of randomized control trial data

RCT=Randomized Control Trial

Pros. Obser.=Prospective Observational Trial

Indicates that length of study follow-up is listed instead of exposure time, if exposure time was not reported.

* Study population consisted of subjects with first episode of psychosis

x Indicates studies with follow-up times >6 months.

Adults treated with olanzapine or OFC and adolescents treated with olanzapine experienced clinically significant mean weight gain analyses of clinical trial databases. Magnitude of weight gain and the proportions of patients who experienced potentially clinically significant weight gain both increased with longer-term exposures. Although no formal statistical comparisons across databases were made, changes in weight appeared to be more pronounced for adolescents than for adults.

II.5.2. Weight Gain: Proposed and Recommended Prescribing Information

II.5.2.1. Olanzapine Weight Labeling: Sponsor Proposal

On May 14, 2008, the sponsor submitted the following proposed labeling language regarding olanzapine and weight in the Warnings and Precautions section:

III. Hyperlipidemia

III.1. Hyperlipidemia: Olanzapine Adult Subjects

III.1.1. Hyperlipidemia: Olanzapine Adult Subjects in Placebo-Controlled Trials

In Last Observation Carried Forward (LOCF) analyses of mean change from baseline to endpoint in lipid-related laboratory analytes reported in Sponsor Table 5.1 (10/04/07 submission), statistically significantly greater mean increases were observed for olanzapine compared to placebo for fasting and non-fasting total cholesterol, fasting LDL cholesterol, and fasting triglycerides. Olanzapine-treated subjects had median exposure times between 6-8 weeks at the time of lipid measurements. In the analysis of fasting triglycerides, olanzapine-treated subjects had a mean increase of 20.77 mg/dL (median exposure 8 weeks) compared with a mean decrease of 10.74 mg/dl in placebo-treated subjects (median exposure 4 weeks) ($P < 0.01$).

**Table 5.1. Lipids-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): All Patients
Olanzapine Adult Placebo-Controlled Database**

Lab Test: Fasting Total Cholesterol (mg/dL)

Therapy	N	Mean Modal Dose (mg)	Exposure (days) (Min, Q1, Q2, Q3, Max)	P-values					
				Baseline		Change to Endpoint			
				Mean	Std	Mean	Std	*With-in Treatment	**Between Treatment
OLZ	744	11.3	Lab: (1, 21, 55, 81, 107) Trt: (1, 22, 56, 83, 112)	193.28	42.85	5.27	30.77	<.001	<.001
PLA	402	0.0	Lab: (1, 21, 28, 80, 102) Trt: (1, 21, 49, 84, 136)	196.40	43.02	-6.07	27.62	<.001	

OLZ = olanzapine, PLA = placebo

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = number of patients having both baseline and post-baseline measurements.

Studies: HBED, HGJZ, HGKK, HGKL, HGKQ

*P-value for one sample t-test.

**P-value is from Type III Sums of Squares from ANOVA model: change = protocol therapy.

**Table 5.1. Lipids-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): All Patients
Olanzapine Adult Placebo-Controlled Database (Continued)**

Lab Test: Non-Fasting Total Cholesterol (mg/dL)

Therapy	N	Mean Modal Dose (mg)	Exposure (days) (Min, Q1, Q2, Q3, Max)	P-values					
				Baseline		Change to Endpoint		-----	
				Mean	Std	Mean	Std	*With-in Treatment	**Between Treatment
OLZ	1082	10.8	Lab: (1,22,41,57,964) Trt: (1,22,42,58,964)	197.44	44.45	6.75	32.81	<.001	<.001
PLA	768	0.0	Lab: (2,21,30,56,604) Trt: (2,21,35,56,604)	200.16	44.54	-4.51	31.61	<.001	

OLZ = olanzapine, PLA = placebo

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = number of patients having both baseline and post-baseline measurements.

Studies: HBED, HGAD, HGAP, HGBH, HGEH, HGGA, HGGF, HGGW, HGGY, HGJZ, HGKK, HGKL, HGKQ

*P-value for one sample t-test.

**P-value is from Type III Sums of Squares from ANOVA model; change = protocol therapy.

**Table 5.1. Lipids-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): All Patients
Olanzapine Adult Placebo-Controlled Database (Continued)**

Lab Test: Fasting LDL (mg/dL)

Therapy	N	Mean Modal Dose (mg)	Exposure (days) (Min, Q1, Q2, Q3, Max)	P-values					
				Baseline		Change to Endpoint		-----	
				Mean	Std	Mean	Std	*With-in Treatment	**Between Treatment
OLZ	535	11.1	Lab: (1,35,56,84,107) Trt: (1,56,56,84,112)	115.36	35.48	3.03	27.74	.012	.001
PLA	304	0.0	Lab: (1,27,55,84,102) Trt: (1,27,57,84,136)	118.75	35.75	-4.26	24.73	.003	

OLZ = olanzapine, PLA = placebo

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = number of patients having both baseline and post-baseline measurements.

Studies: HBED, HGJZ, HGKK, HGKL

*P-value for one sample t-test.

**P-value is from Type III Sums of Squares from ANOVA model; change = protocol therapy.

**Table 5.1. Lipids-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): All Patients
Olanzapine Adult Placebo-Controlled Database (Continued)**

Lab Test: Fasting HDL(mg/dL)

Therapy	N	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	P-values					
				Baseline		Change to Endpoint		*With-in Treatment	**Between Treatment
				Mean	Std	Mean	Std		
OLZ	545	11.0	Lab: (1,32,56,84,107) Trt: (1,56,57,84,112)	48.22	13.83	-0.40	9.35	.320	.742
PLA	306	0.0	Lab: (1,27,55,84,102) Trt: (1,27,57,84,136)	49.06	12.68	-0.21	9.69	.708	

OLZ = olanzapine, PLA = placebo
Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
N = number of patients having both baseline and post-baseline measurements.

Studies: HBED, HGJZ, HGKK, HGKL

*P-value for one sample t-test.

**P-value is from Type III Sums of Squares from ANOVA model: change = protocol therapy.

**Table 5.1. Lipids-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): All Patients
Olanzapine Adult Placebo-Controlled Database (Continued)**

Lab Test: Fasting Triglycerides(mg/dL)

Therapy	N	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	P-values					
				Baseline		Change to Endpoint		*With-in Treatment	**Between Treatment
				Mean	Std	Mean	Std		
OLZ	744	11.3	Lab: (1,21,55,81,107) Trt: (1,22,56,83,112)	138.78	99.98	20.77	91.65	<.001	<.001
PLA	402	0.0	Lab: (1,21,28,80,102) Trt: (1,21,49,84,136)	138.69	88.72	-10.74	70.69	.002	

OLZ = olanzapine, PLA = placebo
Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
N = number of patients having both baseline and post-baseline measurements.

Studies: HBED, HGJZ, HGKK, HGKL, HGKQ

*P-value for one sample t-test.

**P-value is from Type III Sums of Squares from ANOVA model: change = protocol therapy.

Mean increases in fasting lipid measurements (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline (Sponsor Table 5.3 below). The sponsor defined lipid dysregulation at baseline as patients diagnosed with dyslipidemia or related adverse events, patients treated with lipid lowering agents, or patients with diagnosed high baseline lipid levels. Although the sponsor does not specify what proportion of subjects in each subgroup with lipid dysregulation at baseline are treated with lipid lowering drugs, use of lipid lowering drugs may be a large factor in the lesser mean increases in fasting lipid measurements in patients with lipid dysregulation at baseline.

**Table 5.3. Lipids-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): By Baseline Dyslipidemia Status
Olanzapine Adult Placebo-Controlled Database**

Lab Test: Fasting Total Cholesterol (mg/dL)

Potentially Dyslipidemic at baseline	Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	P-values						
				Baseline			Change to Endpoint		-----	
				N	Mean	Std	Mean	Std	*With-in Treatment	**Between Treatment
No	OLZ	10.1	Lab: (4,21,49,83,103) Trt: (4,21,56,84,112)	380	178.04	30.33	8.62	25.32	<.001	<.001
	PLA	0.0	Lab: (1,21,28,82,102) Trt: (1,21,50,84,136)	208	175.18	28.70	-2.42	24.05	.149	
Yes	OLZ	12.5	Lab: (1,22,56,57,107) Trt: (1,23,56,78,107)	364	209.18	47.98	1.77	35.28	.340	<.001
	PLA	0.0	Lab: (1,21,28,73,99) Trt: (1,21,49,83,99)	194	219.16	44.22	-9.98	30.59	<.001	

OLZ = olanzapine, PLA = placebo

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = number of patients having both baseline and post-baseline measurements.

Studies: HBBD, HGJZ, HGKK, HGKL, HGKQ

*P-value for one sample t-test.

**P-value is from Type III Sums of Squares from ANOVA model; change = protocol therapy.

**Table 5.3. Lipids-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): By Baseline Dyslipidemia Status
Olanzapine Adult Placebo-Controlled Database**

Lab Test: Fasting LDL (mg/dL)

Potentially Dyslipidemic at baseline	Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	P-values						
				Baseline			Change to Endpoint		-----	
				N	Mean	Std	Mean	Std	*With-in Treatment	**Between Treatment
No	OLZ	9.2	Lab: (4,55,58,84,103) Trt: (4,56,81,84,112)	249	102.50	25.79	5.70	23.01	<.001	.002
	PLA	0.0	Lab: (1,27,56,84,102) Trt: (1,37,77,84,136)	151	102.32	23.66	-2.76	18.26	.065	
Yes	OLZ	12.8	Lab: (1,29,56,81,107) Trt: (1,42,56,83,107)	286	126.56	38.85	0.71	31.14	.698	.060
	PLA	0.0	Lab: (1,27,52,82,99) Trt: (1,27,56,84,99)	153	134.96	38.24	-5.73	29.76	.018	

OLZ = olanzapine, PLA = placebo

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = number of patients having both baseline and post-baseline measurements.

Studies: HBBD, HGJZ, HGKK, HGKL

*P-value for one sample t-test.

**P-value is from Type III Sums of Squares from ANOVA model; change = protocol therapy.

**Table 5.3. Lipids-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): By Baseline Dyslipidemia Status
Olanzapine Adult Placebo-Controlled Database**

Lab Test: Fasting Triglycerides (mg/dL)										
Potentially Dyslipidemic at baseline	Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)							P-values
				Baseline			Change to Endpoint			
				N	Mean	Std	Mean	Std	*With-in Treatment	**Between Treatment
No	OLZ	10.1	Lab: (4,21,49,83,103) Trt: (4,21,56,84,112)	380	93.65	37.93	23.16	53.30	<.001	<.001
	PLA	0.0	Lab: (1,21,28,82,102) Trt: (1,21,50,84,136)	208	94.75	36.27	2.24	39.01	.409	
Yes	OLZ	12.5	Lab: (1,22,56,57,107) Trt: (1,23,56,78,107)	364	185.89	120.84	18.27	119.22	.004	<.001
	PLA	0.0	Lab: (1,21,28,73,99) Trt: (1,21,49,83,99)	194	185.80	103.11	-24.64	91.52	<.001	

OLZ = olanzapine, PLA = placebo
Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
N = number of patients having both baseline and post-baseline measurements.

Studies: HBED, HGJZ, HGKK, HGKL, HGKQ

*P-value for one sample t-test.

**P-value is from Type III Sums of Squares from ANOVA model: change = protocol therapy.

In long-term studies (at least 48 weeks), patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.6 mg/dL, 2.5 mg/dL, and 18.7 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 0.16 mg/dL. (Sponsor Table 6.4.1. from the 12/19/07 submission.)

**Table 6.4.1. Lipid-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF) Overall
Olanzapine Adult Integrated Database: Patients with at Least 48 Weeks of Exposure**

Lab Test: FASTING TOTAL CHOLESTEROL (mg/dL)									
Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	N	Baseline		Change to Endpoint		Mean Change 95% CI	
				Mean	Std	Mean	Std	Lower	Upper
OLZ	15.1	Lab: (42,405,567,724,909) Trt: (337,475,637,764,937)	489	198.24	46.63	5.57	38.06	2.19	8.95

OLZ = olanzapine
Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
N = Number of patient with both a normal baseline and at least one post-baseline measurement

Included studies: HGEC, HGJZ, HGKA, HGKB.

Lab Test: FASTING LDL(mg/dL)

Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	N	Baseline		Change to Endpoint		Mean Change 95% CI	
				Mean	Std	Mean	Std	Lower	Upper
OLZ	15.1	Lab: (42,405,567,724,909) Trt: (337,476,637,765,937)	483	122.83	39.77	2.50	32.74	-0.43	5.43

OLZ = Olanzapine

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = Number of patient with both a normal baseline and at least one post-baseline measurement

Included studies: HGJZ, HGKA, HGKB.

Lab Test: FASTING TRIGLYCERIDES(mg/dL)

Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	N	Baseline		Change to Endpoint		Mean Change 95% CI	
				Mean	Std	Mean	Std	Lower	Upper
OLZ	15.1	Lab: (42,405,567,724,909) Trt: (337,476,637,765,937)	487	153.82	96.21	18.71	111.71	8.76	28.66

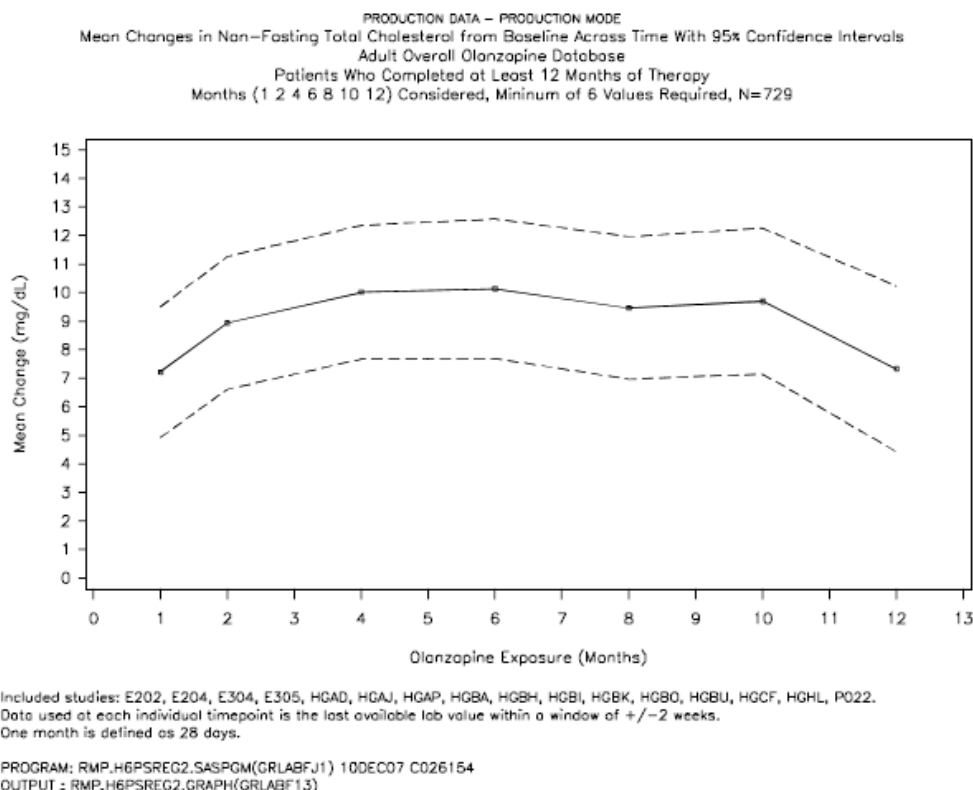
OLZ = Olanzapine

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = Number of patient with both a normal baseline and at least one post-baseline measurement

Included studies: HGJZ, HGKA, HGKB.

Sponsor Figure 2.1 (page 80 of the 12/19/07 submission) below displays mean changes in nonfasting total cholesterol from baseline for patients who completed at least 12 months of olanzapine treatment and who had measurements at a minimum of 6 of the assessed 8 time points (Months 1, 2, 4, 6, 8, 10, and 12). The range of increase in nonfasting cholesterol at various time points was between 4 and 12 mg/dL. Based on this figure, the sponsor includes a statement in the 05/14/08 proposed labeling as follows: "In an analysis of patients who completed 12 months of therapy, the mean nonfasting total cholesterol did not increase further after approximately 4-6 months."



Mean changes in nonfasting total cholesterol from baseline across time for patients from the Olanzapine Adult Integrated database who completed at least 12 months of olanzapine treatment.

The sponsor performed categorical analyses of the proportions of subjects with treatment-emergent significant changes in lipids at any time based on National Cholesterol Education Program (NCEP) criteria. The adult criteria for treatment-emergent significant changes in fasting lipids are shown in Sponsor Table 2.6 below. The adult criteria for treatment-emergent significant changes in nonfasting lipids are shown in Sponsor Table 2.8 below.

Table 2.6. Fasting Lipids: Adults
Criteria for Treatment-Emergent Significant Changes

Analyte and Category	Baseline	Postbaseline
Total cholesterol		
Normal to high	<200 mg/dL	≥240 mg/dL
Borderline to high	≥200 and <240 mg/dL	≥240 mg/dL
Normal/borderline to high	<240 mg/dL	≥240 mg/dL
Normal to borderline/high	<200 mg/dL	≥200 mg/dL
Large increase	minimum of all BL values	≥40 mg/dL over BL
LDL cholesterol		
Normal to high	<100 mg/dL	≥160 mg/dL
Borderline to high	≥100 and <160 mg/dL	≥160 mg/dL
Normal/borderline to high	<160 mg/dL	≥160 mg/dL
Normal to borderline/high	<100 mg/dL	≥100 mg/dL
Large increase	minimum of all BL values	≥30 mg/dL over BL

HDL cholesterol		
Normal to low	≥40 mg/dL	<40 mg/dL
Large decrease	maximum of all BL values	≥20 mg/dL decrease from BL
Triglycerides		
Normal to high	<150 mg/dL	≥200 mg/dL
Normal to very high	<150 mg/dL	≥500 mg/dL
Borderline to high	≥150 and <200 mg/dL	≥200 mg/dL
Borderline to very high	≥150 and <200 mg/dL	≥500 mg/dL
Normal/borderline to high	<200 mg/dL	≥200 mg/dL
Normal/borderline to very high	<200 mg/dL	≥500 mg/dL
Normal to borderline/high/very high	<150 mg/dL	≥150 mg/dL
Large increase	minimum of all BL values	≥50 mg/dL over BL

Note: Categories are based on NCEP ATP III guidelines (NCEP 2002).

Abbreviations: BL = baseline; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NCEP = National Cholesterol Education Program.

Table 2.8. Nonfasting Lipids: Adults
Criteria for Treatment-Emergent Significant Changes

Treatment-Emergent Significant Changes in Nonfasting Lipids		
Analyte and Category	Baseline	Postbaseline
Total cholesterol		
Normal to high	<200 mg/dL	≥240 mg/dL
Borderline to high	≥200 and <240 mg/dL	≥240 mg/dL
Normal /borderline to high	<240 mg/dL	≥240 mg/dL
Normal to borderline/high	<200 mg/dL	≥200 mg/dL
LDL cholesterol		
Normal to high	<130 mg/dL	≥160 mg/dL
Borderline to high	≥130 and <160 mg/dL	≥160 mg/dL
Normal /borderline to high	<160 mg/dL	≥160 mg/dL
Normal to borderline/high	<130 mg/dL	≥130 mg/dL
HDL cholesterol		
Normal to low	≥50 mg/dL	<40 mg/dL
Borderline to low	≥40 and < 50 mg/dL	<40 mg/dL
Normal /borderline to low	≥40 mg/dL	<40 mg/dL
Normal to borderline/low	≥50 mg/dL	<50 mg/dL
Triglycerides		
Normal to high	<150 mg/dL	≥500 mg/dL
Borderline to high	≥150 and <500 mg/dL	≥500 mg/dL
Normal /borderline to high	<500 mg/dL	≥500 mg/dL
Normal to borderline/high	<150 mg/dL	≥150 mg/dL
Normal/borderline/high/very high to extremely high	<1000 mg/dL	≥1000 mg/dL

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Statistically significantly higher proportions of olanzapine-treated patients than placebo-treated patients met criteria indicating treatment-emergent significant increases in lipid analytes in 4 of

4 change categories for non-fasting total cholesterol; 4 of 5 for fasting total cholesterol; 5 of 10 for fasting triglycerides; and in 2 of 5 for fasting LDL cholesterol. Proportions of patients with clinically significant changes in total cholesterol, LDL cholesterol or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low was greater in long-term studies (at least 48 weeks) as compared with short-term studies. Categorical changes in fasting lipid values from olanzapine adult monotherapy studies are summarized in Sponsor (b) (4) (5/14/08 submission) below.

(b) (4) Changes in Fasting Lipids Values from Adult Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure		At least 48 weeks exposure	
			N	Patients	N	Patients
Fasting Triglycerides	Increase by ≥ 50 mg/dL	Olanzapine	745	39.6% ^a	487	61.4%
		Placebo	402	26.1%	NA ^b	NA ^b
	Normal to High (<150 mg/dL to ≥ 200 mg/dL)	Olanzapine	457	9.2% ^a	293	32.4%
		Placebo	251	4.4%	NA ^b	NA ^b
	Borderline to High (≥ 150 mg/dL and <200 mg/dL to ≥ 200 mg/dL)	Olanzapine	135	39.3% ^a	75	70.7%
		Placebo	65	20.0%	NA ^b	NA ^b
Fasting Total Cholesterol	Increase by ≥ 40 mg/dL	Olanzapine	745	21.6% ^a	489	32.9%
		Placebo	402	9.5%	NA ^b	NA ^b
	Normal to High (<200 mg/dL to ≥ 240 mg/dL)	Olanzapine	392	2.8%	283	14.8%
		Placebo	207	2.4%	NA ^b	NA ^b
	Borderline to High (≥ 200 mg/dL and <240 mg/dL to ≥ 240 mg/dL)	Olanzapine	222	23.0% ^a	125	55.2%
		Placebo	112	12.5%	NA ^b	NA ^b
Fasting LDL Cholesterol	Increase by ≥ 30 mg/dL	Olanzapine	536	23.7% ^a	483	39.8%
		Placebo	304	14.1%	NA ^b	NA ^b
	Normal to High (<100 mg/dL to ≥ 160 mg/dL)	Olanzapine	154	0%	123	7.3%
		Placebo	82	1.2%	NA ^b	NA ^b
	Borderline to High (≥ 100 mg/dL and <160 mg/dL to ≥ 160 mg/dL)	Olanzapine	302	10.6%	284	31.0%
		Placebo	173	8.1%	NA ^b	NA ^b

(b) (4) Not Applicable.

III.1.2. Hyperlipidemia: Olanzapine Adult Subjects in Comparator-Controlled Trials

III.1.2.1. Hyperlipidemia: Olanzapine Adult Subjects in Lilly Comparator-Controlled Trials

Sponsor Table 1.4 presents analyses of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides across the 4 databases that compare olanzapine to other atypical antipsychotics.

Risperidone

In the risperidone-controlled database, patients treated with olanzapine had greater mean increases in total cholesterol than did patients treated with risperidone. For example, mean changes in nonfasting total cholesterol among patients in the risperidone-controlled database with normal cholesterol at baseline (<200 mg/dL) showed changes of 17.74 mg/dL for patients treated with olanzapine compared to 4.68 for risperidone ($p<0.001$). Similarly, the proportions of patients going from normal total cholesterol at baseline to high post-baseline (from <200 mg/dL to ≥ 240 mg/dL) were statistically significantly greater for patients treated with olanzapine compared to risperidone.

Clozapine

In the Lilly clozapine-controlled database, patients treated with clozapine and olanzapine appeared to be roughly comparable with respect to changes in total cholesterol. Mean changes in nonfasting total cholesterol among patients with normal nonfasting cholesterol at baseline (<200 mg/dL) were 11.34 mg/dL for patients treated with olanzapine versus 9.24 mg/dL for clozapine (NS); mean changes overall were 2.14 mg/dL for olanzapine versus 3.11 mg/dL for clozapine. The proportions of patients going from normal total cholesterol at baseline to high post-baseline (from <200 mg/dL to ≥ 240 mg/dL) were 8.5% for clozapine versus 4.5% for olanzapine (NS).

Quetiapine

The quetiapine-controlled database included 2 head-to-head studies, HGLR and HGJB. Patients included in HGLR had all been previously treated with olanzapine for at least 15 days at study entry, and were required to be overweight or obese at study entry. The study population in HGJB was not selected based on previous olanzapine exposure and baseline BMI.

There were no statistically significant differences between patients treated with olanzapine compared to quetiapine in mean change in nonfasting or fasting total cholesterol, LDL cholesterol, HDL cholesterol, or triglycerides, nor in categorical changes for nonfasting or fasting total cholesterol, LDL cholesterol, or HDL cholesterol, or fasting triglycerides. In many of these analyses, the median exposure time in olanzapine-treated subjects was significantly greater than the median exposure time for quetiapine-treated subjects.

Ziprasidone

In analyses of fasting measurements from the ziprasidone-controlled database, olanzapine-treated patients experienced decreased HDL cholesterol (decrease of 2.55 mg/dL for olanzapine versus increase of 0.43 mg/dL for ziprasidone; ($P < 0.001$)). Olanzapine-treated patients had a mean fasting LDL decrease of 0.84 mg/dL for olanzapine versus decrease of 10.20 mg/dL for ziprasidone ($P < 0.001$). Mean fasting triglycerides increased in olanzapine-treated patients while they decreased in ziprasidone-treated patients (+21.66 mg/dL for olanzapine versus -21.04 for ziprasidone, $P < 0.001$). Higher proportions of olanzapine-treated than ziprasidone-treated patients had treatment-emergent significant changes in fasting lipids values, with several comparisons statistically significantly different.

Table 1.4. Summary of Lipids Results from Lilly Atypical Antipsychotic–Controlled Databases

Total Cholesterol

Total Cholesterol	olanzapine	clozapine	olanzapine	quetiapine	olanzapine	risperidone	olanzapine	ziprasidone
Mean change to endpoint fasting total chol. (mg/dL)	na	na	-4.96	1.16	na	na	-0.04	-13.56a
N	na	na	78	72	na	na	365	316
Median exposure	na	na	168 days	88 days	na	na	168 days	140 days
—Among pts <200 at BL (mg/dL)	na	na	10.12	6.58	na	na	9.90	-3.26 a
N	na	na	26	33	na	na	200	188
Median exposure	na	na	167 days	91 days	na	na	170 days	166 days
Norm→Hi fasting total chol (<200 to ≥240)	na	na	0%	6.1%	na	na	7.5%	3.2%
N	na	na	26	33	na	na	200	188
Median exposure	na	na	7 days	7 days	na	na	42 days	24 days
Bord→Hi fasting total chol (≥200&<240 to ≥240)	na	na	25.0%	11.8%	na	na	34.6%	20.0%b
N	na	na	32	17	na	na	107	75
Median exposure	na	na	7 days	7 days	na	na	53 days	29 days
≥40 mg/dL increase fasting total cholesterol	na	na	24.4%	22.2%	na	na	21.4%	8.2% a
N	na	na	78	72	na	na	365	316
Median exposure	na	na	7 days	8 days	na	na	42 days	28 days
Mean change nonfasting total cholesterol (mg/dL)	2.14	3.11	4.72	-0.45	8.18	-0.67 a	1.97	-8.12
N	214	212	115	127	528	504	20	19
Median exposure	125 days	124 days	121 days	80 days	89 days	76 days	57 days	49 days
—Among patients <200 at BL (mg/dL)	11.34	9.24	8.35	6.87	17.74	4.68 a	6.82	0.76
N	94	112	62	63	274	269	11	9
Median exposure	124 days	119 days	84 days	69 days	59 days	57 days	57 days	49 days
Norm→Hi nonfasting total chol (<200 to ≥240)	8.5%	4.5%	6.5%	4.8%	9.9%	4.1% b	0	0
N	94	112	62	63	274	269	11	9
Median exposure	8 days	8 days	56 days	56 days	18 days	14 days	57 days	49 days
Bord→Hi nonfasting total chol (≥200&<240 to ≥240)	35.3%	49.2%	25.0%	25.0%	31.3%	30.5%	33.3%	0
N	68	63	40	44	163	131	3	6
Median exposure	11 days	10 days	56 days	56 days	20 days	19 days	57 days	24 days

Table 1.4. Summary of Lipids Results from Lilly Atypical Antipsychotic–Controlled Databases (continued)
LDL Cholesterol

LDL Cholesterol	olanzapine	clozapine	olanzapine	quetiapine	olanzapine	risperidone	olanzapine	ziprasidone
Mean change in fasting LDL cholesterol (mg/dL)	na	na	-2.54	-1.03	na	na	-0.84	-10.20a
N	na	na	77	70	na	na	337	295
Median exposure	na	na	168 days	88 days	na	na	168 days	140 days
—Among patients <100 at BL	na	na	13.62	5.29	na	na	10.38	4.74
N	na	na	14	21	na	na	104	99
Median exposure	na	na	174 days	58 days	na	na	172 days	161 days
Norm→Hi fasting LDL (<100 to >160)	na	na	0%	0%	na	na	1.9%	1.0%
N	na	na	14	21	na	na	104	99
Median exposure	na	na	7 days	7 days	na	na	42 days	23 days
Bord→Hi fasting LDL chol (≥100&<160 to ≥160)	na	na	11.4%	15.2%	na	na	20.3%	11.0% b
N	na	na	44	33	na	na	192	155
Median exposure	na	na	7 days	7 days	na	na	42 days	29 days
≥30 mg/dL increase in fasting LDL (%)	na	na	27.3%	25.7%	na	na	24.3%	12.9% a
N	na	na	77	70	na	na	337	295
Median exposure	na	na	7 days	8 days	na	na	42 days	41 days
Mean change in nonfasting LDL chol. (mg/dL)	na	na	-0.01	-3.36	na	na	-5.64	-9.39
N	na	na	102	104	na	na	18	15
Median exposure	na	na	84 days	80 days	na	na	57 days	54 days
—Among patients <130 at BL	na	na	4.41	1.96	na	na	2.25	-4.41
N	na	na	69	67	na	na	12	9
Median exposure	na	na	84 days	59 days	na	na	57 days	49 days
Norm→Hi nonfasting LDL chol (<130 to >160)	na	na	2.9%	1.5%	na	na	0%	0%
N	na	na	69	67	na	na	12	9
Median exposure	na	na	56 days	56 days	na	na	57 days	49 days
Bord→Hi nonfasting LDL (≥130&<160 to ≥160)	na	na	19.0%	8.0%	na	na	50.0%	0%
N	na	na	21	25	na	na	2	5
Median exposure	na	na	57 days	56 days	na	na	167 days	55 days

Table 1.4. Summary of Lipids Results from Lilly Atypical Antipsychotic–Controlled Databases (continued)
HDL Cholesterol

HDL Cholesterol	olanzapine	clozapine	olanzapine	quetiapine	olanzapine	risperidone	olanzapine	ziprasidone
Mean change in fasting HDL chol. (mg/dL)	na	na	-0.78	-1.04	na	na	-2.55	0.43a
N	na	na	78	71	na	na	357	311
Median exposure	na	na	168 days	88 days	na	na	168 days	140 days
—Among patients ≥40 at BL	na	na	-1.91	-2.14	na	na	-4.37	-1.32 b
N	na	na	45	51	na	na	239	217
Median exposure	na	na	172 days	88 days	na	na	167 days	140 days
Norm→Lo fasting HDL chol (≥40 to <40)	na	na	28.9%	25.5%	na	na	30.1%	23.0%
N	na	na	45	51	na	na	239	217
Median exposure	na	na	7 days	8 days	na	na	42 days	41 days
≥20 mg/dL decrease in fasting HDL chol	na	na	6.4%	5.6%	na	na	9.0%	3.5% b
N	na	na	78	71	na	na	357	311
Median exposure	na	na	7 days	7 days	na	na	42 days	24 days
Mean change in nonfasting HDL chol. (mg/dL)	na	na	-0.10	0.01	na	na	-0.27	-1.89
N	na	na	110	123	na	na	20	19
Median exposure	na	na	135 days	80 days	na	na	57 days	49 days
—Among patients ≥50 at BL	na	na	-2.01	-2.20	na	na	-1.13	-8.01
N	na	na	37	41	na	na	8	6
Median exposure	na	na	165 days	84 days	na	na	116 days	24 days
Norm→Lo nonfasting HDL chol (≥50 to <40)	na	na	10.8%	12.2%	na	na	0%	0%
N	na	na	37	41	na	na	8	6
Median exposure	na	na	57 days	56 days	na	na	57 days	24 days
Bord→Lo nonfasting HDL chol (≥40&<50 to <40)	na	na	22.2%	25.0%	na	na	40.0%	57.1%
N	na	na	27	32	na	na	5	7
Median exposure	na	na	56 days	56 days	na	na	56 days	29 days

Table 1.4. Summary of Lipids Results, Atypical Antipsychotic–Controlled Databases: Triglycerides (continued)

Triglycerides	olanzapine	clozapine	olanzapine	quetiapine	olanzapine	risperidone	olanzapine	ziprasidone
Mean change in fasting triglycerides (mg/dL)	na	na	-12.89	19.09	na	na	21.66	-21.04a
N	na	na	78	72	na	na	365	316
Median exposure	na	na	168 days	88 days	na	na	168 days	140 days
—Among patients <150 at BL	na	na	8.19	35.89	na	na	32.97	7.13 a
N	na	na	27	34	na	na	231	193
Median exposure	na	na	167 days	57 days	na	na	180 days	147 days
Norm→Hi fasting TG (<150 to >200)	na	na	14.8%	17.6%	na	na	25.1%	10.9% a
N	na	na	27	34	na	na	231	193
Median exposure	na	na	7 days	8 days	na	na	42 days	23 days
Bord→Hi fasting TG (≥150&<200 to ≥200)	na	na	61.1%	45.5%	na	na	52.7%	38.5%
N	na	na	18	11	na	na	55	52
Median exposure	na	na	8 days	7 days	na	na	42 days	49 days
≥50 mg/dL increase in fasting triglycerides	na	na	55.1%	44.4%	na	na	49.0%	25.6% a
N	na	na	78	72	na	na	365	316
Median exposure	na	na	8 days	8 days	na	na	43 days	41 days
LOCF mean change in nonfasting TG (mg/dL)	na	na	25.27	35.76	35.52	-29.44 b	36.25	42.08
N	na	na	115	127	96	95	20	19
Median exposure	na	na	121 days	80 days	240 days	173 days	57 days	49 days
—Among patients <150 at BL	na	na	33.39	42.64	47.34	18.82	25.67	1.06
N	na	na	47	45	45	36	6	5
Median exposure	na	na	84 days	113 days	240 days	214 days	116 days	49 days
Norm→Hi nonfasting TG (<150 to >500) Norm→Bord/Hi nonfasting TG (<150 to ≥150)	na na	na na	0% 44.7%	0% 44.4%	0% 64.4%	0% 36.1% b	0% 16.7%	0% 20.0%
N	na	na	47	45	45	36	6	5
Median exposure	na	na	56 days	56 days	56 days	57 days	57 days	49 days
Bord→Hi nonfasting TG (≥150&<500 to ≥500)	na	na	6.2%	13.7%	12.2%	18.5%	7.1%	7.7%
N	na	na	65	73	49	54	14	13
Median exposure	na	na	56 days	56 days	56 days	56 days	57 days	29 days

Table 1.4. Summary of Lipids Results from Lilly Atypical Antipsychotic–Controlled Databases (concluded)

Abbreviations and Footnotes

Abbreviations: bord = borderline; chol = cholesterol; HDL = high-density lipoprotein; Hi = High; LDL = low-density lipoprotein; Lo = low; LOCF = last observation carried forward; N = number of patients in analysis; na = not available; Norm = normal; pts = patients; TG = triglycerides.

^a Statistically significantly different at $p < .001$.

^b Statistically significantly different at $p < .05$.

III.1.2.2. Hyperlipidemia: Olanzapine Adult Subjects in the CATIE Phase 1 Study

Phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)¹ is a National Institutes of Mental Health (NIMH)-sponsored, multicenter randomized controlled trial which compares second generation antipsychotics with perphenazine on endpoints related to safety and efficacy. Results related to mean modal dose, median time to discontinuation, exposure-adjusted mean changes in cholesterol and triglycerides, and the number and percentage of subjects who had cholestatin drugs added are listed in Table below.

Table. CATIE Phase 1 Study Results Related to Lipids

	Ziprasidone	Olanzapine	Risperidone	Quetiapine	Perphenazine	P
Mean Modal Dose (mg/day)	112.8	20.1	3.9	543.4	20.8	
Median Time To Discon. (months)	3.5	9.2	4.8	4.6	5.6	
Δ chol (mg/dL)	-8.2	9.4	-1.3	6.6	1.5	<0.001
Δ trig (mg/dL)	-16.5	40.5	-2.4	21.2	8.3	<0.001
Cholestatin drugs added no./total (%)	2/185 (1)	15/336 (4)	11/341 (3)	14/337 (4)	7/261 (3)	0.28

Patients who received olanzapine had an exposure-adjusted mean increase in total cholesterol of 9.4 mg/dL and an exposure-adjusted mean increase in triglycerides of 40.5 mg/dL. Patients were instructed to fast; non-fasting results were not excluded. No information was provided on the proportion of fasting versus non-fasting lipid measurements. Change from baseline in lipid values was determined as the difference between the baseline value and the average of the two highest post-baseline values. The exposure-adjusted mean is the least-squares mean from an analysis of covariance adjusting for whether the patient had an exacerbation in the preceding three months and for duration of exposure to study drug during phase 1. It is unclear whether this adjustment for exposure completely adjusts for differences in median time to discontinuation.

III.2. Hyperlipidemia: Olanzapine Fluoxetine Combination Subjects (Adults)

The OFC database consisted of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks. HDL and LDL cholesterol were not assessed in this database. Analyses of lipids-related analytes were limited to total cholesterol and triglycerides. Triglycerides were not available for any placebo-treated patients in this database, so comparisons for triglycerides are limited to OFC versus fluoxetine and olanzapine.

OFC-treated subjects had an increase from baseline in mean random total cholesterol of 12.1 mg/dL, which was statistically significant compared to an increase of 4.8 mg/dL for olanzapine-treated subjects and a decrease in mean random total cholesterol of 5.5 mg/dL for placebo-treated subjects. Sponsor (b) (4) (submitted 5/14/06) shows categorical changes in nonfasting lipid values in OFC trials.

¹ Lieberman JA, et al. N Engl J Med. 2005 Sep 22;353(12):1209-23.

(b) (4) **Changes in Nonfasting Lipids Values from Controlled Clinical Studies with Treatment Duration up to 12 Weeks**

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	Patients
Nonfasting Triglycerides	Increase by ≥ 50 mg/dL	OFC	174	67.8%
		Olanzapine	172	72.7%
	Normal to High (<150 mg/dL to ≥ 500 mg/dL)	OFC	57	0%
		Olanzapine	58	0%
	Borderline to High (≥ 150 mg/dL and <500 mg/dL to ≥ 500 mg/dL)	OFC	106	15.1%
		Olanzapine	103	8.7%
Nonfasting Total Cholesterol	Increase by ≥ 40 mg/dL	OFC	685	35% ^{a,b}
		Olanzapine	749	22.7%
		Placebo	390	9%
	Normal to High (<200 mg/dL to ≥ 240 mg/dL)	OFC	256	8.2% ^{a,b}
		Olanzapine	279	2.9%
		Placebo	175	1.7%
	Borderline to High (≥ 200 mg/dL and <240 mg/dL to ≥ 240 mg/dL)	OFC	213	36.2% ^{a,b}
		Olanzapine	261	27.6%
		Placebo	111	9.9%

(b) (4)

In long-term olanzapine and fluoxetine in combination studies (at least 48 weeks), changes in nonfasting total cholesterol from normal at baseline to high occurred at least once in 12% (N=150) and changes from borderline to high occurred in 56.6% (N=143) of subjects. The mean change in nonfasting total cholesterol was 11.3 mg/dL (N= 426).

The incidence of statistically significant changes in lipid parameters in patients treated with OFC and olanzapine in the OFC databases tended to be greater than the incidence of such changes in patients treated with olanzapine in the olanzapine databases. This difference may be due in part to the fact that the OFC and olanzapine databases are largely made up of different patient populations, making them difficult to compare. In particular, patients in the OFC database were less likely to have been previously treated with antipsychotics.

III.3. Hyperlipidemia: Olanzapine Adolescent Subjects

Placebo-controlled analyses of adolescent subjects were limited by short median durations of exposure at the time of lipid measurement, which ranged from 2-3 weeks. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescents, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine-treated adolescents had statistically significant increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 12.9 mg/dL, 6.5 mg/dL, and 28.4 mg/dL, respectively, compared to increases from baseline in mean fasting total cholesterol and LDL cholesterol of 1.3 mg/dL and 1.0 mg/dL, and a decrease in triglycerides of 1.1 mg/dL for placebo-treated adolescents. For fasting HDL cholesterol, no statistically significant

differences were observed between olanzapine-treated adolescents and placebo-treated adolescents (see Sponsor Table 5.10 from the 10/04/07 submission below).

**Table 5.10. Lipids-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): All Patients
Olanzapine Adolescent Placebo-Controlled Database**

Lab Test: Fasting Total Cholesterol (mg/dL)

Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	P-values						
			Baseline		Change to Endpoint				
			N	Mean	Std	Mean	Std	*With-in Treatment	**Between Treatment
OLZ	11.7	Lab: (5,21,22,41,57) Trt: (5,21,22,42,84)	138	161.60	32.65	12.87	22.45	<.001	.001
PLA	0.0	Lab: (4,19,21,34,88) Trt: (4,19,21,35,88)	66	163.59	35.74	1.30	25.66	.682	

OLZ = olanzapine, PLA = placebo

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = number of patients having both baseline and post-baseline measurements.

Studies: HGIN, HGIU, HGKL

*P-value for one sample t-test.

**P-value is from Type III Sums of Squares from ANOVA model; change = protocol therapy.

**Table 5.10. Lipids-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): All Patients
Olanzapine Adolescent Placebo-Controlled Database (Continued)**

Lab Test: Fasting LDL (mg/dL)

Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	P-values						
			Baseline		Change to Endpoint				
			N	Mean	Std	Mean	Std	*With-in Treatment	**Between Treatment
OLZ	11.7	Lab: (5,21,22,41,57) Trt: (5,21,22,42,84)	137	94.35	28.34	6.47	19.17	<.001	.084
PLA	0.0	Lab: (4,19,21,35,88) Trt: (4,19,21,40,88)	63	95.50	32.34	1.01	22.13	.719	

OLZ = olanzapine, PLA = placebo

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = number of patients having both baseline and post-baseline measurements.

Studies: HGIN, HGIU, HGKL

*P-value for one sample t-test.

**P-value is from Type III Sums of Squares from ANOVA model; change = protocol therapy.

Table 5.10. Lipids-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): All Patients
Olanzapine Adolescent Placebo-Controlled Database (Continued)

Lab Test: Fasting Triglycerides (mg/dL)

Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	N	Baseline		Change to Endpoint		P-values	
				-----		-----		*With-in Treatment	**Between Treatment
				Mean	Std	Mean	Std		
OLZ	11.7	Lab: (5,21,22,41,57) Trt: (5,21,22,42,84)	138	104.38	59.05	28.35	78.12	<.001	.006
PLA	0.0	Lab: (4,19,21,34,88) Trt: (4,19,21,35,88)	66	112.91	70.44	-1.07	48.99	.859	

OLZ = olanzapine, PLA = placebo

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = number of patients having both baseline and post-baseline measurements.

Studies: HGIN, HGIU, HGKL

*P-value for one sample t-test.

**P-value is from Type III Sums of Squares from ANOVA model: change = protocol therapy.

Program Location: RMP.H6PSREG2.SASPGM(LOLIPB4) 23JUL07

Output Location: RMP.H6PSREG2.OUTPUT (LOLIPB41)

Table 5.10. Lipids-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): All Patients
Olanzapine Adolescent Placebo-Controlled Database (Continued)

Lab Test: Fasting LDL (mg/dL)

Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	N	Baseline		Change to Endpoint		P-values	
				-----		-----		*With-in Treatment	**Between Treatment
				Mean	Std	Mean	Std		
OLZ	11.7	Lab: (5,21,22,41,57) Trt: (5,21,22,42,84)	137	94.35	28.34	6.47	19.17	<.001	.084
PLA	0.0	Lab: (4,19,21,35,88) Trt: (4,19,21,40,88)	63	95.50	32.34	1.01	22.13	.719	

OLZ = olanzapine, PLA = placebo

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = number of patients having both baseline and post-baseline measurements.

Studies: HGIN, HGIU, HGKL

*P-value for one sample t-test.

**P-value is from Type III Sums of Squares from ANOVA model: change = protocol therapy.

For most lipid analytes, subjects with normal baseline lipid values had greater mean lipid changes compared to those with borderline or high lipid values at baseline. Subjects with borderline fasting and non-fasting triglyceride levels at baseline had greater mean lipid changes than subjects with normal or high triglyceride levels at baseline.

In studies of adolescents with at least 24 weeks of treatment exposure, there were increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.5 mg/dL, 5.4 mg/dL, and 20.5 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 4.5 mg/dL. Table 4 shows categorical changes in fasting lipid values in adolescents (Sponsor Table 6.7.1 from the 12/19/07 submission below.)

**Table 6.7.1. Lipid-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF) Overall
Olanzapine Adolescent Integrated Database: Patients with at Least 24 Weeks of Exposure**

Patient with at Least 24 Week Exposure

Lab Test: FASTING TOTAL CHOLESTEROL(mg/dL)

Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	N	Baseline		Change to Endpoint		Mean Change 95% CI	
				Mean	Std	Mean	Std	Lower	Upper
OLZ	12.2	Lab: (21,184,202,218,268) Trt: (169,189,203,224,333)	122	160.42	32.85	5.49	23.69	1.24	9.73

OLZ = Olanzapine

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = Number of patient with both a normal baseline and at least one post-baseline measurement

Included studies: HGIN, HGIU

**Table 6.7.1. Lipid-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF) Overall
Olanzapine Adolescent Integrated Database: Patients with at Least 24 Weeks of Exposure
(Continued)**

Patient with at Least 24 Week Exposure

Lab Test: FASTING LDL(mg/dL)

Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	N	Baseline		Change to Endpoint		Mean Change 95% CI	
				Mean	Std	Mean	Std	Lower	Upper
OLZ	12.2	Lab: (21,184,202,218,268) Trt: (169,189,203,222,333)	121	93.00	28.81	5.41	21.45	1.54	9.27

OLZ = Olanzapine

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = Number of patient with both a normal baseline and at least one post-baseline measurement

Included studies: HGIN, HGIU

Table 6.7.1. Lipid-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF) Overall
Olanzapine Adolescent Integrated Database: Patients with at Least 24 Weeks of Exposure
(Continued)

Patient with at Least 24 Week Exposure

Lab Test: FASTING HDL (mg/dL)

Therapy	Mean Modal Dose (mg)	Exposure (days) (Min, Q1, Q2, Q3, Max)	N	Baseline		Change to Endpoint		Mean Change 95% CI	
				Mean	Std	Mean	Std	Lower	Upper
OLZ	12.2	Lab: (21, 184, 202, 218, 268) Trt: (169, 189, 203, 224, 333)	122	47.64	12.46	-4.52	8.06	-5.97	-3.08

OLZ = olanzapine

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = Number of patient with both a normal baseline and at least one post-baseline measurement

Included studies: HGIN, HGIU

Table 6.7.1. Lipid-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF) Overall
Olanzapine Adolescent Integrated Database: Patients with at Least 24 Weeks of Exposure
(Continued)

Patient with at Least 24 Week Exposure

Lab Test: FASTING TRIGLYCERIDES (mg/dL)

Therapy	Mean Modal Dose (mg)	Exposure (days) (Min, Q1, Q2, Q3, Max)	N	Baseline		Change to Endpoint		Mean Change 95% CI	
				Mean	Std	Mean	Std	Lower	Upper
OLZ	12.2	Lab: (21, 184, 202, 218, 268) Trt: (169, 189, 203, 224, 333)	122	101.56	63.35	20.49	70.26	7.90	33.09

OLZ = olanzapine

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

N = Number of patient with both a normal baseline and at least one post-baseline measurement

Included studies: HGIN, HGIU

Sponsor (b) (4) (05/14/08 submission) summarizes categorical changes in fasting lipid values from adolescent monotherapy studies. In a median treatment exposure of 3 weeks, 14.5% of olanzapine-treated subjects had an increase in fasting total cholesterol ≥ 40 mg/dL compared to 4.5% of placebo-treated subjects ($P=0.036$); 17.5% of olanzapine subjects had a mean increase in fasting LDL cholesterol ≥ 30 mg/dL, compared with 11.1% of placebo-treated subjects ($P=0.297$); 37.0% of olanzapine-treated subjects had a ≥ 50 mg/dL increase in fasting triglycerides, compared with 15.2% of placebo-treated subjects ($P=0.02$). The proportion of subject meeting significant change criteria increased for all evaluations (except change from borderline to high fasting LDL cholesterol) when duration of treatment exposure was at least 24 weeks.

(b) (4)

Changes in Fasting Lipids Values from Adolescent Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 6 weeks exposure		At least 24 weeks exposure	
			N	Patients	N	Patients
Fasting Triglycerides	Increase by ≥ 50 mg/dL	Olanzapine	138	37.0% ^a	122	45.9%
		Placebo	66	15.2%	NA ^b	NA ^b
	Normal to High (<90 mg/dL to >130 mg/dL)	Olanzapine	67	26.9%	66	36.4%
		Placebo	28	10.7%	NA ^b	NA ^b
	Borderline to High (≥ 90 mg/dL and ≤ 130 mg/dL to >130 mg/dL)	Olanzapine	37	59.5%	31	64.5%
		Placebo	17	35.3%	NA ^b	NA ^b
Fasting Total Cholesterol	Increase by ≥ 40 mg/dL	Olanzapine	138	14.5% ^a	122	14.8%
		Placebo	66	4.5%	NA ^b	NA ^b
	Normal to High (<170 mg/dL to ≥ 200 mg/dL)	Olanzapine	87	6.9%	78	7.7%
		Placebo	43	2.3%	NA ^b	NA ^b
	Borderline to High (≥ 170 mg/dL and <200 mg/dL to ≥ 240 mg/dL)	Olanzapine	36	38.9% ^a	33	57.6%
		Placebo	13	7.7%	NA ^b	NA ^b
Fasting LDL Cholesterol	Increase by ≥ 30 mg/dL	Olanzapine	137	17.5%	121	22.3%
		Placebo	63	11.1%	NA ^b	NA ^b
	Normal to High (<110 mg/dL to ≥ 130 mg/dL)	Olanzapine	98	5.1%	92	10.9%
		Placebo	44	4.5%	NA ^b	NA ^b
	Borderline to High (≥ 110 mg/dL and <130 mg/dL to ≥ 130 mg/dL)	Olanzapine	29	48.3% ^a	21	47.6%
		Placebo	9	0%	NA ^b	NA ^b

(b) (4)

Not Applicable.

Table 5.15 from the 10/04/07 submission (see next page) reports that over a treatment duration of 1 week 3.5% of olanzapine-treated subjects with non-fasting triglyceride levels < 500 mg/dL at baseline had nonfasting triglyceride levels ≥ 500 mg/dL post-treatment, compared to 0% of placebo-treated subjects with baseline non-fasting triglyceride levels <500 mg/dL. One subject had a baseline non-fasting triglyceride level of 154 mg/dL and had a post-baseline level of 1238 mg/dL.

**Table 5.15. Lipids-Related Laboratory Analytes
Treatment-Emergent Clinically Significant Changes (NCEP Guidelines): All Patients
Olanzapine Adolescent Placebo-Controlled Database (Concluded)**

Lab Test: Non-Fasting Triglycerides (mg/dL)

Categories	Therapy	Mean Modal Dose (mg)	Exposure(days) (Min,Q1,Q2,Q3,Max)	-----Treatment-Emergent Change-----							
				-Baseline-		Baseline	Post-Baseline		Mean	Change	%
				N	Mean	n	Mean	Mean			
<500 to >=500	OLZ	12.0	Lab: (4,7,7,8,84) Trt: (4,21,22,41,84)	144	133.96	5	231.95	674.78	442.82	3.5%	.172
	PLA	0.0	Lab: (6,7,7,7,42) Trt: (10,18,21,28,49)	72	127.29	0				0.0%	
<1000 to >=1000	OLZ	12.0	Lab: (4,7,7,8,27) Trt: (4,21,22,41,84)	144	133.96	1	154.16	1238.6	1084.5	0.7%	1.00
	PLA	0.0	Lab: (6,7,7,7,42) Trt: (10,18,21,28,49)	72	127.29	0				0.0%	

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
N = Number of patients with both a baseline and at least one post-baseline measurement
n = Anytime Treatment-Emergent Significant change

Studies: HGIN, HGIU, HGKL

* Frequencies are analyzed using Fisher's exact test

Program Location: RMP.H6PSREG2.SASPGM(FQLIPB4) 07AUG07
Output Location: RMP.H6PSREG2.OUTPUT(FQLIPB41)

III.4. Hyperlipidemia: Antipsychotic-Naïve Subjects

Sponsor Table 2.3.5. (05/08/08 submission) summarizes results for olanzapine-treated antipsychotic-naïve adults versus olanzapine-treated overall populations (naïve and non-naïve.) Olanzapine-treated antipsychotic-naïve adults had mean increases in fasting and nonfasting cholesterol, fasting LDL cholesterol, and fasting and non-fasting triglycerides, all of which were statistically significantly different from decreases observed in placebo-treated antipsychotic-naïve adults. Olanzapine-treated antipsychotic-naïve adults also had statistically significantly higher incidence of increases in fasting total cholesterol of ≥ 40 mg/dL, increases in fasting LDL of ≥ 30 mg/dL, and increases in fasting and nonfasting triglycerides of ≥ 50 mg/dL than did placebo-treated patients and numerically higher incidence of shifts from normal to high or borderline to high for most analyses of total cholesterol, LDL cholesterol, and triglycerides. There were no statistically significant differences between olanzapine and placebo on any of the HDL cholesterol analyses presented by the sponsor. Changes in non-fasting triglycerides were larger in the antipsychotic-naïve subset of patients compared to olanzapine-treated subjects overall.

Table 2.3.5. Comparison of Selected Lipids Results: Adult Olanzapine Antipsychotic-Naïve Databases versus Comparable Databases for Overall Populations (Naïve and Non-Naïve)
Total Cholesterol

	Placebo-Controlled Databases				Haloperidol-Controlled Databases				Overall Integrated Databases			
	AP-naïve		Olz Adult: All		AP-naïve		Olz Adult: All		All Exposures		≥24 Wks Exposure	
	Olz	Pla	Olz	Pla	Olz	Hal	Olz	Hal	AP-nv	All	AP-nv	All
Total Cholesterol^a												
Mean change F chol	4.05	-6.37	5.27	-6.07	na	na	np	np	3.22	3.50	-0.95	2.06
N	206	129	744	402					327	2825	53	1031
Norm→Hi F chol	0.8%	0.0%	2.8%	2.4%	na	na	np	np	0.5%	6.3%	0.0%	10.2%
N	120	76	392	207					197	1581	29	570
Bord→Hi F chol	19.7%	9.4%	23.0%	12.5%	na	na	np	np	28.4%	34.2%	47.1%	42.0%
N	61	32	222	112					88	777	17	293
≥40 mg/dL increase F chol	16.5%	3.1%	21.6%	9.5%	na	na	np	np	16.8%	22.0%	22.6%	25.9%
N	206	129	745	402					327	2826	53	1031
Mean change NF chol	7.71	-2.33	6.75	-4.51	14.44	9.73	6.22	-1.64	4.32	5.33	20.88	6.28
N	90	80	1082	768	67	56	2111	1235	544	7602	50	2953
Norm→Hi NF chol	1.7%	0%	5.2%	1.9%	9.5%	2.8%	8.5%	3.9%	4.2%	8.6%	18.2%	14.3%
N	58	48	521	364	42	36	1018	649	236	3883	33	1465
Bord→Hi NF chol	21.1%	9.1%	31.8%	13.2%	44.4%	36.4%	40.1%	21.0%	29.1%	37.6%	42.9%	49.1%
N	19	22	324	235	18	11	653	352	175	2299	14	931
≥40 mg/dL increase NF chol	8.9%	5%	28.7%	12.6%	47.8%	28.6%	36.0%	21.9%	25.9%	30.9%	48.0%	42.0%
N	90	80	1082	768	67	56	2111	1235	544	7602	50	2953

Abbreviations: AP = antipsychotic; AP-nv = antipsychotic-naïve; Bord = borderline; chol = cholesterol; F = fasting; Hal = haloperidol; Hi = high; N = number of patients in analysis; na = not available; NF = nonfasting; Norm = normal; np = not provided because not needed for comparison; Olz = olanzapine; Pla = placebo.

^a Shaded cells indicate a statistically significant comparison at $p < .05$. There were no statistical comparisons made between databases. Cut-off values for fasting and nonfasting cholesterol: Normal = <200 mg/dL; Borderline = ≥ 200 & <240 mg/dL; High = ≥ 240 mg/dL.

**Table 2.3.5. Comparison of Selected Lipids Results: Adult Olanzapine Antipsychotic-Naïve Databases versus Comparable Databases for Overall Populations (Naïve and Non-Naïve)
LDL Cholesterol (Continued)**

	Placebo-Controlled Databases				Overall Integrated Databases			
	AP-naïve		Olz Adult: All		All Exposures		>24 Wks Exposure	
	Olz	Pla	Olz	Pla	AP-naïve	All	AP-naïve	All
LDL Cholesterol^a								
Mean change in F LDL	0.55	-4.58	3.03	-4.26	0.93	1.58	-2.50	0.49
N	198	127	535	304	295	2397	53	1011
Norm→Hi F LDL	0%	0%	0%	1.2%	0%	2.1%	0%	4.0%
N	71	36	154	82	108	727	14	273
Bord→Hi F LDL	9.3%	4.1%	10.6%	8.1%	10.1%	19.6%	15.2%	25.8%
N	107	73	302	173	158	1314	33	586
≥30 mg/dL increase in F LDL (%)	19.2%	7.1%	23.7%	14.1%	19.3%	25.8%	24.5%	32.0%
N	198	127	536	304	295	2398	53	1011
Mean change in NF LDL	3.28	-1.50	3.69	2.02	1.56	1.39	8.69	3.42
N	77	71	133	90	129	772	15	353
Norm→Hi NF LDL	3.3%	4.2%	2.1%	3.0%	2.0%	5.6%	10.0%	6.9%
N	61	48	95	66	98	514	10	231
Bord→Hi NF LDL	16.7%	5.9%	23.1%	17.4%	15.8%	26.1%	0.0%	27.6%
N	12	17	26	23	19	157	4	76
≥30 mg/dL increase NF LDL (%)	13.0%	9.9%	15.0%	15.3%	12.4%	21.1%	20.0%	24.4%
N	77	71	133	90	129	772	15	353

Abbreviations: AP = antipsychotic; bord = borderline; F = fasting; Hi = High; LDL = low-density lipoprotein; N = number of patients in analysis; NF = nonfasting; Norm = normal; Olz = olanzapine; Pla = placebo; pts = patients.

^aShaded cells indicate a statistically significant comparison at p<.05. There were no statistical comparisons made between databases. Cut-off values for Fasting LDL: Normal = <100 mg/dL; Borderline = ≥100&<160 mg/dL; High = ≥160 mg/dL. Cut-off values for Nonfasting LDL: Normal = <130 mg/dL; Borderline = ≥130&<160 mg/dL; High = ≥160 mg/dL.

**Table 2.3.5. Comparison of Selected Lipids Results: Adult Olanzapine Antipsychotic-Naïve Databases versus Comparable Databases for Overall Populations (Naïve and Non-Naïve)
HDL Cholesterol (Continued)**

HDL Cholesterol ^a	Placebo-Controlled Databases				Overall Integrated Databases			
	AP-naïve		Olz Adult: All		All Exposures		>24 Wks Exposure	
	Olz	Pla	Olz	Pla	AP-naïve	All	AP-naïve	All
Mean change in F HDL (mg/dL)	0.27	-1.07	-0.40	-0.21	0.03	-1.33	-0.84	-1.17
N	206	129	545	306	305	2446	53	1016
Norm→Lo F HDL	11.8%	9.4%	14.5%	12.0%	15.7%	28.3%	19.4%	37.2%
N	152	96	344	208	229	1554	36	629
≥20 mg/dL decrease in F HDL	2.4%	6.2%	3.7%	5.2%	2.6%	5.7%	0%	7.6%
N	206	129	546	306	305	2447	53	1016
Mean change in NF HDL (mg/dL)	-0.93	1.35	-0.16	-0.40	-1.54	-0.59	1.73	-0.67
N	81	73	137	100	133	792	15	353
Norm→Lo NF HDL	10.3%	0%	6.1%	2.0%	5.3%	10.3%	25.0%	15.0%
N	29	34	49	50	57	253	4	107
Bord→Lo NF HDL	15.4%	20.0%	19.0%	23.1%	24.5%	35.0%	25.0%	40.4%
N	26	20	42	26	37	226	4	94
≥20 mg/dL decrease in NF HDL	3.7%	2.7%	2.2%	5.0%	4.5%	3.5%	1%	4.8%
N	81	73	137	100	133	792	15	353

Abbreviations: AP = antipsychotic; bord = borderline; F = fasting; HDL = high-density lipoprotein; Lo = low; N = number of patients in analysis; NF = nonfasting; Norm = normal; Olz = olanzapine; Pla = placebo; pts = patients.

^aShaded cells indicate a statistically significant comparison at p<.05. There were no statistical comparisons made between databases. Cut-off values for Fasting HDL: Normal = ≥40 mg/dL; Low = <40 mg/dL ("Borderline" not assessed for fasting HDL). Cut-off values for Nonfasting HDL: Normal = ≥50 mg/dL; Borderline = ≥40&<50 mg/dL; Low = <40 mg/dL.

Table 2.3.5. Comparison of Selected Lipids Results: Adult Olanzapine Antipsychotic-Naïve Databases versus Comparable Databases for Overall Populations (Naïve and Non-Naïve) Triglycerides (Concluded)

Triglycerides ^a	Placebo-Controlled Databases				Overall Integrated Databases			
	AP-naïve		Olz Adult: All		All Exposures		>24 Wks Exposure	
	Olz	Pla	Olz	Pla	AP-naïve	All	AP-naïve	All
Mean change in F TG	20.24	-4.09	20.77	-10.74	15.71	19.87	13.71	16.72
N	206	129	744	402	327	2761	53	1029
Norm→Hi F TG	1.4%	3.1%	9.2%	4.4%	9.9%	19.9%	6.5%	24.8%
N	145	96	457	251	233	1718	31	640
Bord→Hi F TG	33.3%	20.0%	39.3%	20.0%	34.0%	52.4%	40.0%	65.6%
N	33	15	135	65	47	443	15	163
≥50 mg/dL increase in F TG	38.8%	25.6%	39.6%	26.1%	43.4%	46.2%	58.5%	54.2%
N	206	129	745	402	327	2762	53	1029
Mean change in NF TG	27.14	-4.87	14.35	-6.04	41.73	22.70	28.06	21.30
N	81	74	146	106	285	1535	15	601
Norm→Hi NF TG	0%	0%	0%	0%	0%	0.4%	0%	0.9%
N	43	48	78	71	126	818	10	325
Bord→Hi NF TG	10.8%	4.0%	7.5%	3.0%	9.5%	8.6%	20.0%	11.7%
N	37	25	67	33	147	684	5	266
≥50 mg/dL increase in NF TG	39.5%	23.0%	32.9%	25.5%	57.2%	47.8%	46.7%	50.4%
N	81	74	146	106	285	1535	15	601

Abbreviations: AP = antipsychotic; bord = borderline; F = fasting; Hi = High; N = number of patients in analysis; NF = nonfasting; Norm = normal; Olz = olanzapine; Pla = placebo; pts = patients; TG = triglycerides.

^aShaded cells indicate a statistically significant comparison at $p < .05$. There were no statistical comparisons made between databases. Cut-off values for Fasting TG: Normal = <150 mg/dL; Borderline = ≥150 & <200 mg/dL; High = ≥200 mg/dL. Cut-off values for Nonfasting TG: Normal = <150 mg/dL; Borderline = ≥150 & <500 mg/dL; High = ≥500 mg/dL.

III.5. Hyperlipidemia: Reviewer Comment

III.5.1. Hyperlipidemia: Summary

In the data bases submitted, undesirable changes in lipids were observed during olanzapine and OFC treatment. For total cholesterol and LDL cholesterol, the magnitude of mean changes was greatest for adults treated with OFC, followed by adolescents treated with olanzapine, followed by adults treated with olanzapine. For triglycerides, OFC-treated adults and olanzapine-treated adolescents appeared to have similar magnitude of change, both slightly greater than changes for olanzapine-treated adults. Treatment-emergent increases in fasting triglycerides of at least 50 mg/dL were common in olanzapine-treated adults (occurring in 39.6%), as were increases in fasting total cholesterol of at least 40 mg/dL (21.6%) and increases in fasting LDL cholesterol of at least 30 mg/dL (23.7%). These increases were all statistically significantly greater than those observed for placebo. As in adults, treatment-emergent increases in fasting triglycerides of at least 50 mg/dL, fasting total cholesterol of at least 40 mg/dL, and fasting LDL cholesterol of at least 30 mg/dL were also common in olanzapine-treated adolescents (37.0%, 14.5%, and 17.5%, respectively). The increases in fasting triglycerides and fasting total cholesterol were statistically significantly greater than those observed for placebo. The percentage of patients whose fasting total cholesterol increased by at least 40 mg/dL was greater for adults than for adolescents. The incidence difference between olanzapine and placebo was similar for adults and adolescents.

III.5.2. Hyperlipidemia: Proposed and Recommended Prescribing Information

III.5.2.1. Olanzapine Hyperlipidemia Labeling: Sponsor Proposal

The sponsor submitted the proposed labeling related to hyperlipidemia with olanzapine use (below) on May 14, 2008.

(b) (4)

IV. Hyperglycemia

IV.1. Hyperglycemia: Olanzapine Adult Subjects

IV.1.1. Hyperglycemia: Olanzapine Adult Subjects in Placebo-Controlled Trials

Last observation carried forward (LOCF) mean change from baseline to endpoint in glucose-related laboratory analytes is provided in Sponsor Table 6.1 (10/04/07 submission) for all patients. In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with median treatment duration up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). Mean increases in nonfasting glucose and HbA1c were statistically significantly greater for olanzapine-treated subjects than for placebo-treated subjects.

**Table 6.1. Glucose-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): All Patients
Olanzapine Adult Placebo-Controlled Database**

Analytes	Unit	Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	N	Baseline		Change to Endpoint		p-value* Within Treatment	p-value
						Mean	Std	Mean	Std		
Glucose, Fasting	mg/dL	OLZ	11.5	Lab: (1,21,52,75,107) Trt: (1,22,56,83,112)	769	93.49	19.57	2.76	22.91	<.001	.091
		PLA	0.0	Lab: (1,21,28,77,102) Trt: (1,21,50,84,136)	411	92.98	18.83	0.17	19.82	.861	
Glucose, Non-Fasting	mg/dL	OLZ	11.3	Lab: (1,20,35,56,964) Trt: (1,23,43,57,964)	1150	98.31	28.28	4.22	30.49	<.001	<.001
		PLA	0.0	Lab: (2,20,29,56,604) Trt: (2,21,35,56,604)	787	100.84	32.62	-2.02	29.21	.053	
Hemoglobin A1c	%	OLZ	13.5	Lab: (2,12,21,27,84) Trt: (1,14,25,27,83)	89	5.68	1.22	0.04	0.36	.260	.028
		PLA	0.0	Lab: (1,8,17,27,97) Trt: (1,10,20,27,97)	85	5.55	0.70	-0.06	0.38	.117	

Some of the protocols in this database (HGJZ, HGKK, HGKL) specified that Hemoglobin A1c be collected only for known diabetics or when clinically indicated.

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

OLZ = Olanzapine, PLA = Placebo.

Included studies for Glucose, Fasting: HBBD, HGJZ, HGKK, HGKL, HGKQ.

Included studies for Glucose, Non-Fasting: HBBD, HGAD, HGAP, HGEH, HGGA, HGGF, HGGW, HGGY, HGJZ, HGKK, HGKL, HGKQ.

Included studies for Hemoglobin A1c: HBBD, HGJZ, HGKK, HGKL, HGKQ.

N = Number of patients having both baseline and post-baseline measurements.

*p-value for one sample t-test.

**p-value is from Type III Sum of Square from the ANOVA model: Change=Therapy Protocol.

Program Name: RMP.H6PSREG2.SASPGM(LOGLULAL) 10AUG07
Output Location: RMP.H6PSREG2.OUTPUT(LOGLULAL)

Differences between olanzapine-treated subjects and placebo-treated subjects in glucose-related laboratory analytes were greater in subjects categorized as having baseline potential glucose dysregulation (Sponsor Table 6.5 from the 10/04/07 submission below.)

**Table 6.5. Glucose-Related Laboratory Analytes
Mean Change from Baseline to Maximum: By Baseline Glucose Dysregulation Status
Olanzapine Adult Placebo-Controlled Database**

Analytes	Unit	Potential for Glucose Dysregulation at Baseline	Therapy	Mean Modal Dose (mg)	Exposure (days) (Min, Q1, Q2, Q3, Max)	N	Baseline		Change to Maximum		p-value*	
							Mean	Std	Mean	Std	Treatment	p-value**
Glucose, Fasting	mg/dL	No	OLZ	11.1	Lab: (1,12,28,56,107) Trt: (1,22,56,83,112)	704	90.30	11.94	6.71	17.40	<.001	.513
			PLA	0.0	Lab: (1,12,26,41,99) Trt: (1,21,49,84,136)	384	90.20	11.42	5.81	19.49	<.001	
		Yes	OLZ	15.1	Lab: (2,8,18,56,86) Trt: (1,21,35,56,86)	65	127.98	41.34	10.51	51.91	.108	.130
			PLA	0.0	Lab: (2,7,14,38,86) Trt: (6,23,55,78,92)	27	132.47	44.02	-4.34	51.44	.665	
			OLZ	11.2	Lab: (1,8,28,56,756)	1104	95.71	19.22	11.76	28.59	<.001	<.001
			PLA	0.0	Lab: (1,23,44,57,964) Trt: (2,10,28,55,428) Trt: (2,21,35,56,604)	744	96.20	19.63	4.62	24.51	<.001	
Glucose, Non-Fasting	mg/dL	No	OLZ	13.5	Lab: (5,7,25,42,252) Trt: (7,25,41,56,812)	46	160.63	84.99	27.03	85.95	.038	.044
			PLA	0.0	Lab: (6,14,28,56,196) Trt: (6,25,42,56,366)	43	181.09	78.26	-8.73	91.75	.536	
		Yes	OLZ	12.9	Lab: (4,8,14,21,55) Trt: (4,13,21,27,57)	69	5.41	0.43	0.07	0.30	.057	.116
			PLA	0.0	Lab: (1,6,13,20,97) Trt: (1,8,16,27,97)	76	5.46	0.40	0.02	0.24	.567	
			OLZ	15.6	Lab: (2,7,20,41,84) Trt: (1,21,27,56,83)	20	6.61	2.26	0.23	0.58	.091	.045
			PLA	0.0	Lab: (6,14,27,56,85) Trt: (6,27,27,56,85)	9	6.33	1.68	-0.03	0.70	.890	

Some of the protocols in this database (HGJZ, HGKK, HGKL) specified that Hemoglobin A1c be collected only for known diabetics or when clinically indicated.

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

OLZ = Olanzapine; PLA = Placebo.

Included studies for Glucose, Fasting: HBED, HGJZ, HGKK, HGKL, HGKQ.

Included studies for Glucose, Non-Fasting: HBED, HGAD, HGAP, HGBH, HGBH, HGGA, HGGF, HGOW, HGGY, HGJZ, HGKK, HGKL, HGKQ.

Included studies for Hemoglobin A1c: HBED, HGJZ, HGKK, HGKL, HGKQ.

N = Number of patients having both baseline and post-baseline measurements.

*p-value for one sample t-test.

**p-value is from Type III Sum of Square from the ANOVA model. Change=Therapy Protocol.

Overall, results of the observed case mean change analyses paralleled the LOCF mean change analyses. Increased mean differences in fasting and nonfasting glucose measurements between olanzapine-treated subjects and placebo-treated subjects occurred in the earliest measurements. No clear time-related pattern of increase or decrease in mean change in fasting or nonfasting glucose was noted in subsequent measurements.

There were no statistically significant differences between olanzapine and placebo in proportions of patients with treatment-emergent significant changes in fasting or nonfasting glucose, for all patients overall and for patients both with and without evidence of potential glucose dysregulation at baseline. There was no clear pattern of increased incidence of treatment-emergent adverse glucose changes in subjects with potential glucose dysregulation at baseline. These measurements were limited by brief periods of treatment exposure (8 weeks or less) at the time of glucose measurement.

In the analysis of all patients, several comparisons of treatment-emergent significant changes for fasting glucose were numerically higher for olanzapine compared with placebo; median

treatment exposure at the time of glucose measurement was generally higher in olanzapine-treated subjects compared with placebo-treated subjects (Sponsor Table 6.8 below).

Table 6.8. Glucose Treatment-Emergent Clinically Significant Changes (ADA Guidelines): All Patients Olanzapine Adult Placebo-Controlled Database

Lab test: Glucose, Fasting

Categories	Therapy	Mean Modal Dose	Exposure (days)	N	n	% p-value*
		(mg)	(Min,Q1,Q2,Q3,Max)			
Normal to High (<100 mg/dL to >=126 mg/dL)	OLZ	10.7	Lab: (1,21,56,83,107) Trt: (1,22,56,84,112)	543	12	2.2 .365
	PLA	0.0	Lab: (1,21,28,82,102) Trt: (1,21,55,84,136)	293	10	3.4
Impaired Glucose Tolerance to High (>=100 and < 126 mg/dL to >=126 mg/dL)	OLZ	13.0	Lab: (1,20,27,56,99) Trt: (1,21,36,56,99)	178	31	17.4 .221
	PLA	0.0	Lab: (1,14,22,56,99) Trt: (1,21,27,77,99)	96	11	11.5
Normal/Impaired Glucose Tolerance to High (<126 mg/dL to >=126 mg/dL)	OLZ	11.2	Lab: (1,21,44,80,107) Trt: (1,22,56,83,112)	721	43	6.0 .788
	PLA	0.0	Lab: (1,21,28,75,102) Trt: (1,21,50,84,136)	389	21	5.4
<126 mg/dL to >=140 mg/dL	OLZ	11.2	Lab: (1,21,51,81,107) Trt: (1,22,56,83,112)	721	28	3.9 .301
	PLA	0.0	Lab: (1,21,28,77,102) Trt: (1,21,50,84,136)	389	10	2.6
<126 mg/dL to >=200 mg/dL	OLZ	11.2	Lab: (1,21,54,81,107) Trt: (1,22,56,83,112)	721	3	0.4 1.00
	PLA	0.0	Lab: (1,21,28,77,102) Trt: (1,21,50,84,136)	389	1	0.3
<126 mg/dL to >=300 mg/dL	OLZ	11.2	Lab: (1,21,54,81,107) Trt: (1,22,56,83,112)	721	0	0.0 .350
	PLA	0.0	Lab: (1,21,28,77,102) Trt: (1,21,50,84,136)	389	1	0.3

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
OLZ = Olanzapine; PLA = Placebo.
Included studies: HBBD, HGJZ, HGKK, HGKL, HGKQ.
N = Number of patients having both baseline and post-baseline measurements and meeting the baseline inclusion criteria.
n = Number of patients meeting the post-baseline criteria.
*Frequencies analyzed using Fisher's exact test.

Sponsor Table 6.10 from the 10/04/07 submission summarizes proportions of patients with several specific changes in fasting and nonfasting glucose, based on baseline glucose category. For fasting glucose, there were no statistically significant differences between olanzapine and placebo in proportions of patients with changes of at least 10 mg/dL, regardless of baseline category.

Table 6.10. Glucose Treatment-Emergent Increases of at Least 10 mg/dL (Fasting) or 20 mg/dL (Nonfasting): By Baseline Glucose Category Olanzapine Adult Placebo-Controlled Database

Fasting Glucose ≥ 10 mg/dL Increase							
Baseline Categories	Therapy	Mean Modal Dose (mg)	Exposure (days)		N	n	% p-value*
			(Min,Q1,Q2,Q3,Max)				
<100mg/dL	OLZ	10.7	Lab: (1,17,29,63,107)	543	210	38.7	.331
	PLA	0.0	Lab: (1,22,56,84,112)	293	103	35.2	
>=100 but <126 mg/dL	OLZ	13.0	Lab: (1,16,28,56,102)	178	65	36.5	.517
	PLA	0.0	Lab: (1,21,55,84,136)	96	39	40.6	
>=126 mg/dL	OLZ	15.0	Lab: (1,12,25,56,99)	48	22	45.8	.800
	PLA	0.0	Lab: (1,21,36,56,99)	22	11	50.0	
Total	OLZ	11.5	Lab: (1,7,19,55,86)	769	297	38.6	.660
	PLA	0.0	Lab: (5,21,35,56,86)	411	153	37.2	

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
 OLZ = Olanzapine; PLA = Placebo.
 Included studies: HBBD, HGJZ, HGKK, HGKL, HGKQ.
 N = Number of patients with both a normal baseline and at least one post-baseline measurement.
 n = Number of patients with Treatment-Emergent Significant Change at Anytime.
 *Frequencies analyzed using Fisher's exact test.

For nonfasting glucose, there were statistically significantly greater proportions of olanzapine-treated patients than placebo-treated patients with increases of at least 20 mg/dL for patients who were normal or borderline at baseline. The difference between treatment groups for patients who were high at baseline was not statistically significant (Sponsor Table 6.10 below).

Table 6.10. Glucose Treatment-Emergent Increases of at Least 10 mg/dL (Fasting) or 20 mg/dL (Nonfasting): By Baseline Glucose Category Olanzapine Adult Placebo-Controlled Database (Concluded)

Non-Fasting Glucose ≥ 20 mg/dL Increase								
Baseline Categories	Therapy	Mean Modal Dose (mg)	Exposure (days)		N	n	% p-value*	
			(Min,Q1,Q2,Q3,Max)					
<140mg/dL	OLZ	11.2	Lab:	(1,11,28,56,860)	1074	400	37.2	<.001
			Ttt:	(1,23,45,57,964)				
	PLA	0.0	Lab:	(2,14,28,56,604)	713	176	24.7	
			Ttt:	(2,21,35,56,604)				
≥ 140 but <200 mg/dL	OLZ	12.5	Lab:	(2,7,16,49,638)	62	35	56.5	.027
			Ttt:	(4,22,28,56,728)				
	PLA	0.0	Lab:	(4,7,28,55,196)	57	20	35.1	
			Ttt:	(4,17,42,56,196)				
≥ 200 mg/dL	OLZ	13.9	Lab:	(5,7,17,42,57)	14	5	35.7	1.00
			Ttt:	(7,17,26,56,60)				
	PLA	0.0	Lab:	(6,21,30,56,59)	17	7	41.2	
			Ttt:	(6,24,53,56,366)				
Total	OLZ	11.3	Lab:	(1,9,28,55,860)	1150	440	38.3	<.001
			Ttt:	(1,23,43,57,964)				
	PLA	0.0	Lab:	(2,13,28,56,604)	787	203	25.8	
			Ttt:	(2,21,35,56,604)				

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.
 OLZ = Olanzapine; PLA = Placebo.
 Included studies: HBBD, HGAD, HGAP, HGBH, HGBH, HGGA, HGGF, HGGW, HGGY, HGJZ, HGKK, HGKL, HGKQ.
 N = Number of patients with both a normal baseline and at least one post-baseline measurement.
 n = Number of patients with Treatment-Emergent Significant Change at Anytime.
 *Frequencies analyzed using Fisher's exact test.
 Program Name: RMP.H6PSREG2.SASPGM(FQGLUA4) 10AUG07
 Output Location: RMP.H6PSREG2.OUTPUT(FQGLUA41)

Sponsor Figure 2.4 from the 12/19/08 submission below, which shows mean change in fasting glucose from baseline with 95% confidence intervals in patients who completed 9 months of

therapy and had a minimum of 5 fasting blood glucose values measured at Months 1, 2, 4, 7, 8, or 9.

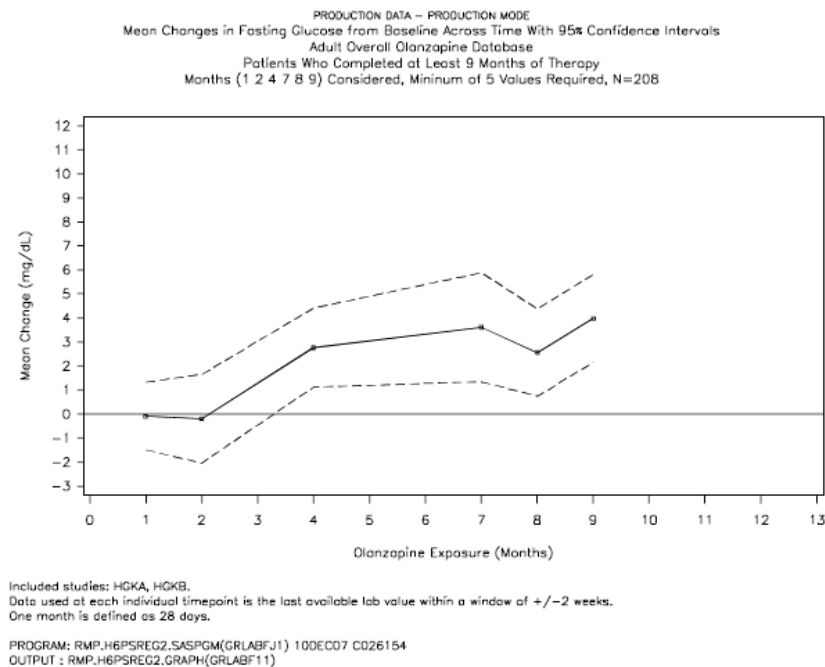


Figure 2.4. Mean changes in fasting glucose from baseline across time for patients from the Olanzapine Adult Integrated database who completed at least 9 months of olanzapine treatment.

Accounting for the 95% confidence intervals of the mean change measurements in this figure, it is not clear that a significant decrease in rate of fasting glucose change occurs after 6 months of therapy.

Sponsor Table 6.11 summarizes proportions of patients with treatment-emergent significant changes in HbA1c and urine glucose. A statistically significantly higher proportion of olanzapine-treated patients than placebo-treated patients had treatment-emergent glycosuria. Glycosuria typically occurs with blood glucose greater than 180 mg/dL. There were no statistically significant differences in the proportion of subjects with treatment-emergent changes in hemoglobin A1c in olanzapine-treated patients compared to placebo-treated patients. However, the median treatment exposure for olanzapine-treated and placebo-treated subjects in the 5 studies analyzed was approximately 3 weeks. Hemoglobin A1c reflects blood glucose over a ninety day time period, so the median treatment duration in these studies was not sufficient to fully see changes in hemoglobin A1c.

**Table 6.11. Hemoglobin A1c and Urine Glucose
Treatment-Emergent Clinically Significant Changes: All Patients
Olanzapine Adult Placebo-Controlled Database**

Laboratory Analytes	Categories	Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	N	n	% p-value*	
UA-Glucose	0 to > 0	OLZ	11.3	Lab: (1,21,33,56,964) Trt: (1,22,36,56,964)	855	52	6.1	.004
		PLA	0.0	Lab: (1,16,28,55,486) Trt: (1,18,28,55,604)	599	17	2.8	
Hemoglobin A1c	< 6.1% to >= 6.1%	OLZ	13.5	Lab: (2,11,20,27,58) Trt: (1,13,23,27,83)	73	4	5.5	.442
		PLA	0.0	Lab: (1,8,16,27,85) Trt: (1,11,20,27,88)	74	2	2.7	
	< 6.1% to >= 8.0%	OLZ	13.5	Lab: (2,12,21,27,58) Trt: (1,13,23,27,83)	73	0	0.0	
		PLA	0.0	Lab: (1,8,16,27,85) Trt: (1,11,20,27,88)	74	0	0.0	
	< 6.1% to >= 10.0%	OLZ	13.5	Lab: (2,12,21,27,58) Trt: (1,13,23,27,83)	73	0	0.0	
		PLA	0.0	Lab: (1,8,16,27,85) Trt: (1,11,20,27,88)	74	0	0.0	
	< 6.1% to >= 12.0%	OLZ	13.5	Lab: (2,12,21,27,58) Trt: (1,13,23,27,83)	73	0	0.0	
		PLA	0.0	Lab: (1,8,16,27,85) Trt: (1,11,20,27,88)	74	0	0.0	

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

Some of the protocols in this database (HGJZ, HGKK, HGKL) specified that Hemoglobin A1c be collected only for known diabetics or when clinically indicated.

OLZ = Olanzapine; PLA = Placebo.

Included studies for UA-Glucose: HBBD, HGAD, HGAP, HGBH, HGEH, HGGF, HGGW, HGGY.

Included studies for Hemoglobin A1c: HBBD, HGJZ, HGKK, HGKL, HGKQ.

N = Number of patients having both baseline and post-baseline measurements and meeting the baseline inclusion criteria.

n = Number of patients meeting the post-baseline criteria.

*Frequencies analyzed using Fisher's exact test.

IV.1.2. Hyperglycemia: Olanzapine Adult Subjects in Comparator-Controlled Trials

IV.1.2.1 Hyperglycemia: Olanzapine Adult Subjects in Lilly Comparator-Controlled Trials

Clozapine

In the clozapine-controlled database, all data were collected under nonfasting conditions. HbA1c and fructosamine were not collected. The incidence of patients who went from normal glucose at baseline to high glucose post-baseline (<140 mg/dL to ≥200 mg/dL) was 3.2% for clozapine versus 1.0% for olanzapine. A statistically significantly greater proportion of clozapine-treated patients than olanzapine-treated patients had increases of at least 20 mg/dL in nonfasting glucose (60.8% versus 49.8%). The incidence of treatment-emergent urine glucose was also higher for clozapine (7.3% versus 1.6%; P=0.060). Mean changes in glucose from baseline to endpoint for patients with normal glucose at baseline were statistically and clinically significantly higher for patients treated with clozapine compared with olanzapine (12.87 mg/dL for clozapine versus 4.20 mg/dL for olanzapine); mean changes overall were also statistically and clinically significantly higher (11.20 mg/dL versus 1.88 mg/dL). Mean changes in glucose for patients in other baseline glucose subgroups were also higher for patients treated with clozapine than for patients treated with olanzapine, although sample sizes were small.

Quetiapine

The quetiapine-controlled database included 2 head-to-head studies, HGLR and HGJB.

Patients included in HGLR had all been previously treated with olanzapine for at least 15 days at study entry, and were required to be overweight or obese at study entry. The study population in HGJB is markedly different, as patients were not selected based on previous olanzapine exposure and baseline BMI. Nearly all the fasting data in this database came from HGJB, while nearly all the nonfasting data came from HGLR. Data interpretation should take into consideration the differences in fasting and nonfasting status of the two studies and the markedly different patient populations. In the combined database, approximately 80% of patients were overweight or obese, because of the contribution from HGLR.

The incidence of patients who went from normal fasting glucose at baseline to high fasting glucose post-baseline was lower for patients treated with olanzapine compared with quetiapine (4.5% for olanzapine versus 8.2% for quetiapine). No patients in either group went from normal or borderline fasting glucose at baseline to at least 300 mg/dL post-baseline. There was no statistically significant difference in the proportions of olanzapine- and quetiapine-treated patients with increases of at least 10 mg/dL in fasting glucose (57.5% versus 46.6%). Mean changes from baseline to endpoint in fasting glucose were small for both groups (0.48 mg/dL for olanzapine versus -1.99 mg/dL for quetiapine).

The incidence of patients who went from normal nonfasting glucose at baseline to high nonfasting glucose post-baseline was higher for patients treated with olanzapine (3.8% for olanzapine versus 2.7% for quetiapine), as was the incidence of patients who went from normal or borderline nonfasting glucose at baseline to at least 300 mg/dL post-baseline (2.9% for olanzapine versus 0.9% for quetiapine). There was no statistically significant difference in the proportions of olanzapine- and quetiapine-treated patients with increases of at least 20 mg/dL in nonfasting glucose (37.6% versus 33.6%). Mean changes from baseline to endpoint in nonfasting glucose were higher for patients treated with olanzapine (14.88 mg/dL for olanzapine versus 8.17 mg/dL for quetiapine). In the quetiapine-controlled database, changes in fructosamine and HbA1c were larger but not statistically significant for patients treated with olanzapine compared to quetiapine.

Risperidone

In the risperidone-controlled database, all data were collected under nonfasting conditions. HbA1c and fructosamine were not collected. Among patients without evidence of potential glucose dysregulation at baseline, a statistically significantly higher proportion of olanzapine-treated than risperidone-treated patients went from normal/borderline nonfasting glucose at baseline to high glucose post-baseline (from <200 to \geq 200 mg/dL; 1.7% versus 0.2%). This was the only statistically significant difference between the two treatment groups. The incidence of patients who went from normal glucose at baseline to high glucose post-baseline (<140 mg/dL to \geq 200 mg/dL) was 1.6% for olanzapine-treated patients versus 0.9% for risperidone-treated patients; and the incidence of patients who went from normal or borderline glucose at baseline to at least 300 mg/dL post-baseline was 0.6% for olanzapine-treated patients versus 0.0% for risperidone-treated patients. Similar proportions of olanzapine-treated and risperidone-treated patients had increases of at least 20 mg/dL in nonfasting glucose (42.9% versus 44.8%). Mean changes from baseline to endpoint tended to be higher for patients treated with olanzapine (4.58 mg/dL for olanzapine versus 1.86 mg/dL for risperidone).

among all patients overall; 5.58 mg/dL versus 5.00 mg/dL among patients with normal glucose at baseline); however, the incidence of treatment-emergent urine glucose was nearly identical for both treatment groups (8.5% versus 8.6%). Given that urine glucose is less affected by fasting status than glucose, this finding may be the best representation from this database of glucose-related changes in patients treated with olanzapine or risperidone. Overall, increases in glucose parameters were greater in patients treated with olanzapine compared to risperidone.

Ziprasidone

Most glucose data in the ziprasidone-controlled database were collected under fasting conditions. There were 5 mean change analyses in which olanzapine-treated patients had statistically significantly greater changes than ziprasidone-treated patients (fasting glucose from baseline to endpoint for all patients [4.43 mg/dL versus -0.68 mg/dL]; HbA1c from baseline to endpoint and from baseline to maximum, in both cases for patients without evidence of baseline glucose dysregulation; and fructosamine from baseline to maximum for all patients and for those without evidence of baseline glucose dysregulation). There were no categorical analyses with statistically significant differences. The incidence of patients who went from normal fasting glucose at baseline to high glucose post-baseline (<100 mg/dL to ≥ 126 mg/dL) was 5.7% for olanzapine versus 4.6% for ziprasidone. Proportions of patients with increases of at least 10 mg/dL in fasting glucose were nearly identical in both groups (53.3% versus 53.8%). Analyses of urine glucose, HbA1c, and fructosamine show numerical advantages for patients treated with ziprasidone compared to olanzapine. These data suggest that patients treated with olanzapine experience greater adverse changes in glucose-related parameters than patients treated with ziprasidone.

Haloperidol

In the haloperidol-controlled database, all data were collected under nonfasting conditions. HbA1c and fructosamine were not collected. Statistically significantly greater proportions of olanzapine-treated patients than haloperidol-treated patients went from normal nonfasting glucose at baseline to high post-baseline (<140 mg/dL to ≥ 200 mg/dL; 1.7% for olanzapine versus 0.6% for haloperidol) and from borderline to high (19.9% versus 6.5%) or had a 20 mg/dL increase at any time (51.2% versus 40.4%). Mean changes in glucose from baseline to endpoint for patients with normal glucose at baseline were statistically significantly higher for olanzapine than for haloperidol (5.06 mg/dL for olanzapine versus 1.28 mg/dL for haloperidol); mean changes overall were also statistically significantly higher (3.90 mg/dL versus -0.98 mg/dL). Thus, these data suggest that patients treated with olanzapine experience greater adverse changes in glucose than patients treated with haloperidol.

Sponsor Table 1.7 summarizes the glucose data from antipsychotic-controlled databases.

Table 1.7. Summary of Glucose Data from Lilly Atypical Antipsychotic–Controlled Databases

	olanzapine	clozapine	olanzapine	quetiapine	olanzapine	risperidone	olanzapine	ziprasidone
Mean change fasting glucose (mg/dL)	na	na	0.48	-1 .99	na	na	4.43	-0.68b
N	na	na	80	73	na	na	379	333
Median exposure	na	na	167 days	88 days	na	na	168 days	133 days
—Among patients <100 mg/dL at baseline	na	na	5.46	4.19	na	na	6.62	3.91
N	na	na	45	49	na	na	229	217
Median exposure	na	na	167 days	57 days	na	na	167 days	104 days
Norm to Hi fasting glucose (<100 to ≥126 mg/dL)	na	na	4.5%	8.2%	na	na	5.7%	4.6%
N	na	na	44	49	na	na	229	217
Median exposure	na	na	151 days	57 days	na	na	166 days	92 days
Norm/bord to v.Hi fasting gluc (<126 to ≥200 mg/dL)	na	na	2.8%	0%	na	na	2.0%	0.3%
N	na	na	71	68	na	na	353	309
Median exposure	na	na	168 days	88 days	na	na	168 days	133 days
≥10 mg/dL increase in fasting glucose (%)	na	na	57.5%	46.6%	na	na	53.3%	53.8%
N	na	na	80	73	na	na	379	333
Median exposure	na	na	56 days	50 days	na	na	56 days	42 days
Patients with upward shift in fasting glucose categ.	na	na	32.5%	27.4%	na	na	33.7%	30.5%
N	na	na	80	73	na	na	377	331
Mean change nonfasting glucose (mg/dL)	1.88	11.20a	14.88	8.17	4.58	1 .86	15.69	12.22
N	219	217	117	128	527	504	24	25
Median exposure	124 days	123 days	116 days	84 days	89 days	76 days	57 days	43 days
—Among patients <140 mg/dL at baseline	4.20	12.87a	15.48	9.81	5.58	5.00	10.81	14.57
N	205	186	104	112	494	460	23	22
Median exposure	124 days	123 days	116 days	84 days	84 days	66 days	112 days	43 days
Norm to Hi nonfasting gluc (<140 to ≥200 mg/dL)	1.0%	3.2%	3.8%	2.7%	1.6%	0.9%	4.3%	0 %
N	205	186	104	112	493	460	23	22
Median exposure	124 days	118 days	116 days	69 days	83 days	66 days	112 days	43 days

Table 1.7. Summary of Glucose Data from Lilly Atypical Antipsychotic–Controlled Databases (concluded)

	olanzapine	clozapine	olanzapine	quetiapine	olanzapine	risperidone	olanzapine	ziprasidone
Norm to v.Hi nonfasting gluc(<140 to ≥300 mg/dL)	0%	0%	2.9%	0.9%	0.6%	0%	0%	0%
N	205	186	104	112	493	460	23	22
Median exposure	124 days	123 days	116 days	84 days	83 days	66 days	112 days	43 days
≥20 mg/dL increase in nonfasting glucose (%)	49.8%	60.8%	37.6%	33.6%	42.9%	44.8%	29.2%	40.0%
N	219	217	117	128	527	504	24	25
Median exposure	48 days	21 days	60 days	57 days	22 days	22 days	57 days	43 days
Patients with upward shift in nonfasting gluc. categ.	15.6%	26.4% b	18.3%	13.3%	12.0%	10.2%	12.5%	24.0%
N	218	216	115	128	525	499	24	25
Urinary glucose present (%)	1.6%	7.3%	na	na	8.5%	8.6%	5.7%	3.5%
N	124	124	na	na	260	243	157	143
Median exposure	125 days	112 days	na	na	176 days	107 days	141 days	63 days
Norm to abn fructosamine (<285 to ≥285 mg/dL) c	na	na	7.1%	2.2%	na	na	2.5%	0%
N	na	na	140	139	na	na	162	140
Median exposure	na	na	166 days	117 days	na	na	147 days	63 days
Mean change in HbA1c (%)	na	na	0.09	-0.03	na	na	0.06	-0.06
N	na	na	213	202	na	na	169	147
Median exposure	na	na	167 days	132 days	na	na	155 days	72 days
Norm to abn HbA1c (<6.1% to ≥6.1%)	na	na	14.2%	9.1%	na	na	8.7%	4.5%
N	na	na	155	143	na	na	126	112
Median exposure	na	na	167 days	119 days	na	na	117 days	57 days

Abbreviations: abn = abnormal; bord = borderline; categ = category; gluc = glucose; HbA1c = hemoglobin A1c; Hi = High; N = number of patients in analysis; na = not available; Norm = normal; v = very.

a Statistically significantly different; $p < .001$.

b Statistically significantly different; $p < .05$.

c For the quetiapine-controlled database, fructosamine results were collected in only one study, HGJB.

IV.1.2.2. Hyperglycemia: Olanzapine Adult Subjects in the CATIE Phase 1 Study

Phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)² is a National Institutes of Mental Health (NIMH)-sponsored, multicenter randomized controlled trial which compares second generation antipsychotics with perphenazine on endpoints related to safety and efficacy. Results related to mean modal dose, median time to discontinuation, exposure-adjusted mean changes in glucose, exposure-adjusted mean changes in glycosylated hemoglobin, and the number and percentage of patients who had oral glucose-lowering drugs or insulin added are listed in Table below.

Table. CATIE Phase 1 Study Results Related to Glucose

	Ziprasidone	Olanzapine	Risperidone	Quetiapine	Perphenazine	P
Mean Modal Dose (mg/day)	112.8	20.1	3.9	543.4	20.8	
Median Time To Discon. (months)	3.5	9.2	4.8	4.6	5.6	
Δ blood glucose (mg/dL)	2.9	13.7	6.6	7.5	5.4	0.59
Δ glycosylated hemoglobin (%)	0.11	0.40	0.07	0.04	0.09	0.01
Oral glucose-lowering drugs or insulin added no./total (%)	4/185 (2)	12/336 (4)	8/341 (2)	7/337 (2)	5/261 (2)	0.28

Patients who received olanzapine had an exposure-adjusted mean increase in blood glucose of 13.7 mg/dL and an exposure-adjusted mean increase in glycosylated hemoglobin of 0.40 %. The mean change in blood glucose without adjustment for exposure in olanzapine-treated patients was 15.0 mg/dL. Patients were instructed to fast; non-fasting results were not excluded. No information was provided on the proportion of fasting versus non-fasting glucose measurements. Change from baseline in glucose values was determined as the difference between the baseline value and the average of the two highest post-baseline values. The exposure-adjusted mean is the least-squares mean from an analysis of covariance adjusting for whether the patient had an exacerbation in the preceding three months and for duration of exposure to study drug during phase 1. It is unclear whether this adjustment for exposure completely adjusts for differences in median time to discontinuation.

IV.1.3. Hyperglycemia: Olanzapine Adult Subjects: Long Term Controlled and Uncontrolled Data

Sponsor Table 2.7 presents glucose-related analyses for the Olanzapine Adult Integrated database. Results are shown in the table for all patients and for the subset with at least 48 weeks of exposure. Mean increases in glucose from baseline to endpoint were 5.34 mg/dL for fasting glucose (median exposure of 84 days) and 5.24 mg/dL for nonfasting glucose (median exposure of 86 days). In analyses of mean change by baseline value, patients with normal glucose at baseline had increases (7.15 mg/dL for fasting glucose and 6.54 mg/dL for nonfasting glucose) while patients with high glucose at baseline had decreases (-2.78 mg/dL for fasting glucose and -32.82 mg/dL for nonfasting glucose). For the subset of patients with at least 48 weeks of exposure, the pattern of results was similar: Overall there was a mean increase in glucose, with a mean increase among patients with normal baseline glucose and a mean decrease among patients with high baseline glucose.

² Lieberman JA, et al. N Engl J Med. 2005 Sep 22;353(12):1209-23.

Among olanzapine-treated adults with normal glucose at baseline, 7.0% experienced high fasting glucose at least once, 2.0% experienced high nonfasting glucose at least once, and 0.6% experienced very high nonfasting glucose at least once. Among patients with borderline glucose at baseline, 21.6% experienced high fasting glucose at least once, and 24.9% experienced high nonfasting glucose at least once. Among olanzapine-treated adults with at least 48 weeks of exposure, 12.8% experienced a shift from normal to high fasting glucose at least once.

The mean increase in HbA1c from baseline to endpoint for the Olanzapine Adult Integrated Database was 0.08% (median exposure of 73 days). Among patients in the integrated database with normal HbA1c at baseline, 10.3% experienced high HbA1c. Among patients with normal fructosamine at baseline, 3.1% experienced high fructosamine. Glucose was detected in the urine of 7.2% of all patients. There were no fructosamine data for the subset of patients with at least 48 weeks of exposure.

Table 2.7. Glucose Data from the Olanzapine Adult Integrated Database

All Patients and Patients with at Least 48 weeks' Exposure

OLANZAPINE ADULT Glucose	All patients		With ≥ 48 weeks' exposure	
	N	estimate (95% CI)	N	estimate (95% CI)
LOCF mean change FGLU (mg/dL)	2925	5.34 (4.3, 6.38)	487	4.20 (2.38, 6.03)
Median exposure		84 days		567 days
—Among pts <100 (Norm) at BL	2064	7.15 (6.19, 8.11)	345	7.24 (5.94, 8.54)
Median exposure		84 days		567 days
—Among pts ≥ 100 & <126 (Bord) at BL	718	1.75 (-0.6, 4.1)	127	-1.67 (-4.6, 1.2)
Median exposure		84 days		560 days
—Among pts ≥ 126 (Hi) at BL	143	-2.78 (-13.6, 8.0)	15	-15.86 (-63.9, 32.1)
Median exposure		63 days		632 days
Norm to Hi FGLU (<100 to ≥ 126)	2063	7.0% (6.0, 8.2)	345	12.8% (9.4, 16.7)
Median exposure		84 days		547 days
Bord to Hi FGLU (≥ 100 & <126 to ≥ 126)	719	21.6% (18.6, 24.7)	127	26.0% (18.6, 34.5)
Median exposure		64 days		414 days
LOCF mean change NFGU (mg/dL)	7613	5.24 (4.47, 6.0)	1453	8.69 (6.73, 10.64)
Median exposure		86 days		570 days
—Among pts <140 (Norm) at BL	7078	6.54 (5.89, 7.18)	1343	9.44 (7.83, 11.05)
Median exposure		87 days		569 days
—Among pts ≥ 140 & <200 (Bord) at BL	397	-4.72 (-11.4, 2.0)	86	6.05 (-10.3, 22.4)
Median exposure		83 days		591 days
—Among pts ≥ 200 (Hi) at BL	138	-32.82 (-49.9, -15.7)	24	-24.27 (-76.6, 28.0)
Median exposure		81 days		623 days
Norm to Hi NFGU (<140 to ≥ 200)	7077	2.0% (1.7, 2.3)	1343	4.3% (3.3, 5.5)
Median exposure		85 days		540 days
Bord to Hi NFGU (≥ 140 & <200 to ≥ 200)	398	24.9% (20.7, 29.4)	86	40.7% (30.2, 51.8)
Median exposure		55 days		372 days

Norm to v.Hi NFGLU (<140 to ≥300) Median exposure	7077 87 days	0.6% (0.4, 0.8)	1343 560 days	1.4% (0.9, 2.2)
Urinary glucose present (%) Median exposure	5258 88 days	7.2% (6.5, 7.9)	1154 526 days	15.0% (13.0, 17.2)
Norm to Hi fructos (<285 to ≥285) Median exposure	701 72 days	3.1% (2.0, 4.7)	0	
LOCF mean change in HbA1c (%) Median exposure	1500 73 days	0.08% (0.05,0.1)	116 393 days	0.03% (-0.1,0.2)
Norm to Hi HbA1c (<6.1% to ≥6.1%) Median exposure	1213 65 days	10.3% (8.7, 12.2)	95 391 days	12.6% (6.7, 21.0)

Abbreviations: bord = borderline; CI = confidence interval; FGLU = fasting glucose; fructos = fructosamine; gluc = glucose; HbA1c = hemoglobin A1c; Hi = High; LOCF = last observation carried forward; N = number of patients in analysis; NFGLU = nonfasting glucose; norm = normal; pts = patients; v = very.

IV.2. Hyperglycemia: Olanzapine Fluoxetine Combination Subjects (Adults)

Sponsor Table 6.27 from the 10/04/07 submission displays an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, treatment with olanzapine fluoxetine combination was associated with a statistically significantly greater mean change in random glucose compared to placebo (8.65 mg/dL versus -3.86 mg/dL).

**Table 6.27. Glucose-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): All Patients
OFC Adult Controlled Database (Continued)**

Lab Test	Unit	Therapy	Mean Modal Dose (mg)	Exposure (days) (min,Q1,Q2,Q3,max)	Baseline			Change to Endpoint		*P-values	**P-values
					N	Mean	Std	Mean	Std	With-in Treatment	Overall vs.
Glucose, Non-Fasting	mg/dL	OFC	8.6/39.3	Lab: (3,49,57,73,112) Trt: (3,53,57,77,116)	684	103.66	41.36	8.65	42.84	<.001	<.001
		FLX	41.9	Lab: (3,49,56,59,115) Trt: (4,53,56,60,130)	407	97.39	25.35	2.19	30.41	.147	.004
		OLZ	9.7	Lab: (1,36,56,57,112) Trt: (1,42,56,58,112)	742	99.26	30.45	6.58	33.39	<.001	.275
		PLA	0.0	Lab: (3,28,47,56,112) Trt: (3,28,43,56,112)	387	104.41	37.15	-3.86	31.36	.016	<.001

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

OFC = olanzapine + fluoxetine combination, FLX = fluoxetine, OLZ = olanzapine, PLA = placebo.

N = number of patients having both baseline and post-baseline measurements.

*P-value for one sample t-test.

**P-value is from Type III Sums of Squares from ANOVA model; change = therapy.

Included studies: HCKB, HDAO, HGFR, HGGA, HGGY, HGHE, HGIE.

In an analysis of 6 trials from the OFC Controlled database, shows that subjects treated with olanzapine fluoxetine combination had a higher rate of treatment-emergent glycosuria compared to placebo-treated subjects (Sponsor Table 6.37 from the 10/04/07 submission below).

**Table 6.37. Urine Glucose
Treatment-Emergent Clinically Significant Changes: All Patients OFC Adult Controlled
Database**

Lab test	Categories	Therapy	Mean Modal Dose (mg)	Exposure (days) (min,Q1,Q2,Q3,max)	N	n	%	*P-values	
								Overall	OFC vs.
UA-Glucose	0 to > 0	OFC	8.1/40.9	Lab: (3,52,57,83,112) Trt: (3,51,57,83,112)	477	21	4.4	.003	
		FLX	43.9	Lab: (3,48,56,62, 94) Trt: (4,48,56,62, 94)	271	1	0.4		.001
		OLZ	9.5	Lab: (1,34,56,57,112) Trt: (1,35,56,57,112)	515	12	2.3		.077
		PLA	0.0	Lab: (3,28,43,56,112) Trt: (3,28,43,56,112)	284	4	1.4		.033

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

OFC = olanzapine + fluoxetine combination, FLX = fluoxetine, OLZ = olanzapine, PLA = placebo.

N = number of randomized patients having both baseline and post-baseline measurements and meeting the baseline inclusion criteria.

n = number of patients meeting the post-baseline criteria.

* Frequencies analyzed using Fisher's exact test.

Included studies: HCKE, HDAO, HGFR, HGGY, HGHZ, HGIE.

Sponsor Table 2.9 below displays glucose-related analyses for the OFC Adult Integrated Database for all patients and for the subset with at least 24 weeks of exposure.

Mean increases in glucose from baseline to endpoint for adults treated with OFC were 3.37 mg/dL for fasting glucose (median exposure of 56 days) and 4.95 mg/dL for nonfasting glucose (median exposure of 125 days). In analyses of mean change by baseline value, patients with normal glucose at baseline had mean increases (3.15 mg/dL for fasting glucose and 6.04 mg/dL for nonfasting glucose). Patients with high fasting glucose at baseline had a mean increase in fasting glucose (13.19 mg/dL), while those with high nonfasting glucose at baseline had a mean decrease in nonfasting (-21.49 mg/dL). For patients with at least 24 weeks of exposure, results for nonfasting glucose were similar to those observed for all patients overall; however, results for fasting glucose were somewhat different. In this subset of patients, mean change overall in fasting glucose was -0.05 mg/dL. Those with normal glucose at baseline had an increase in glucose (2.45 mg/dL), and a single patient with high glucose at baseline had a mean change of -21.62 mg/dL.

Of OFC-treated adults with normal glucose at baseline, 3.1% had a high fasting glucose level at least once, 1.8% experienced a high nonfasting glucose level at least once, and 0.2% experienced a very high nonfasting glucose level at least once. Among patients with borderline glucose at baseline, 11.1% experienced high fasting glucose, and 32.3% experienced high nonfasting glucose at least once.

The mean increase in HbA1c from baseline to endpoint was 0.49% (median exposure of 63 days). Among patients in the OFC Adult Integrated Database with normal HbA1c at baseline, 7.7% experienced abnormal HbA1c. The proportion with treatment-emergent abnormal HbA1c was highest among patients with at least 12 weeks of exposure (9.8%), and slightly less for patients with at least 24 weeks or 48 weeks of exposure (Sponsor Table 2.9). Among patients with normal fructosamine at baseline, 3.2% experienced abnormal fructosamine.

Table 2.9. Glucose Data from the OFC Adult Integrated Database
All Patients and Patients with at Least 24 weeks' Exposure

OFC ADULT Glucose	All patients		With ≥24 weeks' exposure	
	N	estimate (95% CI)	N	estimate (95% CI)
LOCF mean change FGLU (mg/dL)	356	3.37 (0.86, 5.88)	66	-0.05 (-2.93, 2.82)
Median exposure		56 days		175 days
—Among pts <100 (Norm) at BL	261	3.15 (1.79, 4.51)	53	2.45 (-0.23, 5.13)
Median exposure		56 days		175 days
—Among pts ≥100&<126 (Bord) at BL	72	1.03 (-5.6, 7.6)	12	-9.31 (-18.2, -0.4)
Median exposure		56 days		176 days
—Among pts ≥126 (High) at BL	23	13.19 (-18.1, 44.5)	1	-21.62 (na)
Median exposure		57 days		70 days
Norm to Hi FGLU (<100 to ≥126)	261	3.1% (1.3, 5.9)	53	1.9% (0, 10.1)
Median exposure		55 days		175 days
Bord to Hi FGLU (≥100&<126 to ≥126)	72	11.1% (4.9, 20.7)	12	0% (0, 26.5)
Median exposure		55 days		176 days
LOCF mean change NFGLU (mg/dL)	2354	4.95 (3.46, 6.43)	814	5.13 (2.58, 7.68)
Median exposure		125 days		335 days
—Among pts <140 (Norm) at BL	2154	6.04 (4.96, 7.12)	737	7.06 (5.2, 8.9)
Median exposure		123 days		335 days
—Among pts ≥140&<200 (Bord) at BL	124	2.17 (-10.9, 15.2)	42	-7.41 (-23.3, 8.5)
Median exposure		132 days		395
—Among pts ≥200 (High) at BL	76	-21.49 (-48.5, 5.5)	35	-20.41 (-61.9, 21.1)
Median exposure		151 days		276 days
Norm to Hi NFGLU (<140 to ≥200)	2154	1.8% (1.3, 2.5)	737	2.7% (1.7, 4.2)
Median exposure		120 days		330 days
Bord to Hi NFGLU (≥140&<200 to ≥200)	124	32.3% (24.1, 41.2)	42	31.0% (17.6, 47.1)
Median exposure		84 days		287 days
Norm to v.Hi NFGLU (<140 to ≥300)	2154	0.2% (0.1, 0.5)	737	0.1% (0, 0.8)
Median exposure		123 days		334 days
Urinary glucose present (%)	1998	3.3% (2.5, 4.1)	651	4.3% (2.9, 6.2)
Median exposure		119 days		356 days
Norm to Hi fructos (<285 to ≥285)	684	3.2% (2.0, 4.8)	160	2.5% (0.7, 6.3)
Median exposure		63 days		86 days
LOCF mean change in HbA1c (%)	946	0.49% (-0.41, 1.39)	235	0.06% (-0.02, 0.14)
Median exposure		63 days		91 days
Norm to Hi HbA1c (<6.1% to ≥6.1%)	741	7.7% (5.9, 9.9)	203	6.9% (3.8, 11.3)
Median exposure		63 days		94 days

Abbreviations: bord = borderline; FGLU = fasting glucose; fructos = fructosamine; CI = confidence interval; gluc = glucose; HbA1c = hemoglobin A1c; Hi = High; LOCF = last observation carried forward; N = number of patients in analysis; na = not applicable; NFGLU = nonfasting glucose; norm = normal; pts = patients; v = very.

In controlled trials of OFC, statistically significantly higher proportions of OFC-treated subjects had treatment-emergent significant changes in random glucose compared to placebo (Sponsor Table 6.34 from the 10/04/07 submission below.)

Table 6.34.

Glucose
Treatment-Emergent Clinically Significant Changes (ADA Guidelines): All Patients
OFC Adult Controlled Database (Continued)

Lab Test	Categories	Therapy	Mean Modal Dose (mg)	Exposure (days) (min,Q1,Q2,Q3,max)	N	n	%	*P-values	
								Overall	OFC vs.
Glucose, Non-Fasting	Normal to High (<140 mg/dL to >=200 mg/dL)	OFC	8.5/39.2	Lab: (3,44,56,70,112) Trt: (3,53,57,74,116)	609	14	2.3	.088	
		FLX	42.0	Lab: (3,49,56,59,115) Trt: (4,53,56,60,130)	381	6	1.6		.494
		OLZ	9.7	Lab: (1,36,56,57,112) Trt: (1,42,56,58,112)	692	10	1.4		.304
		PLA	0.0	Lab: (3,28,44,56,112) Trt: (3,28,43,56,112)	346	1	0.3		.014
	Borderline to High (>=140-<200 mg/dL to >=200 mg/dL)	OFC	7.9/39.2	Lab: (5,16,56,64, 92) Trt: (6,53,57,84, 94)	44	15	34.1	.002	
		FLX	36.8	Lab: (6,35,56,61, 92) Trt: (6,51,58,61, 92)	17	2	11.8		.114
		OLZ	10.9	Lab: (7,28,51,56, 64) Trt: (26,34,55,58, 83)	35	13	37.1		.816
		PLA	0.0	Lab: (6,28,41,56, 59) Trt: (6,28,43,56, 58)	28	1	3.6		.003
	Normal/Borderline to High (<200 mg/dL to >=200 mg/dL)	OFC	8.5/39.2	Lab: (3,43,56,70,112) Trt: (3,53,57,77,116)	653	29	4.4	.001	
		FLX	41.8	Lab: (3,48,56,59,115) Trt: (4,53,56,61,130)	398	8	2.0		.039
		OLZ	9.7	Lab: (1,35,55,57,112) Trt: (1,42,56,58,112)	727	23	3.2		.257
		PLA	0.0	Lab: (3,28,43,56,112) Trt: (3,28,43,56,112)	374	2	0.5		<.001

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

OFC = olanzapine + fluoxetine combination, FLX = fluoxetine, OLZ = olanzapine, PLA = placebo.

N = number of randomized patients having both baseline and post-baseline measurements and meeting the baseline inclusion criteria.

n = number of patients meeting the post-baseline criteria.

* Frequencies analyzed using Fisher's exact test.

Included studies: HCKB, HDAO, HGFR, HGGG, HGGY, HGHZ, HGIE.

Sponsor Table 7.12.1 from the 12/19/07 submission summarizes mean changes for glucose-related laboratory analytes for patients with at least 48 weeks of exposure. The mean change in nonfasting glucose in patients exposed at least 48 weeks, was 5.9 mg/dL (N=425).

Table 7.12.1.

Glucose-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF) Overall
OFC Adult Integrated Database: Patients with at Least 48 Weeks of Exposure

All patients with at least 48 weeks of exposure

Analytes	Unit	Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	N	Baseline		Change to Endpoint		95% CI for Mean Change	
						Mean	Std	Mean	Std	Lower	Upper
Glucose, Non-Fasting	mg/dL	OFC	8.4/49.8	Lab: (85,371,447,532,669)	425	104.16	37.68	5.86	38.56	2.18	9.54
				Trt: (337,383,448,532,669)							
Fructosamine	umol/L	OFC	8.2/50.0	Lab: (60,84,86,361,470)	128	229.88	36.08	8.46	35.45	2.26	14.66
				Trt: (348,387,437,455,538)							
Hemoglobin A1c	%	OFC	8.3/50.2	Lab: (7,84,86,357,470)	123	5.78	0.97	0.10	0.79	-0.04	0.24
				Trt: (348,391,440,455,538)							

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

OFC = olanzapine + fluoxetine combination.

Included studies for Glucose, Non-Fasting: HGGG, HGIE, HGIP.

Included studies for Fructosamine: HGIE.

Included studies for Hemoglobin A1c: HGIE.

N = Number of patients having both baseline and post-baseline measurements.

Sponsor Table 7.12.6 from the 12/19/07 submission displays the proportion of OFC-treated subjects with at least 48 weeks of treatment exposure who had clinically treatment-emergent changes in glucose; proportions for each category in this table are numerically higher compared to similar analyses for subjects with up to 12 weeks of treatment exposure.

**Table 7.12.6. Fasting and Nonfasting Glucose
Treatment-Emergent Significant Changes Overall
OFC Adult Integrated Database: Patients with at Least 48 Weeks of Exposure**

All patients with at least 48 weeks of exposure

Lab test: Glucose, Non-Fasting

Categories	Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	N	n	95% CI for Percent		
						%	Lower	Upper
Normal to High (<140 mg/dL to >=200 mg/dL)	OFC	8.4/49.9	Lab: (25,369,440,532,669) Trt: (337,379,448,533,669)	382	12	3.1	1.6	5.4
Borderline to High (>=140 and < 200 mg/dL to >=200 mg/dL)	OFC	8.2/50.9	Lab: (15,84,407,495,549) Trt: (356,407,473,537,567)	27	10	37.0	19.4	57.6
Normal/Borderline to High (<200 mg/dL to >=200 mg/dL)	OFC	8.4/49.9	Lab: (15,366,440,532,669) Trt: (337,383,448,533,669)	409	22	5.4	3.4	8.0
<140 mg/dL to >=300 mg/dL	OFC	8.4/49.9	Lab: (25,370,445,532,669) Trt: (337,379,448,533,669)	382	1	0.3	0.0	1.4

OFC = olanzapine + fluoxetine combination.

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

Included studies: HGGA, HGIN, HGIP.

N = Number of patients having both baseline and post-baseline measurements and meeting the baseline inclusion criteria.

n = Number of patients meeting the post-baseline criteria.

IV.3. Hyperglycemia: Olanzapine Adolescent Subjects

Sponsor Table 6.14 below displays results for adolescent subjects in placebo-controlled trials for mean change in fasting glucose, which was statistically significantly different for olanzapine (+2.68 mg/dL) and placebo (-2.59 mg/dL).

**Table 6.14. Glucose-Related Laboratory Analytes
Mean Change from Baseline to Endpoint (LOCF): All Patients
Olanzapine Adolescent Placebo-Controlled Database**

Analytes	Unit	Therapy	Mean Modal Dose (mg)	Exposure (days) (Min,Q1,Q2,Q3,Max)	N	Baseline		Change to Endpoint		p-value*	
						Mean	Std	Mean	Std	Within Treatment	p-value
Glucose, Fasting	mg/dL	OLZ	11.7	Lab: (5,21,22,41,57) Trt: (5,21,22,42,84)	138	88.30	9.86	2.68	10.46	.003	<.001
		PLA	0.0	Lab: (4,19,21,34,88) Trt: (4,19,21,35,88)	66	89.60	10.17	-2.59	10.10	.041	
Glucose, Non-Fasting	mg/dL	OLZ	11.5	Lab: (4,14,21,35,338) Trt: (4,21,23,42,338)	160	90.27	14.57	2.33	20.03	.143	.610
		PLA	0.0	Lab: (5,14,15,35,382) Trt: (5,20,22,42,382)	93	89.62	14.40	0.58	20.91	.790	
Hemoglobin A1c	%	OLZ	7.9	Lab: (5,11,18,49,49) Trt: (5,11,18,49,49)	6	5.05	0.26	-0.03	0.05	.175	.952
		PLA	0.0	Lab: (21,21,21,43,43) Trt: (21,21,21,43,43)	3	4.97	0.59	-0.03	0.06	.423	

All of the protocols in this database specified that Hemoglobin A1c be collected only for known diabetics or when clinically indicated.

Q1 = 1st quartile, Q2 = 2nd quartile (median), Q3 = 3rd quartile.

OLZ = Olanzapine; PLA = Placebo.

Included studies for Glucose, Fasting: HGIN, HGIU, HGKL.

Included studies for Glucose, Non-Fasting: HGGF, HGIN, HGIU, HGKL.

Included studies for Hemoglobin A1c: HGIN, HGIU.

N = Number of patients having both baseline and post-baseline measurements.

*p-value for one sample t-test.

**p-value is from Type III Sum of Square from the ANOVA model: Change=Therapy Protocol.

Program Name: RMP.H6PSREG2.SASPGM(LOGLULB1) 12JUL07

Output Location: RMP.H6PSREG2.OUTPUT(LOGLULB1)

In the 3 placebo-controlled olanzapine monotherapy studies of adolescent patients (trial duration 3-6 weeks) olanzapine-treated subjects had a statistically significantly greater mean change in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). In patients with baseline normal fasting glucose levels (<100 mg/dL), zero out of 124 (0%) of those treated with olanzapine were found to have high glucose levels (≥ 126 mg/dL) during olanzapine treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥ 100 mg/dL and <126 mg/dL), 2 out of 14 (14.3%) of those treated with olanzapine were found to have high glucose levels (≥ 126 mg/dL) during olanzapine treatment versus zero out of 13 (0%) of those treated with placebo.

Sponsor Table 2.8 below displays glucose-related analyses for olanzapine long term integrated controlled and non-controlled data. Mean increases in glucose from baseline to endpoint were 1.74 mg/dL for fasting glucose (median exposure of 63 days) and 3.66 mg/dL for nonfasting glucose (median exposure of 126 days). In analyses of mean change by baseline value for the Olanzapine Adolescent Integrated database, patients with normal glucose at baseline had increases from baseline to endpoint (3.14 mg/dL for fasting glucose and 4.28 mg/dL for nonfasting glucose), while patients with borderline glucose at baseline had an overall mean decrease (-3.83 mg/dL for fasting glucose and -48.02 mg/dL for nonfasting glucose [N=4 in the latter analysis]). There were only 2 patients who had high glucose at baseline (both with fasting only); these patients had a mean decrease from baseline to endpoint (-44.14 mg/dL). In the subset of patients with at least 24 weeks of exposure, there was a mean increase in glucose, with larger mean increases among patients with normal baseline glucose and a smaller mean increase (fasting) or mean decrease (nonfasting) among patients with borderline baseline values.

Among olanzapine-treated adolescents with normal glucose at baseline, 1.2% experienced high fasting glucose at least once, 0.3% experienced high nonfasting glucose at least once, and none experienced “very high” nonfasting glucose. Among patients with borderline fasting glucose at baseline, 12.5% experienced high fasting glucose at least once; no patients had shifts from borderline to high nonfasting glucose. No patients experienced a shift from normal nonfasting glucose to very high. Mean change in HbA1c from baseline to endpoint was a decrease, -0.04% (median exposure of 37 days). No patients experienced a shift from normal to abnormal HbA1c. Glucose was detected in the urine of 0.6% of all patients.

Table 2.8. Glucose Data from the Olanzapine Adolescent Integrated Database
All Patients and Patients with at Least 24 weeks' Exposure

OLANZAPINE ADOLESCENT Glucose	All patients		With ≥24 weeks' exposure	
	N	estimate (95% CI)	N	estimate (95% CI)
LOCF mean change FGLU (mg/dL)	306	1.74 (0.29, 3.19)	121	3.13 (0.70, 5.55)
Median exposure		63 days		202 days
—Among pts <100 (Norm) at BL	256	3.14 (1.86, 4.41)	108	3.45 (1.59, 5.32)
Median exposure		82 days		202 days
—Among pts ≥100&<126 (Bord) at BL	48	-3.83 (-9.1, 1.4)	13	0.42 (-18.3, 19.1)
Median exposure		33 days		202 days
Norm to Hi FGLU (<100 to ≥126)	256	1.2% (0.2, 3.4)	108	0.9% (0.0, 5.1)
Median exposure		78 days		202 days
Bord to Hi FGLU (≥100&<126 to ≥126)	48	12.5% (4.7, 25.2)	13	23.1% (5, 53.8)
Median exposure		33 days		186 days
LOCF mean change NFGU (mg/dL)	341	3.66 (1.27, 6.06)	159	5.96 (2.27, 9.64)
Median exposure		126 days		173 days
—Among pts <140 (Norm) at BL	337	4.28 (1.96, 6.60)	158	6.62 (3.15, 10.09)
Median exposure		127 days		173 days
—Among pts ≥140&<200 (Bord) at BL	4	-48.02 (-109.7, 13.7)	1	-99.10 (na)
Median exposure		42 days		127 days
Norm to Hi NFGU (<140 to ≥200)	337	0.3% (0, 1.6)	158	0.6% (0, 3.5)
Median exposure		127 days		173 days
Bord to Hi NFGU (≥140&<200 to ≥200)	4	0% (0, 60.2)	1	0% (0, 97.5)
Median exposure		42 days		127 days
Norm to v.Hi NFGU (<140 to ≥300)	337	0% (0, 1.1)	158	0% (0, 2.3)
Median exposure		127 days		173 days
Urinary glucose present (%)	357	0.6% (0.1, 2.0)	146	1.4% (0.2, 4.9)
Median exposure		72 days		202 days
LOCF mean change in HbA1c (%)	24	-0.04% (-0.15, 0.08)	7	-0.04% (-0.16, 0.07)
Median exposure		37 days		99 days
Norm to Hi HbA1c (<6.1% to ≥6.1%)	24	0% (0, 14.2)	7	0% (0, 41.0)
Median exposure		37 days		99 days

Abbreviations: bord = borderline; FGLU = fasting glucose; CI = confidence interval; gluc = glucose; HbA1c = hemoglobin A1c; Hi = High; LOCF = last observation carried forward; N = number of patients in analysis; NFGU = nonfasting glucose; norm = normal; pts = patients; v = very.

IV.4. Hyperglycemia: Antipsychotic-Naïve Subjects

Sponsor Table 2.4.5 presents glucose data for the adult olanzapine antipsychotic-naïve databases (placebo-controlled, haloperidol-controlled, and overall integrated), with comparison data from the 3 comparable databases in adults.

In the Olanzapine Adult Antipsychotic-Naïve, Placebo-Controlled Database, olanzapine-treated antipsychotic-naïve adults had mean increases in both fasting and nonfasting glucose, which were greater than increases observed in placebo-treated antipsychotic-naïve adults, but not statistically significant. Compared to placebo-treated antipsychotic-naïve adults, numerically lower proportions of olanzapine-treated antipsychotic-naïve adults had categorical

changes for fasting glucose, but numerically higher proportions had categorical changes for nonfasting glucose.

Compared to the olanzapine-treated adults as a whole, mean changes in fasting and nonfasting glucose were greater for olanzapine-treated antipsychotic-naïve adults, but proportions with categorical changes were lower (with the exception of proportion with shift from normal to high nonfasting glucose). Differences in proportions of olanzapine-treated antipsychotic-naïve adults and olanzapine-treated adults overall with treatment-emergent categorical changes that exceeded 5 percentage points included those for proportions with shifts from borderline to high fasting glucose, and absolute increases of a given magnitude for both fasting and nonfasting glucose, all of which were higher in the adult population as a whole.

In the Olanzapine Adult Antipsychotic-Naïve, Haloperidol-Controlled Database, fasting glucose measurements were not collected. In the nonfasting glucose analyses, olanzapine-treated antipsychotic-naïve adults had a statistically significantly higher mean increase in nonfasting glucose and a statistically significantly higher incidence of increases in nonfasting glucose of ≥ 20 mg/dL than did haloperidol-treated antipsychotic-naïve patients. In addition, proportions of olanzapine-treated antipsychotic-naïve adults with shifts from normal to high and with upward shifts in general were numerically higher than for haloperidol-treated patients. Compared to adults overall, the magnitude of mean increase in nonfasting glucose for olanzapine-treated antipsychotic-naïve adults was greater (between 2 and 3 mg/dL), and proportions with categorical changes were either similar (shifts from normal to high and with upward shift overall) or substantially higher (proportions with increase of at least 20 mg/dL). (The sample size for analysis of borderline to high is too small to compare the 2 databases.)

In the Olanzapine Adult Antipsychotic-Naïve, Overall Integrated Database, olanzapine-treated antipsychotic-naïve adults had mean increases in fasting and nonfasting glucose, as did olanzapine-treated adults overall. The increases were about 2 mg/dL smaller for the antipsychotic-naïve population than for the adult population overall. For fasting glucose, proportions of olanzapine-treated antipsychotic-naïve adults with shifts to high, upward shifts in general, or absolute increases of at least 10 mg/dL were lower than proportions from the adult population overall. For nonfasting glucose, proportions of olanzapine-treated antipsychotic-naïve adults with these kinds of changes were generally more similar to corresponding proportions of adult patients, with no comparison differing by more than 4 percentage points except that for shifts from borderline to high in the subset of patients with at least 24 weeks of exposure, the analysis for which the antipsychotic-naïve sample size was 1 patient.

Table 2.4.5. Comparison of Selected Glucose Results: Adult Olanzapine Antipsychotic-Naïve Databases versus Comparable Databases for Overall Populations (Naïve and Non-Naïve)

Glucose (mg/dL) ^a	Placebo-Controlled Databases				Haloperidol-Controlled Databases				Overall Integrated Databases			
	AP-naïve Adults		Adults		AP-naïve Adults		Adults		All Exposures		≥24 Wks Exposure	
	Olz	Pla	Olz	Pla	Olz	Hal	Olz	Hal	AP-nv	All	AP-nv	All
Mean change FGLU	2.96	0.17	2.76	0.17	na	na	na	na	3.49	5.34	5.03	3.95
N	206	129	769	411					328	2925	53	1038
Norm→Hi FGLU (<100 to ≥126)	0%	1.9%	2.2%	3.4%	na	na	na	na	0.7%	7.0%	0%	8.9%
N	176	104	543	293					275	2063	43	716
Bord→Hi FGLU (≥100 & <126 to ≥126)	7.1%	13.6%	17.4%	11.5%	na	na	na	na	7%	21.6%	20%	21.7%
N	28	22	178	96					43	719	10	276
≥10 mg/dL increase in FGLU	31.1%	25.6%	38.6%	37.2%	na	na	na	na	37.8%	50.3%	49.1%	59.6%
N	206	129	769	411					328	2925	53	1038
Upward shift in FGLU categ. ^b	14.1%	10.1%	19.5%	16.3%	na	na	na	na	19.5%	36.3%	26.4%	45.2%
N	206	129	769	410					328	2922	53	1036
Mean change NFGU	7.11	1.93	4.22	-2.02	6.39	-4.38	3.90	-0.98	7.73	5.24	5.43	5.85
N	83	76	1150	787	67	55	2435	1304	534	7613	49	2930
Norm→Hi NFGU (<140 to ≥200)	2.4%	0%	0.9%	0.6%	1.6%	0%	1.7%	0.6%	2.0%	2.0%	2.1%	3.1%
N	82	75	1074	713	64	50	2248	1206	506	7077	48	2721
Bord→Hi NFGU (≥140 & <200 to ≥200)	0%	0%	19.4%	8.8%	0%	0%	19.9%	6.5%	28.6%	24.9%	0%	27.9%
N	1	1	62	57	3	5	141	77	21	398	1	154
≥20 mg/dL increase in NFGU	20.5%	15.8%	38.3%	25.8%	67.2%	30.9%	51.2%	40.4%	47.2%	46.4%	61.2%	57.8%
N	83	76	1150	787	67	55	2435	1304	534	7613	49	2930
Upward shift in NFGU categ. ^b	6.0%	1.3%	9.8%	5.1%	11.9%	3.6%	12.5%	9.4%	12.4%	14.5%	18.4%	20.7%
N	83	76	1145	784	67	55	2424	1298	531	7566	49	2912

Abbreviations: AP = antipsychotic; AP-nv = antipsychotic-naïve; Bord = borderline; categ. = category; FGLU = fasting glucose; Hal = haloperidol; Hi = high;

N = number of patients in analysis; na = not available; NFGU = nonfasting glucose; Norm = normal; Olz = olanzapine; Pla = placebo; Wks = weeks.

^a Shaded cells indicate statistically significant comparison between olanzapine and comparator at p<.05. No statistical comparisons made between databases.

^b Treatment groups in Olz Adult Placebo-Controlled Database not compared statistically for this analysis; N is patients not in highest category at baseline.

Sponsor Table 2.4.7 from the 05/08/08 submission compares the OFC Overall Integrated Antipsychotic-Naïve Databases with the OFC Adult Overall Integrated Database (Naïve and Non-Naïve). Mean increases in glucose were generally greater in antipsychotic naïve adults treated with OFC than in OFC-treated adults overall. Proportions of OFC-treated antipsychotic-naïve adults with categorical changes were consistently higher than were proportions of adults overall.

Table 2.4.7. Comparison of Selected Glucose Results: OFC Overall Integrated Antipsychotic-Naïve Databases versus OFC Adult Overall Integrated Database (Naïve and Non-Naïve)

Glucose (mg/dL) ^a	All Exposures		With ≥24 Wks Exposure	
	AP-Naïve	Overall	AP-Naïve	Overall
Mean change FGLU	16.33	3.37	na	np
N	61	356		
Norm to Hi FGLU (<100 to ≥126)	9.8%	3.1%	na	np
N	41	261		
Bord to Hi FGLU (≥100 & <126 to ≥126)	21.4%	11.1%	na	np
N	14	72		
≥10 mg/dL increase in FGLU	44.3%	29.8%	na	np
N	61	356		
Upward shift in FGLU categ. ^b	36.1%	20.2%	na	np
N	61	356		
Mean change NFGLU	6.29	4.95	5.60	5.13
N	1257	2354	507	814
Norm to Hi NFGLU (<140 to ≥200)	2.3%	1.8%	3.1%	2.7%
N	1153	2154	457	737
Bord to High NFGLU (≥140 & <200 to ≥200)	33.3%	32.3%	31%	31.0%
N	60	124	29	42
≥20 mg/dL increase in NFGLU	53.1%	44.8%	59.6%	53.8%
N	1257	2354	507	814
Upward shift in NFGLU categ. ^b	18.1%	15.0%	20.8%	18.5%
N	1243	2329	500	802

Abbreviations: AP = antipsychotic; Bord = borderline; categ. = category; FGLU = fasting glucose; Hi = high; N = number of patients in analysis; na = not available because there were no patients with this much exposure; NFGLU = nonfasting glucose; Norm = normal; np = not presented; OFC = olanzapine-fluoxetine combination; Pla = placebo; Wks = weeks.

^a There were no statistical comparisons made between databases.

^b N is the number of patients not in highest category at baseline.

Sponsor Table 2.4.6 from the 05/12/08 submission compares Olanzapine Adolescent Antipsychotic-Naïve, Placebo-Controlled Database and the Olanzapine Adolescent Antipsychotic-Naïve, Overall Integrated Database with corresponding databases combining naïve and non-naïve subjects. Olanzapine-treated antipsychotic-naïve adolescents had mean increases in both fasting and nonfasting glucose, while placebo-treated antipsychotic-naïve adolescents had mean decreases. The difference between treatment groups was statistically significant for fasting glucose. Compared to olanzapine adolescents overall, olanzapine-treated

antipsychotic-naïve adolescents had slightly higher mean increases in fasting and nonfasting glucose.

Table 2.4.6. Comparison of Selected Glucose Results: Adolescent Olanzapine Antipsychotic-Naïve Databases versus Comparable Databases for Overall Adolescent Populations (Naïve and Non-Naïve)

	Placebo-Controlled Adolescent Databases				Overall Integrated Adolescent Databases			
	AP-naïve Adol		Adolescents		All Exposures		≥24 Wks Exposure	
Glucose (mg/dL) ^a	Olz	Pla	Olz	Pla	AP-naïve	All	AP-naïve	All
Mean change FGLU	3.26	-2.75	2.68	-2.59	2.07	1.74	4.03	3.13
N	84	38	138	66	186	306	72	121
Norm to Hi FGLU (<100 to ≥126)	0%	0%	0%	1.9%	0%	1.2%	0%	0.9%
N	74	33	124	53	162	256	65	108
Bord to Hi FGLU (≥100 & <126 to ≥126)	10%	0%	14.3%	0%	13%	12.5%	14.3%	23.1%
N	10	5	14	13	23	48	7	13
≥10 mg/dL increase in FGLU	29.8%	15.8%	26.8%	13.6%	30.6%	34.6%	33.3%	38.8%
N	84	38	138	66	186	306	72	121
Upward shift in FGLU categ. ^b	19%	0%	16.7%	1.5%	21.5%	22.9%	27.8%	32.2%
N	84	38	138	66	186	306	72	121
Mean change NFGU	4.22	-0.22	2.33	0.58	4.97	3.66	6.61	5.96
N	100	61	160	93	205	341	88	159
Norm to Hi NFGU (<140 to ≥200)	0%	0%	0.0%	1.1%	0.5%	0.3%	1.1%	0.6%
N	100	61	160	93	204	337	88	158
Bord to High NFGU (≥140 & <200 to ≥200)	na	na	na	na	0%	0%	na	0%
N					1	4		1
≥20 mg/dL increase in NFGU	31%	11.5%	31.9%	15.1%	44.9%	46.3%	52.3%	53.5%
N	100	61	160	93	205	341	88	159
Upward shift in NFGU categ. ^b	4%	0%	6.9%	2.2%	7.8%	8.5%	9.1%	11.3%
N	100	61	160	93	205	341	88	159

Abbreviations: Adol = adolescent; AP = antipsychotic; Bord = borderline; categ. = category; FGLU = fasting glucose; Hi = high; N = number of patients in analysis; NFGU = nonfasting glucose; Norm = normal; Olz = olanzapine; Pla = placebo; Wks = weeks.

^a Shaded cells indicate a statistically significant comparison at $p < .05$. There were no statistical comparisons made between databases.

^b Treatment groups in the Olz Adolescent Placebo-Controlled Database were not compared statistically. N is patients not in highest category at baseline.

IV.5. Hyperglycemia: Lilly Healthy Volunteer Glucose Clamp Studies

IV.5.1. Lilly Study S013

Lilly Study S013 was a single blind study comparing olanzapine, risperidone, and placebo. A euglycemic glucose clamp as performed before and after three weeks of treatment. The stated purpose of the study was to determine if olanzapine had any adverse effects on metabolic parameters in non-diabetic subjects. The results for olanzapine versus placebo comparison will be discussed below.

The olanzapine group consisted of 17 males and 5 females. They were 91% Caucasian with mean age of 35 years. The placebo group consisted of 13 males and 6 females. They were 58% Caucasian with mean age of 32 years. Olanzapine was given at 2.5 mg per day for two days, 5 mg per day for 2 days and 10-mg per day thereafter for a total of three weeks. The study was performed in a metabolic unit. Patients were allowed up to three, 72 hour passes. The blinded period was preceded by 3-7 days of diet stabilization.

At baseline, approximate mean values for both groups were glucose 87 mg/dl, C peptide 1.6 ng/ml, and insulin 6-7 uU/ml. At endpoint, fasting blood glucose increased 2.3 mg/dl ($P=0.028$) in the olanzapine-treated group and increased 0.34 mg/dl (NS) in the placebo-treated group. C peptide rose 0.34 ($P=0.002$) in the olanzapine-treated group with no change in the placebo-treated group. Mean triglyceride level in the olanzapine-treated group was 88 mg/dl at baseline; triglycerides increased 26 mg/dl ($P=0.006$) post-treatment. Mean triglycerides at

baseline were 119 mg/dl in the placebo group; triglycerides fell 4 mg/dl (NS) post-treatment. Mean body weight in both groups at baseline was approximately 70 kg. The mean weight change in the olanzapine-treated group was +1.95 kg ($P<0.001$), compared with -0.22 kg (NS) in the placebo-treated group. Meal tolerance tests showed an increase in glucose AUC from baseline to endpoint ($P=0.02$) in the olanzapine group, which was statistically different ($P=0.033$) from the small decrease (NS) in the placebo group.

IV.5.2. Lilly Study HGIM

Study HGIM was a double-blind placebo-controlled study to evaluate whether olanzapine or risperidone had a direct effect to impair insulin secretion as assessed by a hyperglycemic clamp. The study consisted of 2-4 days of diet stabilization followed by a 14-16 day comparison of olanzapine 10 mg/day, risperidone, 4 mg/day and placebo. Hyperglycemic clamps were performed at baseline and endpoint.

The study was performed in a clinical research center, except that subjects were allowed up to three 72-hour passes. The olanzapine arm contained 13 males and 4 females, 11 Caucasian and 6 African American, mean age 33 years. The placebo arm contained 13 males and 5 females, 13 Caucasian, and 5 African Americans, mean age 31 years.

Weight gain was reported as an adverse event in 8/17 olanzapine patients and zero placebo patients. From a mean baseline of about 73 kg in both groups, mean weight gain was 2.8 kg ($P<0.001$) in olanzapine-treated subjects compared with 0.5 kg in placebo-treated subjects ($P=0.10$). The difference between the two treatments was statistically significant ($P<0.001$). There was little change in fasting glucose or insulin in the placebo group. For glucose, there was a mean increase 0.43 mg/dl in olanzapine-treated subjects versus a change of -1.5 mg/dl in placebo-treated subjects; neither the intragroup change nor the between group differences were statistically significant. There was a mean increase in fasting insulin of 3.3 uU/ml in olanzapine-treated subjects ($p=0.03$), versus a decrease of 2.3 uU/ml on placebo (NS). The difference between the two groups was statistically significant ($P=0.01$). However, using BMI as a covariate, neither the change in baseline nor between-group difference was statistically significant.

There was a statistically significant decrease ($P=0.038$) in insulin sensitivity index with olanzapine for the final four clamp measurements. The difference from placebo was marginally significant ($P=0.06$) using a parametric test and significant ($P=0.025$) using a non-parametric test. The decrease in insulin sensitivity index in olanzapine-treated subjects was 18% (absolute values not stated.) When BMI change was used as a covariate, neither the change from baseline with olanzapine nor the difference from placebo was statistically significant.

IV.6. Hyperglycemia: Reviewer Comment

IV.6.1. Hyperglycemia: Summary

Mean increases in nonfasting glucose were statistically significantly greater for adult patients treated with olanzapine than for patients treated with placebo. Mean increases in fasting

glucose were also higher for adult patients treated with olanzapine, but the differences were not statistically significant. Differences between olanzapine-treated subjects and placebo-treated subjects in glucose-related laboratory analytes were greater in subjects categorized as having baseline potential glucose dysregulation. In categorical analyses, patients with baseline borderline glucose levels, olanzapine-treated patients experienced a greater percentage in upward shift (high) of glucose levels compared with the placebo-treated patients. The incidence of treatment-emergent glycosuria was statistically significantly higher for olanzapine-treated patients compared with placebo-treated patients.

Mean increases in glucose were generally greater in antipsychotic-naïve adults treated with OFC than in OFC-treated adults overall. Mean increases in glucose were generally greater in antipsychotic-naïve adolescents treated with olanzapine than in adolescents overall.

When comparing within-group changes in nonfasting glucose for OFC and olanzapine with within-group changes for olanzapine in the Olanzapine Adult Placebo-Controlled Database, the nonfasting glucose mean change is greater overall in the OFC Controlled database, and most pronounced in patients with baseline glucose elevations or with baseline potential glucose dysregulation. In categorical analyses of patients with normal baseline nonfasting glucose who developed borderline or high post-baseline values, higher proportions of OFC-treated patients experienced shifts upward compared with placebo-treated patients. Furthermore, among patients with borderline glucose at baseline, a higher percentage of OFC-treated patients than placebo-treated patients had an upward shift in glucose level (to “high”).

IV.6.2. Hyperglycemia: Proposed and Recommended Prescribing Information

IV.6.2.1. Zyprexa Hyperglycemia Labeling: Sponsor Proposal

On May 14, 2008 the sponsor proposed the following labeling language in the Warnings and Precautions section:

(b) (4)

V. Future FDA Actions

Labeling recommendations outlines in this review will be communicated to the sponsor. A proposal for a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide, will be requested from the sponsor.

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

/s/

Evelyn K Mentari
7/15/2008 03:20:26 PM
MEDICAL OFFICER

Sally Yasuda
7/15/2008 04:43:35 PM
BIOPHARMACEUTICS

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

DATE: March 23, 2007

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

SUBJECT: Recommendation for approvable action for Symbyax (olanzapine/fluoxetine) for treatment resistant depression (TRD) (short-term efficacy only)

TO: File NDA 21-520/S-012
[Note: This overview should be filed with the 9-28-06 original submission of this supplement.]

1.0 BACKGROUND

Symbyax (olanzapine/fluoxetine) is currently approved for bipolar depression. This NDA seeks a claim for the short-term treatment of “treatment resistant depression (TRD)” in a dose range of 3/25 to 12/50 mg/day. There are, as yet, no drugs approved for the treatment of TRD. Although it is widely appreciated in the clinical community that a substantial fraction of patients with MDD do not respond adequately to available antidepressant treatments, there is not, to my knowledge, a widely accepted definition of TRD. In fact, Lilly modified its definition of this entity over the course of its development program. In its original pilot study (HGFR), patients must have failed 2 treatments in the current episode. However, in the next 2 studies (HGIE and HGHZ), patients needed only a history of failure on an antidepressant, along with failure in the current episode. When Lilly recognized that this more liberal approach to defining TRD was not succeeding, they went back to their original definition for the final 2 trials (HDAO 1 and 2).

The studies supporting this claim were conducted under IND 28,705. We had several meetings with Lilly over the course of this development program.

2.0 CHEMISTRY

There were no CMC issues requiring review as part of this application, except for EA. The sponsor sought a categorical exclusion from this requirement, which was granted.

3.0 PHARMACOLOGY

There were no pharmacology/toxicology issues requiring review as part of this application.

4.0 BIOPHARMACEUTICS

There were no biopharmaceutics issues requiring review as part of this application.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

The focus of our review was on 5 double-blind, randomized, parallel-group, multicenter, short-term efficacy and safety trials involving the olanzapine/fluoxetine combination (OFC) in adult patients with “treatment resistant depression (TRD).” These studies were, in order of their conduct: HGFR; HGIE; HGHZ; HDAO-1; HDAO-2. All 5 studies compared OFC to each of olanzapine and fluoxetine alone. These studies ranged in duration from 8 to 12 weeks, and except for HGIE, were of flexible dose design (6/25, 6/50, 12/25, 12/50, or 18/50). Study HGIE was the only 12 week study; the others were all 8 weeks. The primary endpoint was change from baseline to endpoint in MADRS total score for all studies except for HGFR, where it was change from baseline to endpoint in HAMD-21 total score.

All of these studies required patients to meet criteria for MDD and to have failed to respond to adequate treatment with at least 2 antidepressants (i.e., adequate dose and duration). For all 5 studies, one of these failures had to be during a prospective 6-8 week lead-in phase on one of the following drugs: fluoxetine (HDAO and HGFR); venlafaxine (HGIE); nortriptyline (HGHZ). For 3 of these studies (HGFR; HDAO-1; HDAO-2), both of the failures had to be in the current episode of MDD.

Results of individual studies:

-HGFR: This small pilot study failed to show superiority of OFC to fluoxetine and olanzapine on the primary endpoint of HAMD-21 ($p=0.06$ and 0.19 , respectively), however it did show superiority of OFC to both individual arms on the MADRS.

-HGIE: This was the only fixed dose study, comparing 4 doses of OFC (6/25, 6/50, 12/25, 12/50) vs olanzapine alone, fluoxetine alone, and venlafaxine alone. All 4 OFC doses were superior to olanzapine (with no evidence for dose/response), but none was superior to fluoxetine or venlafaxine on the MADRS at the 12-week endpoint (however, both were comparisons were positive at 8 weeks). However, when the analysis was restricted to the subset of patients who failed on antidepressant treatment within the same episode (one failure by history and one prospective failure, i.e., the same criteria as those used in studies HGFR, and HDAO 1 & 2, OFC was superior to both fluoxetine ($p=0.021$) and olanzapine ($p=0.003$) at 12 weeks. Dr. Chen does

note that the superiority over olanzapine in this subset is only seen at week 12, and not at week 8.

-HGHZ: This study showed superiority of OFC to olanzapine alone, but not to fluoxetine alone or to nortriptyline alone. In addition, when the analysis was restricted to the subset of patients who failed on antidepressant treatment within the same episode (one failure by history and one prospective failure, i.e., the same criteria as those used in studies HGFR, and HDAO 1 & 2, OFC was superior only to olanzapine, and, again, not to fluoxetine or nortriptyline.

-HDAO-1: This was a negative study that showed no benefit of OFC over each drug alone.

-HDAO-2: This was a positive study, showing superiority for OFC over both individual drugs on the primary endpoint.

5.1.2 Comment on Other Important Clinical Issues Regarding the Efficacy Data

Evidence Bearing on the Question of Dose/Response for Efficacy

The only information pertinent to dose/response for efficacy in this program came from study HGIE, and these data did not suggest dose/response.

Secondary Efficacy Variables

There was some additional support for OFC from secondary endpoints, (b) (4)

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of age, gender, and race. There was no indication of any difference in effectiveness based on gender.

Size of Treatment Effect

The effect sizes observed in the positive trials were substantial compared to those seen in typical MDD trials.

Duration of Treatment

The sponsor presented no data pertinent to longer-term efficacy for TRD in this supplement. We will request such studies as a phase 4 commitment.

5.1.3 Conclusions Regarding Efficacy Data

In summary, the results are mixed from this set of 5 studies of OFC in TRD. Study HDAO-2 is clearly positive, while studies HDAO-1 and HGHZ are negative. I agree with Drs. Zhang and Mathis that the 2 other studies (HGFR and HGIE) provide substantial support. Although not positive on the primary endpoint for the OFC vs fluoxetine comparison, study HGFR was positive for this comparison on the MADRS, which is probably a more specific measure of core

depressive symptoms than the HAMD-21. Although not positive on the primary endpoint for the OFC vs fluoxetine comparison in the originally randomized sample, study HGIE was positive for this comparison for the subset of patients who met the stricter criteria for TRD. Although this is a post-hoc comparison, I think it is an eminently reasonable comparison. Thus, I consider these data, overall, to provide sufficient support for the efficacy of OFC in TRD (more conservatively defined) to justify the approval of this new claim. Dr. Chen, the statistical reviewer, is more circumspect in her views on this application, and considers HDAO-2 to be the only reliable source of evidence to support this new claim. She expresses reservations about accepting evidence from studies HGFR and HGIE as supportive. However, she does seem to concede that study HGIE, at least for the subgroup of interest, might be considered a source of support. We will request longer-term efficacy trials as a phase 4 commitment.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review and Overview of Findings

The safety data for this supplement were derived from a total of n=771 patients exposed to OFC across 10 short-term (up to 12 weeks) placebo-controlled clinical trials comprising programs for TRD, bipolar depression, and MDD. The observed common adverse events profile seen in TRD patients was consistent with that seen in the other indications studied, as were the laboratory, vital signs, and ECG data, generally. However, there were findings regarding changes in weight, glucose and lipids, for both OFC and olanzapine alone, that are not adequately reflected in current Symbyax or Zyprexa labeling, and are not adequately addressed by the new changes proposed for this supplement. Thus, we are asking for an extensive search for data by the sponsor to address these concerns. This information will be needed to support relevant changes to labeling.

5.2.2 Conclusions Regarding Safety

The adverse event profile and other safety findings for OFC in the treatment of TRD were quite similar to those seen in the other indications studied for this combination product. However, as noted, we will need more information and more changes regarding weight, glucose and lipids.

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 apparently did not provide a literature review as part of this supplement. Dr. Zhang did conduct a PubMed search and found 31 pertinent papers. She indicated that papers revealed no new, important adverse events.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Symbyax is not approved anywhere at this time for TRD.

8.0 DSI INSPECTIONS

Inspections were conducted at 2 sites, one from each of the 2 studies we consider positive (or supportive), i.e., the positive HDAO study and study HGIE. Data from both sites were deemed to be acceptable.

9.0 LABELING AND APPROVABLE LETTER

9.1 Labeling

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

9.2 Foreign Labeling

To my knowledge, Symbyax is not approved anywhere at this time for TRD.

9.3 Approvable Letter

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

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has submitted sufficient data to support the conclusion that Symbyax is effective and acceptably safe in the treatment of TRD. However, before we can take an approval action, we will need to obtain all relevant safety information pertinent to our concerns about weight change, hyperglycemia, and hyperlipidemia. In addition, we need to reach agreement on labeling. Thus, we will issue the attached approvable letter along with our requests for additional information and our proposal for labeling, in anticipation of final approval.

cc:

Orig NDA 21-520

HFD-130

HFD-130/TLaughren/MMathis/NKhin/JZhang/RGrewal/WBender

DOC: Symbyax_TRD_Laughren_AE_Memo.doc

**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
3/23/2007 02:02:16 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: 23 March 2007

FROM: Mitchell V. Mathis, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 21-520/SE012 (This overview should be filed with the 28 September 2006 submission.)

SUBJECT: Recommendation of Approvable Action for olanzapine and fluoxetine in combination (Symbyax®) for the Treatment of Treatment Resistant Depression

1.0 BACKGROUND

Symbyax® (olanzapine/fluoxetine combination or OFC) is approved for the treatment of bipolar depression. It is a combination of two psychotropic medications—olanzapine, an atypical antipsychotic, and fluoxetine, a selective serotonin reuptake inhibitor. Lilly is seeking approval for the indication of treatment resistant depression (TRD) with this application.

On 18 August 1999 DPP met with Lilly and agreed that TRD was a legitimate target for pharmacologic intervention. Furthermore, it was agreed that TRD could be reasonably defined as failure to respond to two trials of antidepressants (of adequate dose and duration) within the current depressive episode.

Lilly's first trials did not meet their primary efficacy endpoints, and so on 16 January 2002 we met with them and agreed that more studies would be required. We also agreed that according to FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products, we would require at least one positive study and additional supporting studies to satisfy the efficacy requirements for claim in TRD.

On 14 April 2005 we met for pre-NDA discussion and agreed that the overall content and format of the planned submission would support a priority review for TRD. The submission was received as this sNDA on 28 September 2006 and filed on 7 November 2006.

This sNDA has been reviewed by Jing Zhang, M.D., Medical Officer, DPP and Yeh-Fong Chen, Ph.D., Office of Biostatistics. Because this is an approved product, the most relevant reviews are clinical and statistical.

2.0 CHEMISTRY

Symbyax® is an approved product and so there are no pending chemistry review issues other than an environmental assessment.

3.0 PHARMACOLOGY

Symbyax® is an approved product and so there are no pending pharmacology review issues.

4.0 CLINICAL PHARMACOLOGY

The Clinical Pharmacologists have no new information to review for this application.

5.0 CLINICAL DATA

5.1 Overview of Studies

A total of 5 double-blind, active-controlled studies (1 pilot and 4 pivotal) were conducted from May 1997 to May 2005 to evaluate the efficacy of OFC in the treatment of TRD. The database included efficacy data from each individual study report and a summary of clinical efficacy. The safety database is made up of patients from studies of several different depressive-spectrum diagnoses.

5.1.2 Definition of Treatment Resistant Depression

The definition of TRD is, of course, crucial in evaluating the efficacy of OFC in treatment-resistant patients. We have agreed with Lilly that treatment resistance is best defined as having failed two appropriately-dosed antidepressants (given for an adequate treatment period to expect response) during the current depressive episode. Studies HDAO 1 and 2, as well as study HGFR (pilot study, n=28) used this definition as an inclusion criterion, whereas HGIE and HGHZ, while requiring two treatment failures, did not by design require the two failures to occur during the current episode. For supportive evidence of the studies designed with the more conservative definition of TRD, the sponsor selected subsets of patients from studies HGIE and HGHZ who met the accepted definition of two antidepressant failures in the current episode and we reviewed those data (see Table 1 for inclusion criteria and Table 2 for summary of patients by study meeting the conservative definition of TRD).

Table 1: Summary of Key Inclusion Criteria in Each Individual Study

Study	HDAO 1&2	HGFR	HGIE	HGHZ
Age	18 - 65	18 - 65	18 or older	18 - 65
Severity of depression	HAMD-17 \geq 22	HAMD-21 \geq 20	CGI-Severity \geq 4	MADRS \geq 20
Historical failure to one adequate antidepressant trial*	Any antidepressant other than FLX for minimum 6 wks	Any non-SSRI for minimum 4 wks	Any SSRI for minimum 6 wks	Any SSRI for minimum 4 wks
Failed lead-in phase treatment**	FLX, 25-50 mg, for 8 wks	FLX, 20-60 mg, for 6 wks	VNL, 75-375 mg, for 7 wks	NRT, 25-175 mg, for 8 wks
Two failures in current episode	Yes	Yes	No	No

* defined as treatment with at least one antidepressant for at least 4 weeks at an acceptable dose

** defined by a < 30% improvement on the MADRS during lead-in phase

Table 2: Efficacy Summary of Patients with Two Antidepressant Failures in Current Depressive Episode by Study

Study	HDAO-1	HDAO-2	HGFR	HGIE	HGHZ
Sample Evaluated for Efficacy	OFC=101 FLX=102 OLZ=95	OFC=97 FLX=101 OLZ=102	OFC=10 FLX=10 OLZ=8	OFC=163 FLX=41 OLZ=47	OFC=91 FLX=88 OLZ=90

Source: Dr. Zhang's review.

5.1.3 Primary Efficacy Endpoint

Either change in MADRS (Study HDAO, HGIE and HGHZ) or change in HAM-D (Study HGFR) was used as the primary endpoint in the TRD studies reviewed in this submission.

Team Leader Comment: Both the MADRS and HAM-D are considered validated measures of efficacy for the evaluation of depression in clinical trials. Compared to the HAM-D, the MADRS is more heavily weighted with items that measure core mood symptoms of depression, as opposed to somatic and other non-core mood symptoms which are more heavily weighted in the HAM-D. Because olanzapine is sedating and appetite stimulating, it may improve sleep and appetite without changing the core symptoms of depression. Therefore, the MADRS should be the more accurate outcome measure in short-term studies that include olanzapine.

5.1.4 Study Design

All five studies shared a similar design: randomized, double-blind, parallel-group, multi-center trials which compared OFC to olanzapine monotherapy and fluoxetine monotherapy in patients with TRD. All studies consisted of 3 phases: lead-in, acute treatment, and open-label.

Patients with a history of having failed drug treatment for depression received fluoxetine (HDAO and HGFR), venlafaxine (HGIE), or nortriptyline (HGHZ) treatment for 6-8 weeks during the lead-in phase. Patients not responding to treatment during lead-in phase (TRD patients) were randomized to an 8-12 week acute treatment phase. A 1:1:1 ratio was used for treatment-group randomization to OFC, fluoxetine, and olanzapine in Study HDAO and HGFR. In Study HGHZ, a ratio of 1:1:1:0.5 was used for OFC, fluoxetine, olanzapine and nortriptyline treatment groups. Study HGIE was a dose ranging study with patients randomized to OFC 6/25, OFC 6/50, OFC 12/25, OFC 12/50, FLX, OLZ, VNL, and OFC 1/5 group. All studies except HGIE utilized flexible dosing designs (see table 3).

Table 3: Summary of Dose Information

Study	Lead-in Phase	Acute Treatment Phase
HDAO	FLX 25 or 50 mg/d, once daily	OFC 6/25, 12/50, or 18/50 mg/d, once daily in the evening FLX 50 mg/d, once daily in the evening OLZ 6, 12 or 18 mg/d, once daily in the evening
HGFR	FLX 20 to 60 mg/d, once daily in AM	FLX 20 to 60 mg/d, once daily in AM OLZ 5 to 20 mg/d, once daily in PM OLZ 5-20/FLX 20-60 mg/d, once daily PM/AM
HGIE	VNL 75 to 375 mg/d, once daily in PM	OFC 6/25, 6/50, 12/25, 12/50 or 1/5 mg/d, once daily in PM FLX 25 to 50 mg/d, once daily in PM OLZ 6-12 mg/d, once daily in PM VNL 75 to 375 mg/d, once daily in PM
HGHZ	NRT 25 to 175 mg/d, once daily in PM	OFC 6/25 or 12/50 mg/d, once daily in PM FLX 25 or 50 mg/d, once daily in PM OLZ 6 or 12 mg/d, once daily in PM NRT 25 to 175 mg/d, once daily in PM

Source: Dr. Zhang's review

The acute treatment phase was followed by an open-label extension phase throughout which eligible patients received OFC for 8 weeks to 6 months depending on study design.

5.2 Efficacy Data

5.2.1 Summary of Studies Pertinent to Efficacy Claim

HDAO-2

The mean change from baseline to endpoint on MADRS total score in Study HDAO-2 (LOCF) is shown in Table 4. OFC-treated patients had a statistically significantly greater mean decrease in the MADRS total score (-14.62) than both fluoxetine-treated patients (-8.96) and olanzapine-treated patients (-7.71). Patients treated with OFC had statistically significantly greater decreases on the MADRS total score than did the fluoxetine-treated patients at every week of the study, including endpoint; they also had statistically significantly greater decreases than did the olanzapine-treated patients at Week 1 and from Week 4 through endpoint (Week 8). The visit-wise OC analysis is consistent with these findings.

Table 4: Mean Change from Baseline to Endpoint on MADRS Total Score in Study HDAO-2 (LOCF)

	OFC N=97	FLX N=101	OLZ N=102	p-Values		
				Overall	OFC vs. FLX	OFC vs. OLZ
Baseline Mean (SD)	30.64 (6.12)	30.13 (5.91)	30.08 (6.33)			
Mean Change (SD)	-14.62 (10.22)	-8.96 (9.49)	-7.71 (8.2)	<0.001	<0.001	<0.001

Source: Dr. Zhang's review

Team Leader Comment: This study is pivotal in establishing the efficacy of OFC for TRD.

HGFR

The pre-specified primary outcome variable of Study HGFR was mean change from baseline to endpoint in HAMD-21 total score. The secondary variables were mean change from baseline to endpoint in MADRS total score and CGI-Severity scale. The study failed in the sense that OFC-

treated patients did not show statistically significant decrease in HAMD-21 total score compared to fluoxetine (OFC vs. FLX $p=0.061$) or olanzapine (OFC vs. OLZ $p=0.19$) monotherapy. However, for both MADRS and CGI-Severity, OFC treatment demonstrated statistical superiority to fluoxetine monotherapy and to olanzapine monotherapy. Table 5 summarizes the results for these endpoints; visit-wise OC analysis of mean change from baseline to endpoint in MADRS was consistent with the findings from the LOCF analysis.

Table 5: Mean Change from Baseline to Endpoint on MADRS Total Score and CGI-Severity in Study HGFR (LOCF)

	OFC N=10	FLX N=10	OLZ N=8	p-Values		
				Overall	OFC vs. FLX	OFC vs. OLZ
MADRS Total						
Baseline Mean (SD)	29.5 (9.2)	23.8 (8.3)	25 (3.8)			
Mean Change (SD)	-13.6 (11.9)	-1.2 (11.0)	-2.8 (6.0)	0.026	0.012	0.035
CGI-Severity						
Baseline Mean (SD)	4.6 (0.8)	4.3 (0.7)	4.3 (0.7)			
Mean Change (SD)	-2 (1.3)	-0.4 (1.2)	0 (0.9)	0.003	0.005	0.001

Source: Dr. Zhang's review.

Team Leader Comment: Although a small study, the more conservative definition of TRD was employed in patient selection and statistically significant separation from monotherapies was demonstrated using MADRS. I believe the MADRS to be the more appropriate clinical scale to measure the effect of olanzapine on the core symptoms of depression for the reasons cited in section 5.1.3 above. I consider this study to be supportive of the efficacy claim of OFC in TRD.

HGIE

Study HGIE was a dose-ranging study. Four different OFC doses (6/25, 6/50, 12/25 and 12/50) were chosen to assess the efficacy of OFC as compared to olanzapine, fluoxetine and venlafaxine in the treatment of TRD measured by mean change from baseline to endpoint (12 weeks) in MADRS total score. The OFC 6/25, OFC 6/50, OFC 12/25, and OFC 12/50 treatment groups each had statistically significantly greater mean decreases in MADRS total score compared with the OLZ treatment group. However, none of the individual OFC treatment groups were statistically significantly different from the FLX or VNL treatment groups. Examination of the mean change from baseline in MADRS suggested no evidence of dose-response. The composite OFC treatment group (composite of OFC 6/25, 6/50, 12/25 and 12/50 group) had a statistically significantly greater mean decrease in MADRS total score from baseline to endpoint compared with the OLZ treatment group. However, the composite OFC treatment group was not statistically significantly different at endpoint from the FLX or VNL treatment groups.

Mean change in MADRS total score was also examined within the subset of patients with two drug treatment failures during their current episode of MDD ($n = 251$). In this subset, the composite OFC treatment group demonstrated a statistically significantly greater mean decrease in MADRS total score compared with both the FLX ($p=0.021$) and OLZ ($p=0.003$) treatment group at endpoint.

Team Leader Comment: Study HGIE was conducted earlier in the development of OFC for TRD; at that time the definition of TRD included patients who had historically failed one antidepressant (not necessarily during the current depressive episode), and then failed to respond to the lead-in

treatment (second antidepressant). When the data are examined using the more conservative definition of having failed two drugs during the current episode, the results are more significant and more relevant to the proposed treatment population. Therefore, I would consider Study HGIE to be a positive supportive study based on change in MADRS in the subset of patients who failed two antidepressants in current depressive episode, even though the study failed to demonstrate an effect of OFC on MADRS total score in all patients.

HGHZ

The primary efficacy analysis in Study HGHZ was mean change from baseline to endpoint for MADRS total score. Using pair-wise comparisons, the OFC treatment group had a statistically significantly ($p = .044$) greater mean decrease at endpoint in MADRS total score compared with the OLZ treatment group. There were no statistically significant differences between the OFC and FLX treatment groups, or between the OFC and NRT treatment groups. Visit-wise analyses (LOCF) revealed that the OFC treatment group had a statistically significantly greater mean decrease in MADRS total score compared with the FLX treatment group at Weeks 1, 2, 3, 4, and 5. The OFC treatment group had a statistically significantly greater mean decrease in MADRS total score compared with the OLZ treatment group at Weeks 1, 2, 4, 6, 7, and 8. Table 6 summarizes mean change from baseline to endpoint in the primary efficacy measure (MADRS total score) for all patients during the acute phase (LOCF).

Table 6: Mean Change from Baseline to Endpoint on MADRS Total Score in Study HGHZ (LOCF)

	OFC N=145	FLX N=142	OLZ N=144	NRT N=68	p-Values			
					Overall	OFC vs. FLX	OFC vs. OLZ	OFC vs. NRT
Baseline (\pm SE)	28.7 (0.6)	28.4 (0.6)	28.4 (0.6)	28.8 (0.8)				
Mean Δ (\pm SE)	-8.6 (0.8)	-7.6 (0.8)	-6.5 (0.8)	-7.2 (1.3)	0.225	0.332	0.044	0.393

Mean change in MADRS total score was also examined within the subset of patients with failure to respond to two treatment courses during their current depressive episode. The results were consistent with the findings from all patients (OFC vs. FLX: $p = 0.106$; OFC vs. OLZ $p = 0.007$).

HDAO-1

This study was designed exactly as was HADO-2 (same protocol), but demonstrated no statistical separation of OFC from fluoxetine or olanzapine.

5.3 Conclusions Regarding Efficacy Data

In summary, when the most medication-resistant subset of patients with depression (those having failed two drug therapies during the current depressive episode) is examined with the more proper measure of efficacy for a sedating and appetite-stimulating drug like olanzapine (MADRS), the analyses presented by the Sponsor support the efficacy claim of Symbyax® in the treatment of TRD.

The Sponsor has submitted one clearly positive pivotal study (HDAO-2) and two supportive studies (HGFR and HGIE) for the use of Symbyax® for the indication of TRD. These data taken together with FDA's Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug

and Biological Product, Part II C section 2, provide sufficient evidence of efficacy in the treatment of TRD. The efficacy summary is presented in Table 7.

Table 7: Efficacy Summary for Acute Treatment Phase in Patients with Two Antidepressant Failures in Current Depressive Episode by Studies

Study		HDAO-2	HGFR	HGIE	HGHZ	HDAO-1
Sample Evaluated for Efficacy		OFC=97 FLX=101 OLZ=102	OFC=10 FLX=10 OLZ=8	OFC=163 FLX=41 OLZ=47	OFC=91 FLX=88 OLZ=90	OFC=101 FLX=102 OLZ=95
MADRS	OFC	-14.6 p vs. OFC	-13.6 p vs. OFC	-13.3 p vs. OFC	-9.0 p vs. OFC	-10.8 p vs. OFC
LOCF	FLX	-9.0 p<0.001	-1.2 p=0.012	-10.0 p=0.021	-7.0 p=0.106	-9.4 p=0.346
Endpoint	OLZ	-7.7 p<0.001	-2.8 p=0.035	-8.8 p=0.003	-5.1 p=0.007	-10.1 p=0.624

Source: Dr. Zhang's review.

6.0 Safety Data

6.1 Safety Findings from the Placebo-Controlled Trials

The controlled trial safety database for Symbyax® includes patients who participated in the double-blind, acute phases of 10 controlled clinical depression trials of up to 12 weeks duration. These 10 clinical trials were conducted in patients with several forms of depression: treatment-resistant depression (5 studies), bipolar depression (2 studies), major depressive disorder (MDD) with psychotic features (2 studies), and MDD with sexual dysfunction (1 study).

In addition to controlled trial safety data, OFC has been marketed since January 2004 and its safety profile has been established. Dr. Zhang's safety review for this sNDA detected an increase in treatment-emergent hyperglycemia which is not well characterized in labeling, and we will need to address this issue prior to approval.

Team Leader Comment: The issue of olanzapine-induced hyperglycemia is addressed in labeling as a general warning applied to all atypical antipsychotics, but it is evident from the data presented as part of this OFC supplement (see below) that patients most vulnerable to this adverse event are those with borderline to high serum glucose pre-treatment. There is no specific warning against or contraindication to using olanzapine-containing products in patients with baseline impaired glucose regulation, although current labeling does instruct the prescriber to monitor for worsening of glucose control in such patients.

6.1.2 Safety Findings and Issues of Particular Interest

6.1.2.1 Common and Drug-Related Adverse Events

OFC treated patients exhibited an overall AE rate of approximately 83%. This is minimally higher than placebo-treated patients (74%), but similar to olanzapine-treated (82.7%) and fluoxetine-treated (82.3%) patients.

The most frequently reported adverse events in the OFC treatment group (reported by ≥5% of OFC-treated patients) were: increased weight, increased appetite, dry mouth, somnolence, fatigue, headache, peripheral edema, tremor, dizziness, sedation, diarrhea, nausea, and anxiety.

There were no commonly reported events for which event rates were statistically significantly higher (after adjusted for exposure) for OFC than for olanzapine.

6.1.2.2 Adverse Events Leading to Dropout

Most of the adverse events that led to discontinuation for OFC-treated patients were events that were common with OFC and olanzapine (weight gain, somnolence, sedation) or that were associated with the underlying disease (suicidal ideation). The only events that led to discontinuation at a statistically significantly higher rate for OFC-treated patients than for another group were increased weight (2.1%) and sedation (1.3%). In general, rates of discontinuation due to adverse events, both overall and for individual events, were similar for OFC- and olanzapine-treated patients. See page 28 of Dr. Zhang's review for details.

6.1.2.3 Serious Adverse Events (SAEs) in Clinical Trials

Serious adverse events (SAEs) were reported by 4.0% of OFC-treated, 2.8% of fluoxetine-treated, 3.4% of olanzapine-treated, and 5.9% of placebo-treated patients. SAEs that were reported by two or more of the 771 OFC-treated patients were depression (8), suicidal ideation (6), chest pain (2), dyspnea (2), and peripheral edema (2). Depression was statistically significantly more common in OFC-treated than in fluoxetine-treated patients, but the majority of these events occurred in Studies HGGY and HGGA, which were studies in bipolar and psychotic depression and did not have fluoxetine treatment arms. Given the smaller sample size for fluoxetine compared to OFC and the lack of fluoxetine arms in the studies with the highest rates of serious depression events, it is difficult to assess the potential relationship to fluoxetine. There were no other statistically significant differences between OFC and other treatment groups with respect to rates of individual SAEs.

There were no deaths among subjects in the clinical trials that were likely related to OFC.

6.1.2.4 Laboratory Findings

Statistically significant differences were seen between treatment groups for several laboratory measures. In general, the changes observed in OFC-treated patients were consistent with changes observed with its component monotherapies, particularly olanzapine. The most common treatment-emergent laboratory abnormalities seen OFC-treated patients included: high prolactin (incidence rate of OFC vs. PLA: 27.6% vs. 4.8%), low total bilirubin (15.3% vs. 3.9%), low bicarbonate (14.1% vs. 8.8%), high ALT (7.8% vs. 0.5%), high fasting glucose (7.1% vs. 0%), high hemoglobin A1c (5.9% vs. 0%), and high triglycerides (5.2% vs. 0%). Rates of abnormalities in OFC-treated patients were, in general, similar to or lower than rates seen in olanzapine-treated patients. In contrast, numerous abnormalities were seen at higher rates in OFC-treated than in fluoxetine- or placebo-treated patients; this suggest that OFC's laboratory profile is similar to that of olanzapine.

Abnormalities in Hepatic Laboratory Measures

OFC-treated patients had statistically significantly greater mean change to maximum than placebo- or fluoxetine-treated patients for AST, ALT, and alkaline phosphatase; they also had a statistically significantly greater change to maximum on alkaline phosphatase as compared to olanzapine-treated patients. This increase in alkaline phosphatase does not seem to be clinically significant and is similar to what was submitted in the original OFC safety package; there were no statistically significant differences in exposure-adjusted rates of hepatic-related adverse events between OFC and any of the other treatment groups.

Abnormalities in Glucose and Lipids

Analyses of the exposure-adjusted incidence of patients with specified increases (taken from American Diabetes Association and National Cholesterol Education Program outlier criteria) in fasting and nonfasting glucose, cholesterol, and triglycerides revealed no statistically significant differences between OFC and comparators in exposure-adjusted event rates for fasting glucose or for triglycerides. However, OFC-treated patients had statistically significantly higher rates of treatment-emergent increase in non-fasting glucose than placebo-treated patients. OFC-treated patients also had statistically significantly higher rates of treatment-emergent high cholesterol than both fluoxetine- and placebo-treated patients. OFC-treated patients also had higher rates of treatment-emergent high cholesterol than olanzapine-treated patients, although the differences were not statistically significant. See Table 8 and page 36 of Dr. Zhang's review for more detail.

Table 8: Incidence of Treatment-Emergent Abnormalities in Selected Metabolic Analytes at Any Time in the Integrated Safety Database

Event Classification	OFC		FLX		OLZ		PLA	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose Fasting								
Normal to High (baseline <126 mg/dl to ≥ 126 mg/dl during treatment)	29	2 (6.9)	32	1 (3.1)	20	1 (5.0)	0	0 (0.0)
Glucose Non-Fasting								
Normal to High (baseline <140 mg/dl to ≥ 200 mg/dl during treatment)	628	18 (2.9)	391	8 (2.0)	706	17 (2.4)	353	1 (0.3)
Borderline to High (baseline between 140 - 200 mg/dl to ≥ 200 mg/dl during treatment)	35	16(45.7)	11	2 (18.2)	27	9 (33.3)	22	1 (4.5)
Cholesterol								
Normal to High (baseline <200 mg/dl to ≥ 240 mg/dl during treatment)	319	31 (9.7)	171	5 (2.9)	360	19 (5.3)	207	4 (1.9)
Triglycerides								
Normal to High (baseline <150 mg/dl to ≥ 500 mg/dl during treatment)	87	0 (0.0)	103	0 (0.0)	107	1 (0.9)	0	0 (0.0)

Source: Dr. Zhang's review.

Treatment-emergent impaired glucose tolerance (defined as fasting serum glucose <100 mg/dL at baseline and between 100 and 126 mg/dL post-baseline) or potential diabetes (fasting serum glucose <100 mg/dL at baseline and ≥126 mg/dL post-baseline) were not statistically significant between treatment groups, but the data presented are not adequately refined enough to determine clinical significance (see Table 9).

Table 9: Incidence of Treatment-Emergent Impaired Glucose Tolerance and Potential Diabetes in the Integrated Safety Database

Fasting Glucose	OFC		FLX		OLZ		PLA	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Baseline \leq 100 mg/dl to any post-baseline $>$ 126	22	0 (0.0)	27	1 (3.7)	15	1 (6.7)	0	0 (0.0)
Baseline \leq 100 mg/dl to any post-baseline $>$ 100 but \leq 126	22	9 (40.9)	27	5 (18.5)	15	5 (33.3)	0	0 (0.0)

Source: Dr. Zhang's review.

A statistically significantly higher proportion of OFC-treated patients had glycosuria (4.4%) than did fluoxetine- (0.4%) or placebo-treated (1.4%) patients; the proportion in OFC-treated patients was close to statistically significantly greater than that of olanzapine-treated patients (2.3%).

Team Leader Comment: The effects of OFC on glucose and lipids are related and similar to the effects seen with olanzapine. These are potentially important safety issues when using olanzapine or OFC and they have been identified as such in labeling. However, the effect of olanzapine on patients with borderline or high glucose prior to taking the drug has not been fully elucidated in labeling (see recommendations).

Because hypercholesterolemia, hyperglycemia, and obesity are independent risk factors for heart attack and stroke, we should consider grouping these together in the Warnings/Precautions section of labeling.

6.1.2.5 ECG Findings

Statistically significant differences in mean change at endpoint in heart rate and QT interval were observed between OFC and other treatment groups. These changes were consistent with known safety profiles of the individual drugs that make up OFC. As an example, heart rate decreased for fluoxetine, increased for olanzapine, and decreased only slightly for OFC, resulting in statistically significant differences between OFC and both of its component monotherapies. QT prolongation (corrected by regression) in OFC treated patients was statistically significantly different from a shortening of the QT interval seen in olanzapine- and placebo-treated patients and a slightly prolonged QT seen in fluoxetine-treated patients. However, the placebo-adjusted mean change (5.3 ms) in OFC treatment is not considered to be clinically significant.

The most common treatment-emergent ECG abnormalities in OFC-treated patients were rhythm abnormalities (8.3%), morphology abnormalities (6.2%), and T-wave abnormalities (5.9%). However, there were no statistically significant differences between OFC and any of the other treatment groups for any abnormality category. No SAEs or dropouts were due to ECG abnormalities in the integrated safety database.

6.1.2.5 Vital Signs Findings

Several statistically significant changes in vital signs were identified by Dr. Zhang, but the clinical significance of these changes is minimal.

With regard to statistically significant changes in supine and standing pulse, OFC-treated patients had small decreases, while fluoxetine-treated patients had larger decreases, and olanzapine-treated

patients had increases, suggesting that any potential effect of OFC on pulse is intermediate to those of fluoxetine and olanzapine.

The incidence of potentially clinically significant changes in vital signs for OFC-treated patients was low (with no measure having incidence greater than 4%), with no statistically significant differences in exposure-adjusted event rates between OFC and any of the other treatment groups. No patient dropouts were attributed to abnormal vital signs.

Changes in Weight

Sixteen percent of OFC-treated patients gained a clinically significant ($\geq 10\%$) amount of weight compared to 0.7% of fluoxetine-treated patients, 14.6% of olanzapine-treated patients, and 0.2% of placebo-treated patients. Exposure-adjusted rates of potentially clinically significant weight gain were statistically significantly greater for OFC as compared to both fluoxetine and placebo, but not statistically different from olanzapine. Dropouts due to weight gain were 2.1% of OFC-treated patients and 1.7% of olanzapine-treated patients.

Team Leader Comment: Weight gain is a known adverse event with olanzapine and therefore OFC; this is potentially clinically significant and has been addressed in labeling. The sponsor has revised their labeling so that this is in the Warnings/Precautions section and I agree with this increased prominence in labeling but would group it together with hypercholesterolemia and hyperglycemia.

6.2 Conclusion Regarding Safety

Short-term treatment with OFC appears to have been reasonably safe in the populations studied and there were no unexpected adverse events in normoglycemic patients. The majority of potentially clinically relevant adverse events are related to the olanzapine component of OFC. Primary among these is the high rate of treatment-emergent hyperglycemia in patients with borderline to high serum glucose pre-treatment, as well as hypercholesterolemia.

7.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

This NDA was not presented to the PDAC.

8.0 DSI INSPECTIONS

Two sites (for study HDAO-2 and HGIE) were inspected by DSI and found to have no deviation from regulations.

9.0 LABELING AND ACTION LETTER

9.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed labeling is presented in the new PLR format and will require some modification. The issue of how to most appropriately label for hyperglycemic patients will have to be addressed internally. We will need to request that the sponsor identify all olanzapine and OFC trial data wherein patients with impaired glucose tolerance were enrolled and glucose levels (preferably fasting) followed during treatment. It is likely that using OFC in this at-risk group will require a specific caution in labeling. We will include our request for these data in the Action Letter and negotiate labeling with the sponsor.

9.2.2 DMETS

Symbyax® is an approved product with the approved trade name.

10.0 Phase 4 Commitments

TRD is not a condition expected to be reasonably prevalent in children and adolescents and so requiring evaluation of Symbyax® for the treatment of TRD in these populations is not warranted as a Phase 4 commitment.

TRD is a chronic illness and long-term efficacy should be assessed post approval; we should specifically ask for an evaluation of the drug's effect on blood glucose, lipids, and weight gain in any future studies.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that Symbyax® is effective and reasonably safe in the treatment of TRD, but we will require more information to adequately label the product. There is evidence of treatment-emergent hyperglycemia and diabetes in patients with pre-treatment borderline normal to high fasting glucose, and this has not been adequately addressed in current labeling. We should request that the sponsor provide data from all of their olanzapine and OFC programs that analyzed the effect of olanzapine on treatment-emergent hyperglycemia/diabetes and then incorporate this information into labeling.

We should integrate any information request from the Safety Team into our Action Letter since they have been examining the effects of olanzapine on hyperlipidemia and may require more data from the sponsor to complete their review.

We should request a Phase 4 commitment to study maintenance therapy as outlined in section 10 above.

Annotated Draft Labeling as revised by the Division should be attached to the Action Letter.

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

/s/

Mitchell Mathis
3/23/2007 01:21:12 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA
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Reviewer Name Jing Zhang, MD, PhD
Review Completion Date February 9, 2007

Established Name Symbyax
Trade Name OFC
Therapeutic Class Atypical
antipsychotic/antidepressant
Applicant Eli Lilly and Company

Priority Designation P

Formulation 6/25, 12/25, 6/50, 12/50 mg tablet
Dosing Regimen 6/25 to 18/50 mg/d
Indication Treatment resistant depression
Intended Population Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this supplement NDA be granted approvable status.

The following regulatory action is recommended:

- The sponsor should commit to conducting a phase 4 study to address the long term efficacy and safety of Symbyax. Detail recommendation can be found in section 1.2.2 Required Phase 4 Commitments.
- The sponsor should address the recommended labeling changes. Details can be found in section 9.4 Labeling Review.
- The sponsor should respond to our Feb. 5, 2007 request for data clarification.

The sponsor's responses will be reviewed in an addendum. Final approval is contingent on satisfactory responses to the concerns conveyed in these requests and mutual agreement on labeling.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no additional recommendations.

1.2.2 Required Phase 4 Commitments

The sponsor should conduct a phase 4 study to assess the long term efficacy and safety of Symbyax/olanzapine and fluoxetine in combination (OFC) in the treatment of treatment resistant depression (TRD) in adult population after this sNDA is approved. The study should have a double blind, randomized, and controlled study design, and the study should last at least 3 months or longer after patients are fully stabilized by Symbyax. The sponsor should commit to conducting such a study prior to the final approval of this sNDA.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

A total of 5 TRD studies were conducted from May 1997 to May 2005 to evaluate the efficacy of OFC in the treatment of TRD in adult population. All studies have a double-blind, multicenter, parallel, randomized study design to compare OFC to fluoxetine and olanzapine monotherapies.

The efficacy of OFC in the treatment of TRD in adult population is based on the efficacy data from one positive pivotal study, Study HDAO-2 and two supportive studies, Study HGFR and HGIE (based on a subset of patients who failed two antidepressants during current depressive episode).

The OFC safety evaluation in this sNDA is mainly based on an integrated safety database which included patients randomized in double-blind, acute treatment phase of 10 controlled OFC depression clinical trials.

1.3.2 Efficacy

Results from Study HDAO-2 demonstrated that OFC treatment was statistically significantly more effective than olanzapine or fluoxetine monotherapy in reducing depressive symptoms in adult TRD population over the 8-week study as assessed by the primary variable of change from baseline on MADRS total score.

Results from Study HGFR and Study HGIE (based on results from the subset of patients who failed two adequate antidepressant trials in current depressive episode) provided additional supportive evidence for OFC in treatment TRD.

1.3.3 Safety

The safety findings from an integrated safety database included patients who participated in the double-blind, acute phase of 10 controlled OFC depression trials, were consistent with the previously observed OFC safety profile.

1.3.4 Dosing Regimen and Administration

All studies are flexible dosed studies except Study HGIE which is a dose ranging study. Patients randomized to OFC arms in Study HDAO, HGIE, and HGHZ received Symbyax once daily, dose ranged from 6/25 to 18/50 mg per day. Patients randomized to OFC arm in Study HGFR received olanzapine (5 to 20 mg/d) and fluoxetine (20 to 60 mg/d) separately. A mandatory dose titration for the non-responding patients who had no dose-limiting side effects from OFC was incorporated into the protocol to facilitate the chance for optimal dosing. All study drugs were administered orally.

HGIE was a dose ranging study, included 4 OFC arms—OFC 6/25 mg, 6/50 mg, 12/25 mg and 12/50 mg. Patients randomized to each individual dose group took fixed dose OFC through to the end of the study. The results of this study did not suggest a dose-response relationship.

1.3.5 Drug-Drug Interactions

The existing OFC label addresses safety outcomes related to potential drug-drug and drug-food interactions. There have been no new data generated on these topics from this submission.

1.3.6 Special Populations

The existing OFC label addresses safety outcomes as they relate to sex, race, advanced age, renal/hepatic impairment, smoking status, and several other special groups. There have been no new data generated on these topics that have not already been addressed in labeling.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Symbyax is a combination of two psychiatric agents—olanzapine, an antipsychotic of the thienobenzodiazepine class and fluoxetine, a selective serotonin reuptake inhibitor. Symbyax was approved by FDA for bipolar depression in December 2003.

2.2 Currently Available Treatment for Indications

No drugs or drug combinations are approved by FDA for the indication of TRD in the United States.

2.3 Availability of Proposed Active Ingredient in the United States

Two active ingredients of Symbyax, olanzapine and fluoxetine, are approved drugs in the United State.

2.4 Important Issues With Pharmacologically Related Products

The safety concerns regarding to agranulocytosis, metabolic syndrome with atypical antipsychotic treatment, and primary pulmonary hypertension of the newborn with SSRI treatment from post marketing data are under review by our safety team. At this point no any final conclusions regarding to these issues have been reached. No any cases of agranulocytosis, or liver failure were reported in TRD studies. A total of 8 pregnant women were included in the controlled-placebo OFC studies and 4 of them have reached full term. No birth-related abnormalities or primary pulmonary hypertension were reported (see 7.1.14 Human Reproduction and Pregnancy Data).

2.5 Presubmission Regulatory Activity

On August 18, 1999, the FDA met with Lilly and agreed with Lilly that TRD was a reasonable target for new indication. The FDA also agreed with Lilly's definition of TRD as the failure to respond to trials with two different classes of antidepressant therapy of adequate duration and dose.

On January 16, 2002, the FDA met with Lilly and stated that because studies HGIE, HGHZ, and HGFR did not meet their primary endpoints, two additional positive studies would be required for an indication of TRD.

On April, 14, 2005, Lilly had a pre-NDA meeting with FDA, at which the FDA agreed that the overall content and format for submission of clinical trial data to support an indication of TRD for Symbyax. In addition, FDA agreed that submission would warrant a Priority Review, and that it would likely go to an Advisory Committee.

On December 21, 2005, Lilly had a pre-submission teleconference with FDA, at which the FDA agreed that TRD application was filable and that a rolling submission was acceptable.

On April 24, 2006, the FDA responded in an e-mail correspondence in response to an e-mail correspondence sent by Lilly on April 21, 2006 regarding to additional pre-submission questions related to the TRD submission. In summary, FDA agreed with Lilly's proposed safety analyses and plan to submit labeling for the co-administration of Zyprexa and Prozac for an indication of TRD.

On September 28, 2006, this sNDA was submitted. It was judged to be fileable on November 7, 2006.

2.6 Other Relevant Background Information

Symbyax was approved for marketing only in USA and Symbyax has not been withdrawn from the market for any reason.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Environmental assessment was previously submitted by Lilly for both olanzapine (NDA20592, 21 September, 1995) and fluoxetine (NDA 20187, 6 August, 1993). In these assessments, it was concluded that given their projected use rates, neither of these compounds posed a threat to the aquatic environment.

Lilly claim that even with the addition of the TRD indication, the conclusion from previous assessment does not changed. Therefore, Lilly claims a categorical exclusion from the need to

conduct and environment assessment for olanzapine and fluoxetine for current application. Our CMC review regarding to this issue is pending at the time of completion of this review.

3.2 Animal Pharmacology/Toxicology

There is no animal pharmacology/toxicology data provided in this submission and these studies were not deemed necessary.

3.3 Statistical Review and Evaluation

Yeh-Fong Chen, PhD., is the statistical reviewer for this sNDA. Up to the time of completion of this review, her review is still pending.

3.4 DSI Clinical Site Inspection

The Division of Scientific Investigations (DSI) inspected 2 sites, and Dr. Richard Bergeron and Dr. Louise Beckett were the principle investigators. These two sites were selected due to larger enrollment in two positive studies—Study HDAO-2 and Study HGIE. The inspection of Dr. Bergeron revealed no significant problems that would adversely impact data acceptability. The inspection of Dr. Beckett revealed problems with the informed consent procedures, a protocol deviation, inadequate records, and inadequate drug accountability record keeping. However, in general these deviations do not adversely impact data acceptability. In summary, DSI concluded that data from these two investigators are acceptable to support of this submission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The efficacy data to support this submission are from 5 double-blind, active-controlled clinical studies:

- H6P-MC-HDAO (HDAO) Study 1
- H6P-MC-HDAO (HDAO) Study 2
- F1D-MC-HGFR (HGFR)
- F1D-MC-HGIE (HGIE)
- F1D-MC-HGHZ (HGHZ)

The safety data to support this submission are from 10 controlled OFC depression studies included patients who participated in the double-blind, acute phase:

- H6P-MC-HDAO Study 1&2
- F1D-MC-HGIE
- F1D-MC-HGGY Study 1&2
- F1D-MC-HGGA Study 1&2
- F1D-MC-HGFR

- B1Y-MC-HCKB
- F1D-MC-HGHZ

A 60 day safety update which summarized the safety data from one completed bipolar depression study (F1D-SU-HGMA) submitted on Nov. 28, 2006 was also reviewed.

4.2 Tables of Clinical Studies

Table 1 describes clinical studies included in both efficacy and safety review.

Table 1 Clinical Studies Included in Efficacy and Safety Review

Protocol No. Study Design	Study Objective	Treatment Duration, Phase, Drug Type, Dose, and Regimen	
H6P-MC-HDAO (Study 1 and Study 2) Two double-blind, multicenter, parallel, randomized studies in patients with MDD without psychotic features who meet study criteria for TRD, with an OFC open-label period.	Assess efficacy and safety of OFC compared with fluoxetine and olanzapine monotherapies.	8-wk lead-in:	FLX 25 mg/day titrated to 50 mg/day
		8-wk DB:	OFC 6/50, 12/50, or 18/50 mg/day OLZ 6, 12, or 18 mg/day FLX 50 mg/day
		8-wk OL:	OFC 6/50, 12/50, or 18/50 mg/day
F1D-MC-HGGY (Study 1 and Study 2) Two double-blind, multicenter, parallel, randomized studies in patients with bipolar I disorder – depressed, with an olanzapine or OFC open-label period.	Assess efficacy of acute olanzapine or OFC therapy compared with placebo.	8-wk DB:	PLA OLZ 5, 10, 15, or 20 mg/day OFC 6/25, 6/50, or 12/50 mg/day
		6-m OL:	OLZ 5, 10, 15, or 20 mg/day OFC 6/25, 6/50, or 12/50 mg/day
F1D-MC-HGHZ Double-blind, multicenter, parallel, randomized, comparative study in patients with TRD, starting with a nortriptyline lead-in period and ending with an OFC open-label period.	Evaluate the efficacy and safety of OFC compared to olanzapine, fluoxetine, and nortriptyline monotherapies.	7-wk lead-in:	NRT 25, 50, 75, 100, 125, 150, or 175 mg/day
		8-wk DB:	NRT 25, 50, 75, 100, 125, 150, or 175 mg/day fixed OLZ 6 or 12 mg/day FLX 25 or 50 mg/day OFC 6/25 or 12/50 mg/day
		5-m OL:	OFC (OLZ 6, 12, or 18 mg/day + FLX 25, 50, or 75 mg/day)
F1D-MC-HGIE Double-blind, multicenter, parallel, randomized, dose-ranging, comparative study in patients with TRD, starting with a venlafaxine lead-in period and ending with an OFC open-label period.	Evaluate the efficacy and safety of OFC compared to olanzapine, fluoxetine, and venlafaxine monotherapies.	7-wk lead-in:	VNL 75, 150, 225, 300, or 375 mg/day
		12-wk DB:	VNL 75, 150, 225, 300, or 375 mg/day fixed OLZ 6 or 12 mg/day FLX 25 or 50 mg/day OFC 1/5 mg/day OFC 6/25 mg/day OFC 12/25 mg/day OFC 6/50 mg/day OFC 12/50 mg/day
		52-wk OL:	OFC (OLZ 6, 12, or 18 mg/day + FLX 25, 50, or 75 mg/day)
F1D-MC-HGFR Double-blind, multicenter, parallel, randomized study in patients with TRD, starting with a fluoxetine lead-in period and ending with an OFC open-label period.	Evaluate the efficacy and safety of OFC compared to olanzapine and fluoxetine monotherapies.	6-wk lead-in:	FLX 20, 40, or 60 mg/day
		8-wk DB:	OLZ 5, 10, 15, or 20 mg/day FLX 20, 40, or 60 mg/day OFC (OLZ 5, 10, 15, or 20 mg/day + FLX 20, 40, or 60 mg/day)
		8-wk OL:	OFC (OLZ 5, 10, 15, or 20 mg/day + FLX 20, 40, or 60 mg/day)

FID-MC-HGGA Two double-blind, multicenter, parallel, placebo-controlled, randomized studies in MDD patients with psychotic features, ending with an OFC open-label period.	Assess efficacy of olanzapine alone and in combination with fluoxetine compared with placebo.	8-wk DB:	OLZ 5, 10, 15, or 20 mg/day OFC (OLZ 5, 10, 15, or 20 mg/day + FLX 20, 40, 60, or 80 mg/day) PLA
		48-w OL:	OFC (OLZ 0, 5, 10, 15, 20, or 25 + FLX 0, 20, 40, or 60 mg/day)
BIY-MC-HCKB Double-blind, parallel, randomized, fluoxetine-controlled, multicenter study of premenopausal women (patients) experiencing sexual dysfunction while receiving fluoxetine treatment.	Assess the efficacy of once-daily mirtazapine, olanzapine, and yohimbine in ameliorating fluoxetine-associated sexual dysfunction.	4-wk lead-in:	FLX 20, 40, or 60 mg/day
		6-wk DB:	FLX 20, 40, or 60 mg/day fixed + PLA FLX 20, 40, or 60 + MTZ 15 or 30 mg/day OFC (FLX 20, 40, or 60 mg/day + OLZ 2.5 or 5 mg/day) FLX 20, 40, or 60 + YHB 5.4 or 10.8 mg/day

4.3 Review Strategy

A list of the items examined during the course of this review is provided in Table 2. The efficacy results from each study were reviewed individually. The safety results from these 10 controlled studies were reviewed as a pool.

Table 2 Items Utilized in the Review

Submission Date	Items Reviewed
September 28, 2006	Study report: HDAO1&2, HGFR, HGIE, HGHZ The Controlled Clinical Studies Database Clinical Summary Clinical Review Case Report Tabulations (.xpt files) Case Report Forms
November 28, 2006	60 day safety update
December 11, 2006	Response to FDA request for information
December 14, 2006	Response to FDA request for information

4.4 Data Quality and Integrity

DSI inspected two sites, Dr. Richard Bergeron and Dr. Louise Beckett sites, and concluded that data from these two investigators are acceptable in support this sNDA.

Dr. Greg Dubisky reviewed case report forms, narrative summaries, and adverse events (.xpt file), as well as AE coding (compared investigator's verbatim terms with MedDRA preferred terms) for consistency of adverse event information across documents and acceptability of AE coding. No significant inconsistency was found.

4.5 Compliance with Good Clinical Practices

All studies were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

4.6 Financial Disclosures

For purposes of this sNDA, 5 studies (HDAO 1&2, HGFR, HGIE, and HGHZ) are considered “covered clinical studies” in accordance with 21 CFR 54.2 (e).

Study HDAO

(b) (6), a sub-investigator at Site (b) (6) for Study HDAO, received \$29,900 in speaker fees from 1/12003 to 12/31/2003. Since (b) (6) patients were recruited from the site, the financial payments the investigator received could not influence the outcome of the trial.

(b) (6), a sub-investigator at Site (b) (6) for Study HDAO, received a sum of \$64,000.00 equity interest. Study HDAO was a multi-site, double-blind, randomized study and Site (b) (6) only contributed (b) (6) patients of 605 randomized patients. The equity interest the investigator holds is unlikely to influence the outcome of the trial.

(b) (6), a sub-investigator at Site (b) (6) for Study HDAO, received \$29,900 in speaker fees from 1/12003 to 12/31/2003. Since no patients were recruited from the site, the financial payments the investigator received could not influence the outcome of the trial.

(b) (6), a primary investigator at Site (b) (6) for Study HDAO, received \$ 71,275.00 for speaker training, teleconference, speaker fee, lecture bureau and preceptor from 11/16/02 to 1/24/2006. Since Site (b) (6) only contributed (b) (6) of 605 randomized patients, the financial payment the investigator received unlikely biased the study results.

Study HGHZ

(b) (6) an investigator at Site (b) (6) for Study HGHZ, reported \$60,000 financial disclosure. The details are not provided by the sponsor. Site (b) (6) contributed (b) (6) of 944 enrolled patients. It is unlikely the financial payment the investigator received would affect the outcome of the study.

(b) (6), an investigator at Site (b) (6) for Study HGHZ, received \$35,250 in speaker fees. Since Site (b) (6) only contributed (b) (6) of 944 enrolled patients, the financial payments the investigator received are unlikely influence the study outcome.

(b) (6), an investigator at Site (b) (6) for Study HGHZ, received \$93,494 for consulting fees, honorarium, and speaker fees. His site contributed (b) (6) out of 944 enrolled patients. So, his financial payment unlikely biased the outcome of the trial.

(b) (6), an investigator at Site (b) (6) for Study HGHZ, received \$33,000 for speaker fees. Since his site only contributed (b) (6) of 944 enrolled patients and the study was a multi-site, double-blind, randomized trial, it is less likely that his financial payment would influence the outcome of the trial.

(b) (6), an investigator at Site (b) (6) for Study HGHZ, received \$66,933 for consulting fees, honorarium, and speaker fees. Since his site only contributed (b) (6) of 944 enrolled patients and the study was a multi-site, double-blind, randomized trial, it is less likely that his financial payment would influence the outcome of the trial.

(b) (6), an investigator at Site (b) (6) for Study HGHZ, received \$54,000 for speaker fees. Since his site only contributed (b) (6) of 944 enrolled patients and the study was a multi-site, double-blind, randomized trial, it is less likely that his financial payment would influence the outcome of the trial.

Study HGIE

(b) (6), an investigator at Site (b) (6) for Study HGIE, received \$31,111 for participation with the Lilly Lecture Bureau. Since Site (b) (6) only contributed (b) (6) of 483 enrolled patients and the study was a multi-site, double-blind, randomized trial, it is unlikely that the financial payment the investigator received would influence the outcome of the trial.

(b) (6), an investigator at Site (b) (6) for Study HGIE, received \$26,245.00 in honorarium and expense. Since Site (b) (6) only contributed (b) (6) of 483 enrolled patients and the study was a multi-site, double-blind, randomized trial, it is unlikely that the financial payment the investigator received would influence the outcome of the trial.

(b) (6), an investigator at Site (b) (6) for Study HGIE, received \$118,496.00 for honorarium and from Lilly Lecture Bureau. Since Site (b) (6) only contributed (b) (6) of 483 enrolled patients and the study was a multi-site, double-blind, randomized trial, it is unlikely that the financial payment the investigator received would influence the outcome of the trial.

No investigators from Study HGFR needed to file the financial disclosure.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Since Symbyax is a marketed drug and the pharmacokinetics are described in current labeling. Further pharmacokinetic data were not deemed necessary at this time point.

5.2 Pharmacodynamics

No new pharmacodynamic data were provided in this submission.

5.3 Exposure-Response Relationships

Exposure-response relationship was not studied in all TRD studies, except Study HGIE. In Study HGIE, a dose-response relationship was not observed based on the examination of mean change from baseline in MADRS total score.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This submission is for the use of Symbyax (or OFC) for an indication of treatment resistant depression (TRD).

6.1.1 Methods

A total of 5 double-blind, active-controlled studies (1 pilot and 4 pivotal) have been conducted from May 1997 to May 2005 to evaluate the efficacy of OFC in the treatment of TRD. The data from all 5 studies were reviewed. The database reviewed included efficacy data from each individual study report and the summary of clinical efficacy of each individual study. The efficacy review was performed in consultation with the statistical reviewer, Yeh-Fong Chen PhD.

6.1.2 General Discussion of Endpoints

Either MADRS (Study HDAO, HGIE and HGHZ) or HAM-D (Study HGFR) was used as primary endpoint in the TRD studies reviewed in this submission. Both MADRS and HAM-D were considered acceptable measures for evaluation of depression in clinical trials. Compared to the HAM-D, the MADRS is more heavily weighted on items that measure core mood symptoms of depression, as opposed to somatic and other non-core mood symptoms. Because olanzapine tends to improve patient's sleep and appetite—symptom improvements that may be detected most easily on the HAM-D—using the MADRS as the primary analysis measure in studies that include olanzapine helps to differentiate direct effects on mood from effects on sleep and appetite. Table 3 summarized the primary and secondary endpoints in each individual study.

Table 3 the Primary and Secondary Endpoints in individual Study

Study	HDAO 1&2	HGFR	HGIE	HGHZ
Primary endpoint	Mean change from baseline to endpoint in MADRS total score	Mean change from baseline to endpoint in HAMD-21 total score	Mean change from baseline to endpoint in MADRS total score	Mean change from baseline to endpoint in MADRS total score
Secondary endpoints	<ul style="list-style-type: none"> Onset of action (time to $\geq 50\%$ \downarrow MADRS total score) Rate & time to full response ($\geq 50\%$ \downarrow MADRS total score) Rate & time to remission (MADRS total score ≤ 10) HAM-A total and individual item score Mean Δ in BPRS 	<ul style="list-style-type: none"> Mean Δ in MADRS Mean Δ in CGI-Severity 	<ul style="list-style-type: none"> Mean Δ in HAM-A Mean Δ in CGI-Severity Total Δ in HAM-A Total Δ in BPRS 	<ul style="list-style-type: none"> Mean Δ in CGI-Severity Mean Δ in HAM-A Total Δ in BPRS

MADRS: the Montgomery-Asberg Depression Rating Scale

HAM-A: the Hamilton Rating Scale for Anxiety

CGI-Severity: the Clinical Global Impression-Severity of illness

BPRS: the Brief Psychiatric Rating Scale

6.1.3 Study Design

6.1.3.1 Investigators/Sites

Study HDAO-1 and Study HGFR were conducted in the United States. Study HDAO-2, HGIE and HGHZ were conducted in more than one country including USA.

Table 4 summarized the investigators and study sites in each study. A full list of clinical study sites and investigators for Study HDAO-2, HGFR and HGIE is included in Appendices 10.1.

Table 4 Summary of Investigators and Study Sites

Study	HDAO-2	HGFR	HGIE	HGHZ	HDAO-1
Study period	4/02-5/05	5/97-6/98	3/00-9/01	8/99-6/01	4/02-5/05
Investigators	52	2	90	71	49
Study sites	52 sites in USA and Canada	2 sites in USA	90 sites in 16 countries including USA	71 sites in USA and Canada	49 sites in USA

6.1.3.2 Objectives

The primary objective of all five studies was to assess the efficacy of OFC versus fluoxetine and olanzapine monotherapy in the treatment of TRD. In addition, Study HGIE and Study HGHZ

also assessed the efficacy of OFC versus Venlafaxine (HGIE) and Nortriptyline (GHZ) monotherapy in the treatment of TRD.

6.1.3.3 Subjects

Inclusion criteria:

Eligible patients for TRD studies were male or female, 18 or older, met DSM-IV criteria for MDD without psychotic features, historical failure to achieve satisfactory antidepressant response when treated with an acceptable antidepressant and reasonable dose for at least 4 weeks and prospectively failure to another antidepressant drug during a 6-8 week lead-in phase. The key inclusion criteria for each individual study were summarized in Table 5.

Table 5 Summary of Key Inclusion Criteria in Each Individual Study

Study	HDAO 1&2	HGFR	HGIE	HGHZ
Age	18 - 65	18 - 65	18 or older	18 - 65
Severity of depression	HAMD-17 \geq 22	HAMD-21 \geq 20	CGI-Severity \geq 4	MADRS \geq 20
Historical failure to one adequate antidepressant trial*	Any antidepressant other than FLX for minimum 6 wks	Any non-SSRI for minimum 4 wks	Any SSRI for minimum 6 wks	Any SSRI for minimum 4 wks
Failed lead-in phase treatment**	FLX, 25-50 mg, for 8 wks	FLX, 20-60 mg, for 6 wks	VNL, 75-375 mg, for 7 wks	NRT, 25-175 mg, for 8 wks
Two failures in current episode	Yes	Yes	No	No

*: defined as treatment with at least one antidepressant for at least 4 weeks at an acceptable dose

**: defined by a < 30% improvement on the MADRS during lead-in phase

Key Exclusion Criteria:

- MDD with psychotic feature
- Historical failure to respond to treatment with OFC or to adequate trials of electroconvulsive therapy (ECT)
- History of treatment with clozapine or an injectable depot antipsychotic
- Recent treatment with ECT, remoxipride, a monoamine oxidase inhibitor (MAOI), guanethidine, or guanadrel
- Potential need for treatment with ECT or any other disallowed medication with primarily central nervous system (CNS) activity during study participation
- Potential need to use a MAOI within 35 days after discontinuing study drug
- Recent treatment with an investigational drug, or previous participation in a Lilly-sponsored study of olanzapine or of OFC
- Presence of serious or unstable illnesses
- Presence of suicidal risk

6.1.3.4 Overall Study design

All five studies had similar design---a randomized, double-blind, parallel-group, multicenter design to compare OFC to olanzapine and fluoxetine monotherapies (Study HGIE also comparing to venlafaxine monotherapy and Study HGHZ also comparing to nortriptyline monotherapy) in patients with TRD. Study HDAO-1 and 2 have exactly same protocol. All studies consisted of 3 phases—Lead-in phase, acute treatment phase and open-label phase.

Patients who met the inclusion criteria received fluoxetine (HDAO and HGFR), venlafaxine (HGIE) or nortriptyline (HGHZ) treatment for 6-8 weeks in lead-in phase. Patients who did not respond to above treatments during lead-in phase and who were not ineligible by interim exclusion criteria (see Table 6 for the criteria) were randomized to an 8-12 week acute treatment phase. A 1:1:1 ratio was used for treatment-group randomization to OFC, fluoxetine, olanzapine in Study HDAO and HGFR. In Study HGHZ, a ratio of 1:1:1:0.5 was use to OFC, fluoxetine, olanzapine and nortriptyline treatment groups. Study HGIE was a dose ranging study. Equal numbers of patients were randomized into OFC 6/25, OFC 6/50, OFC 12/25, OFC 12/50, FLX, OLZ, VNL, and OFC 1/5 group.

Acute treatment phase was followed by an open-label extension phase throughout which eligible patients received OFC for 8 weeks to 6 months depending on study design. The results of open-label phase will be analyzed separately and were not included in this submission.

The major features of each individual study design were summarized in Table 6.

Table 6 Summary of Study design by Individual Study

Study	HDAO	HGFR	HGIE	HGHZ
Lead-in phase	FLX 8 weeks	FLX 6 weeks	VNL 7 weeks	NRT 8 weeks
Interim exclusion criteria	<ul style="list-style-type: none"> • HAMD-17 \geq 18, \downarrow HAMD-17 \geq 25% or \geq15% between last 2 visits • Psychotic feature 	<ul style="list-style-type: none"> • \downarrowHAMD-21 \geq 30% • BPRS positive item** \geq 3 	<ul style="list-style-type: none"> • \downarrowMADRS \geq 30% • BPRS positive item **\geq 3 	<ul style="list-style-type: none"> • \downarrowMADRS \geq 30% • BPRS positive item** \geq 3
Acute treatment phase	OFC:FLX:OLZ 1:1:1 8 weeks	OFC:FLX:OLZ 1:1:1 8 weeks	OFC, FLX, OLZ, VNL* 12 weeks	OFC:FLX:OLZ:NRT 1:1:1:1/2 8 weeks
Open-label phase	OFC 8 weeks	OFC 8 weeks	OFC 52 weeks	OFC 5-6 months

*: randomization ratio in Study HGIE is OLZ:FLX:VNL:OFC 6/25:OFC 6/50:OFC 12/25:OFC 12/50:OFC 1/5 = 1:1:1:1:1:1:1

**: BPRS positive items include conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content

6.1.3.5 Dose and Administration

All TRD studies were flexible dose studies except Study HGIE which was a dose ranging study. The detail dose information is summarized in Table 7. All study drugs were administered orally.

Since a clear dose response for OFC has not yet been established, a mandatory dose titration (except HGIE which is a dose ranging study) for the non-responding patients who had no dose-limiting side effects from OFC was incorporated into the protocol to facilitate the chance for optimal dosing. The patients who couldn't tolerate the minimum required doses of study drugs were removed from the studies. Same dose titration principle also applied to lead-in phase.

Table 7 Summary of Dose Information

Study	Lead-in Phase	Acute Treatment Phase
HDAO	FLX 25 or 50 mg/d, once daily	OFC 6/25, 12/50, or 18/50 mg/d, once daily in the evening FLX 50 mg/d, once daily in the evening OLZ 6, 12 or 18 mg/d, once daily in the evening
HGFR	FLX 20 to 60 mg/d, once daily in AM	FLX 20 to 60 mg/d, once daily in AM OLZ 5 to 20 mg/d, once daily in PM OLZ 5-20/FLX 20-60 mg/d, once daily PM/AM
HGIE	VNL 75 to 375 mg/d, once daily in PM	OFC 6/25, 6/50, 12/25, 12/50 or 1/5 mg/d, once daily in PM FLX 25 to 50 mg/d, once daily in PM OLZ 6-12 mg/d, once daily in PM VNL 75 to 375 mg/d, once daily in PM
HGHZ	NRT 25 to 175 mg/d, once daily in PM	OFC 6/25 or 12/50 mg/d, once daily in PM FLX 25 or 50 mg/d, once daily in PM OLZ 6 or 12 mg/d, once daily in PM NRT 25 to 175 mg/d, once daily in PM

6.1.3.6 Statistical Analysis Plan

All data from the studies were analyzed on an intent to treat (ITT) basis. An ITT analysis is an analysis of data by groups to which the patients were assigned by random allocation, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Analysis of variance (ANOVA) models were used to evaluate continuous data, and Fisher's exact test was used to evaluate most categorical data except Study HGIE. In HGIE, Chi square test was used for categorical data. For continuous measures, last-observation-carried-forward (LOCF) methodology was used to assess mean change (unless otherwise specified). When LOCF mean change from baseline to endpoint was assessed, patients were included in the analysis only if the patient had a baseline and a post-baseline measure. All comparisons between treatment groups were made using a two-sided significance level of 0.05.

6.1.4 Efficacy Findings

6.1.4.1 Demographic Characteristics

Demographic Characteristics in Acute Phase at baseline were summarized in Table 8 by studies.

Table 8 Baseline Demographic Characteristics in Acute Phase by studies

Study	Treatment group	n	Gender		Age	Race		
			Female (%)	Male (%)	Mean (yr)	Caucasian (%)	African Descent (%)	Others (%)
HDAO-2	OFC	98	69 (70.4)	29 (29.6)	45.28	90 (91.8)	3 (3.1)	5 (5.1)
	FLX	102	67 (65.7)	35 (34.3)	44.45	90 (88.2)	5 (4.9)	7 (6.9)
	OLZ	103	67 (65.0)	36 (35.0)	42.97	91 (88.3)	8 (7.8)	4 (3.9)
	Total	303	203 (67.0)	100 (33.0)	44.22	271 (89.4)	16 (5.3)	16 (5.2)
HGFR	OFC	10	8 (80.0)	2 (20.0)	45.77	10 (100)	0	0
	FLX	10	7 (70.0)	3 (30.0)	38.15	9 (90.0)	1 (10.0)	0
	OLZ	8	6 (75.0)	2 (25.0)	40.99	8 (100)	0	0
	Total	28	21 (75.0)	7 (25.0)	41.68	27 (96.4)	1 (3.6)	0
HGIE	OFC 6/25	63	45 (71.4)	18 (28.6)	44.84	56 (88.9)	1 (1.6)	6 (9.5)
	OFC 6/50	63	47 (74.6)	16 (25.4)	45.69	57 (90.5)	2 (3.2)	4 (6.4)
	OFC 12/25	60	42 (70.0)	18 (30.0)	46.00	51 (85.0)	3 (5.0)	6 (10.0)
	OFC 12/50	57	39 (68.4)	18 (31.6)	46.82	52 (91.2)	0	5 (8.8)
	FLX	60	43 (71.7)	17 (28.3)	45.15	53 (88.3)	2 (3.3)	5 (8.3)
	OLZ	62	44 (71.0)	18 (29.0)	47.14	55 (88.7)	2 (3.2)	5 (8.0)
	VNL	59	46 (78.0)	13 (22.0)	44.22	52 (88.1)	4 (6.8)	3 (5.1)
	OFC 1/5	59	44 (74.6)	15 (25.4)	45.70	58 (98.3)	0	1 (1.7)
	Total	483	350 (72.5)	133 (27.5)	45.69	434 (89.9)	14 (2.9)	35 (7.2)
HGHZ	OFC	145	97 (66.9)	48 (33.1)	42.58	131 (90.3)	8 (5.5)	6 (4.1)
	FLX	142	103 (72.5)	39 (27.5)	41.71	129 (90.8)	7 (4.9)	6 (4.2)
	OLZ	144	93 (64.6)	51 (35.4)	43.35	119 (82.6)	14 (9.7)	11 (7.6)
	NRT	68	46 (67.6)	22 (32.4)	41.5	60 (88.2)	6 (8.8)	2 (3.0)
	Total	499	339 (67.9)	160 (32.1)	42.41	439 (88.0)	35 (7.0)	25 (5.0)
HDOA-1	OFC	102	63 (61.8)	39 (38.2)	43.33	87 (85.3)	6 (5.9)	9 (8.9)
	FLX	104	61 (58.7)	43 (41.3)	44.83	87 (83.7)	4 (3.8)	13 (12.5)
	OLZ	96	56 (58.3)	40 (41.7)	45.67	73 (76.0)	11 (11.5)	12 (12.5)
	Total	302	180 (59.6)	122 (40.4)	44.59	247 (81.8)	21 (7.0)	34 (11.2)

The demographic profiles of all studies were very similar and were roughly balanced across treatment groups in each individual study. Females constituted about 2/3 of the ITT population in all 5 studies. The mean ages were closely matched among all studies ranged from 41.68 to 45.69. Most of the population of all studies was Caucasian, from 88% to 96% in all studies except Study HDAO-1 in which Caucasian population (82%) was slightly lower.

6.1.4.2 Disease Characteristics

The baseline disease characteristics in acute treatment phase were summarized in Table 9.

Table 9 Baseline Disease Characteristics in Acute Treatment Phase by studies

Study	Treatment group	n	Age of onset of 1 st episode (years)	Length of current episode (days)	MADRS total score	CGI-Severity
			Mean	Mean	Mean	Mean
HDAO-2	OFC	98	28.83	502.44 (n=25)	30.52	4.68
	FLX	102	26.26	485.04 (n=57)	30.14	4.74
	OLZ	103	26.37	361.53 (n=53)	30.12	4.73
	Total	303	27.13	445.64 (n=83)	30.25	4.72
HGFR	OFC	10	33.8	461.7	29.5	4.6
	FLX	10	19.22 (n=9)	349.4	23.8	4.3
	OLZ	8	19.63	807.0 (n=7)	25.0	4.25
	Total	28	24.74 (n=27)	509.63 (n=27)	26.18	4.39
HGIE	OFC 6/25	63	32.43	416.89	28.34 (n=62)	4.37 (n=62)
	OFC 6/50	63	32.13	820.33	28.65	4.41
	OFC 12/25	60	30.83	610.80	30.35	4.48
	OFC 12/50	57	28.95	625.95	30.54	4.42
	FLX	60	30.82	569.25	31.63 (n=57)	4.46 (n=56)
	OLZ	62	31.53	659.18	30.51 (n=61)	4.57 (n=61)
	VNL	59	32.0	417.86	30.02 (n=58)	4.38 (n=58)
	OFC 1/5	59	32.14	633.25	30.35 (n=57)	4.38 (n=56)
	Total	483	31.38	594.85	30.02 (n=475)	4.44 (n=473)
HGHZ	OFC	145	23.77	925.71	28.5 (n=143)	4.38 (n=143)
	FLX	142	23.86	834.5	28.4 (n=141)	4.33 (n=140)
	OLZ	144	23.92	753.99	28.44	4.33
	NRT	68	25.96	832.69	28.77 (n=66)	4.41 (n=66)
	Total	499	24.14	837.52	28.49 (n=494)	4.36 (n=493)
HDOA-1	OFC	102	26.63	372.75 (n=51)	29.6	4.54
	FLX	104	25.95	391.79 (n=43)	29.67	4.7
	OLZ	96	29.4	370.28 (n=40)	29.72	4.58
	Total	302	27.27	378.12 (n=134)	29.66	4.61

The populations of all studies were similar with respect to severity of their depression measured by MADRS and CGI-Severity and there was no significant difference among treatment groups in each individual study. Most patients in all studies were moderately to severely depressed, with mean MADRS total scores of approximately 29 to 30 points and CGI-Severity total score ~4.4 to 4.7 points.

6.1.4.3 Concomitant Medications

The allowed concomitant medications in TRD studies included lorazepam (up to 4 mg/week), simple analgesics, and vitamins. Table 10 summarized the concomitant lorazepam use during acute treatment phase by studies.

Table 10 Concomitant Lorazepam Use during Acute Treatment Phase

Study	Treatment group	n	Lorazepam use (%)	Study	Treatment group	n	Lorazepam use (%)
HDAO-2	OFC	98	33 (33.7)	HDAO-1	OFC	102	23 (22.5)
	FLX	102	34 (33.3)		FLX	104	34 (32.7)
	OLZ	103	35 (34.0)		OLZ	96	26 (27.1)
	Total	303	102 (33.7)		Total	302	83 (27.5)
HGIE	OFC 6/25	63	5 (7.94)	HGFR	OFC	10	0
	OFC 6/50	63	13 (20.63)		FLX	10	2 (20.0)
	OFC 12/25	60	14 (23.33)		OLZ	8	1 (12.5)
	OFC 12/50	57	9 (15.79)		Total	28	3 (10.7)
	FLX	60	19 (31.67)	HGHZ	OFC	145	49 (33.79)
	OLZ	62	16 (25.81)		FLX	142	53 (37.32)
	VNL	59	11 (18.64)		OLZ	144	48 (33.33)
	OFC 1/5	59	13 (22.03)		NRT	68	24 (35.29)
	Total	483	100 (20.7)		Total	499	174 (34.87)

Deviations from the protocol list of excluded medications were recorded from a small number of patients. One patient in Study HDAO-1 (quetiapine), 1 in HDAO-2 (quetiapine), 1 in Study HDFR, 5 in Study HGIE (included 2 on quetiapine) and 1 in Study HGHZ were found taking antidepressants during acute treatment phase of the studies. The dose and duration of antidepressant use was unclear. Since the violations only involved in a very small number of patients, it is very unlikely that these violations would affect the efficacy results.

6.1.4.4 Disposition of Patients

Patient disposition was summarized in Table 11 by studies.

Table 11 Disposition of Patients by Studies

Study	Treatment group	Lead-in Phase	Acute Phase	Acute Phase	
				Completed (%)	Discontinued (%)
HDAO-2	Total	675	303 (44.9)	221 (72.9)	82 (27.1)
	OFC		98	75 (76.5)	23 (23.5)
	FLX		102	83 (81.4)	19 (18.6)
	OLZ		103	63 (61.2)	40 (38.8)
HGFR	Total	34	28 (82.4)	22 (78.6)	6 (21.4)
	OFC		10	9 (90.0)	1 (10.0)
	FLX		10	7 (70.0)	3 (30.0)
	OLZ		8	6 (75.0)	2 (25.0)
HGIE	Total	807	483 (59.9)	365 (75.6)	118 (24.4)
	OFC 6/25		63	51 (81.0)	12 (19.0)
	OFC 6/50		63	48 (76.2)	15 (23.8)
	OFC 12/25		60	46 (76.7)	14 (23.3)
	OFC 12/50		57	38 (66.7)	19 (33.3)
	FLX		60	48 (77.4)	12 (25.0)
	OLZ		62	44 (71.0)	18 (29.0)
	VNL		59	44 (74.6)	15 (25.4)
	OFC 1/5		59	46 (78.0)	13 (22.0)

HGHZ	Total	945	499 (52.8)	402 (80.6)	97 (19.4)
	OFC		145	116 (80.0)	29 (20.0)
	FLX		142	114 (80.3)	28 (19.7)
	OLZ		144	112 (77.8)	32 (22.2)
	NRT		68	60 (88.2)	8 (11.8)
HDAO-1	Total	638	302 (47.3)	220 (72.8)	82 (27.2)
	OFC		102	73 (71.6)	29 (28.4)
	FLX		104	83 (79.8)	21 (20.2)
	OLZ		96	64 (66.7)	32 (33.3)

In each individual study, roughly equal numbers of patients who were eligible for double-blind acute treatment phase were randomized to each treatment group except in Study HGHZ in which nortriptyline group was consisted of only about half amount of patients compared with other treatment groups. The overall completion rate cross all studies was similar, ranged from 73% to 81%. Olanzapine treated groups were associated with lowest completion rate (61% to 77%), followed by OFC treated groups (72% to 80%) except in Study HGFR. In HGFR, fluoxetine treated group had lowest completion rate (70%).

6.1.4.5 Discontinuation

Primary reasons for discontinuation in acute treatment phase were summarized by studies and treatment groups in Table 12.

Table 12 Discontinuation in Acute Treatment Phase by reasons

Study	Treatment Group	n	Discontinued (%)	Reasons for discontinuation			
				Adverse Events (%)	Lack of Efficacy (%)	Lost to Follow up (%)	Protocol Violation (%)
HDAO-2	OFC	98	23 (23.47)	12 (12.24)	1 (1.02)	3 (3.06)	
	FLX	102	19 (18.63)	2 (1.96)	5 (4.90)	3 (2.94)	3 (2.94)
	OLZ	103	40 (38.83)	22 (21.36)	8 (7.77)	1 (0.97)	3 (2.91)
	Total	303	82 (27.06)	36 (11.88)	14 (4.62)	7 (2.31)	6 (1.98)
HGFR	OFC	10	1 (10.0)	0	0		1 (10.0)
	FLX	10	3 (30.0)	0	1 (10.0)		1 (10.0)
	OLZ	8	1 (12.5)	1 (12.5)	0		1 (12.5)
	Total	28	6 (21.4)	1 (3.6)	1 (3.6)		3 (10.7)
HGIE	OFC 6/25	63	12 (19)	2 (3)	6 (9.5)	0	0
	OFC 6/50	63	15 (24)	3 (5)	5 (7.9)	2 (3)	0
	OFC 12/25	60	14 (23)	11 (18)	1 (1.7)	1 (2)	0
	OFC 12/50	57	19 (33)	13 (23)	1 (1.8)	1 (2)	0
	FLX	60	12 (20)	3 (5)	4 (6.7)	1 (2)	0
	OLZ	62	18 (29)	5 (8)	5 (8.1)	2 (3)	1 (2)
	VNL	59	15 (25)	1 (2)	7 (11.9)	2 (3)	1 (2)
	OFC 1/5	59	13 (22)	2 (3)	4 (6.8)	1 (2)	1 (2)
	Total	483	118 (24)	40 (8)	33 (6.8)	10 (2)	3 (1)
HGHZ	OFC	145	29 (20.0)	10 (6.9)	4 (12.8)	7 (4.8)	2 (1.4)
	FLX	142	28 (19.7)	4 (2.8)	9 (6.3)	4 (2.8)	2 (1.4)
	OLZ	144	32 (22.2)	13 (9.0)	6 (4.2)	3 (2.1)	2 (1.4)
	NRT	68	8 (11.8)	2 (2.9)	2 (3.0)	3 (4.4)	0

	Total	499	97 (19.4)	29 (5.8)	21 (4.2)	17 (3.4)	6 (1.2)
HDAO-1	OFC	102	29 (28.43)	15 (14.71)	6 (5.88)	3 (2.94)	4 (3.92)
	FLX	104	21 (20.19)	3 (2.88)	8 (7.69)	5 (4.81)	1 (0.96)
	OLZ	96	32 (33.33)	10 (10.42)	11 (11.46)	3 (3.13)	1 (1.04)
	Total	302	82 (27.15)	28 (9.27)	25 (8.28)	11 (3.64)	6 (1.99)

The most common reason for discontinuation among all studies was “adverse events”, followed by “lack of efficacy”, “lost to follow up” and “personal conflict”. Olanzapine and OFC treatments were associated with higher discontinuation rate caused by adverse events.

6.1.4.6 Efficacy Results

6.1.4.6.1 Study HDAO

Primary variable: MADRS total score change from baseline to end point

The primary variable of this study was to assess the antidepressant efficacy of OFC versus olanzapine and fluoxetine up to 8 weeks in patients with TRD as measured by LOCF mean change from baseline to endpoint in the MADRS total score.

HDAO-1

The mean change from baseline to endpoint on MADRS total score in Study HDAO-1 (LOCF) was shown in Table 13. As shown in the table, OFC did not statistically separate from fluoxetine or olanzapine monotherapy. The result from visit-wise OC analysis on mean change from baseline to endpoint on MADRS total score was consistent with the result from LOCF (see Table 34 in Appendices 10.2).

Table 13 Mean Change from Baseline to Endpoint on MADRS Total Score in Study HDAO-1 (LOCF)

	OFC N=101	FLX N=102	OLZ N=95	p-Values		
				Overall	OFC vs. FLX	OFC vs. OLZ
Baseline Mean (SD)	29.47 (7.11)	29.66 (6.9)	29.72 (7.06)			
Mean Change (SD)	-10.75 (10.04)	-9.42 (9.94)	-10.14 (9.6)	0.64	0.346	0.624

HDAO-2

The mean change from baseline to endpoint on MADRS total score in Study HDAO-2 (LOCF) was shown in Table 14. OFC-treated patients had a statistically significantly greater mean decrease in the MADRS total score (-14.62) than both fluoxetine-treated patients (-8.96) and olanzapine-treated patients (-7.71). Patients treated with OFC had statistically significantly greater decreases on the MADRS total score than did the fluoxetine-treated patients at every week of the study, including endpoint, and had statistically significantly greater decreases than did olanzapine-treated patients at Week 1 and from Week 4 through endpoint (Week 8). The

visitwise OC analysis further confirmed the findings from LOCF analysis. Patients treated with OFC had statistically significant decrease on the MADRS than did the fluoxetine treated patients at every week of the study and had statistically significant decrease on the MADRS than did the olanzapine treated patients at week 1 and from week 6 to endpoint (see Table 35 in Appendices 10.2).

Table 14 Mean Change from Baseline to Endpoint on MADRS Total Score in Study HDAO-2 (LOCF)

	OFC N=97	FLX N=101	OLZ N=102	p-Values		
				Overall	OFC vs. FLX	OFC vs. OLZ
Baseline Mean (SD)	30.64 (6.12)	30.13 (5.91)	30.08 (6.33)			
Mean Change (SD)	-14.62 (10.22)	-8.96 (9.49)	-7.71 (8.2)	<0.001	<0.001	<0.001

Non- Key Secondary variables: CGI-Severity scale and Remission Rates Based on MADRS Total Scores

Since HDAO-1 failed its primary and secondary variables, the efficacy data from secondary variables will not be presented in this review.

CGI-Severity Scale

The mean change from baseline to endpoint in CGI-Severity (LOCF) is summarized in Table 15. OFC-treated patients had statistically significantly greater decreases in CGI-Severity scale than did fluoxetine- or olanzapine-treated patients at endpoint (8 weeks) in acute treatment phase.

Table 15 Mean Change from Baseline to Endpoint on CGI-Severity in Study HDAO-2 (LOCF)

	OFC N=97	FLX N=101	OLZ N=102	p-Values		
				Overall	OFC vs. FLX	OFC vs. OLZ
CGI-Severity						
Baseline Mean (SD)	4.72 (0.63)	4.73 (0.75)	4.73 (0.73)			
Mean Change (SD)	-1.53 (1.33)	-1.05 (1.17)	-0.81 (1.09)	<0.001	0.004	<0.001

Remission rates based on MADRS total scores

The incidence of and time to two types of remission were analyzed: remission (defined as having an endpoint MADRS total score ≤ 10) and sustained remission (defined as having at least two consecutive MADRS total scores ≤ 10 , including the endpoint visit). Statistically significantly higher proportions of OFC-treated patients exhibited remission at endpoint compared with both fluoxetine-treated and olanzapine-treated patients (31% versus 16% and 11%, respectively), and the time-to-remission curves were statistically significantly different overall, with OFC-treated patients achieving remission statistically significantly earlier than both fluoxetine-treated and olanzapine-treated patients.

Similarly, A statistically significantly higher proportion of OFC-treated patients exhibited sustained remission at endpoint compared with both fluoxetine-treated and olanzapine-treated patients (26% versus 12% and 9%, respectively), and the time-to-sustained remission curves were statistically significantly different overall, with OFC-treated patients achieving sustained remission statistically significantly earlier than both fluoxetine-treated and olanzapine-treated patients.

Incidence of remission for acute treatment phase in HDAO-2 is summarized in Table 16.

Table 16 Incidence of Remission and Sustained Remission for Acute Treatment Phase in Study HDAO-2

Variable	OFC (N=97)	FLX (N=101)	OLZ (N=102)	Overall	p-Values		
					OFC vs FLX	OFC vs OLZ	FLX vs OLZ
Remission ^a	30 (30.9%)	16 (15.8%)	11 (10.8%)	.001	.018	<.001	.309
Sustained remission ^b	25 (25.8%)	12 (11.9%)	9 (8.8%)	.003	.017	.002	.499

Proportions analyzed using two-tailed Fisher's exact test.

Abbreviations: FLX = fluoxetine; N = total number of patients; OFC = olanzapine plus fluoxetine in combination; OLZ = olanzapine; vs = versus.

^a Remission is defined as MADRS score ≤10 at endpoint.

^b Sustained remission is defined as MADRS ≤10 for at least 2 consecutive visits, including endpoint.

6.1.4.6.2 Study HGFR

The primary variable of Study HGFR was mean change from baseline to endpoint in HAMD-21 total score. The non-key secondary variables were mean change from baseline to endpoint in MADRS total score and CGI-Severity scale. The study failed its primary variable: OFC treated patients did not show statistically significant decrease in HAMD-21 total score than did fluoxetine (OFC vs. FLX p=0.061) and olanzapine (OFC vs. OLZ p=0.19) monotherapy. But in both MADRS and CGI-Severity, OFC treatment showed statistical superiority to fluoxetine and olanzapine monotherapies. Table 17 summarized mean change from baseline to endpoint in MADRS and CGI-Severity in Study HGFR. The visitwise OC analysis on mean change from baseline to endpoint in MADRS was consistent with the findings from LOCF (see Table 36 in Appendices 10.3).

Table 17 Mean Change from Baseline to Endpoint on MADRS Total Score and CGI-Severity in Study HGFR (LOCF)

	OFC N=10	FLX N=10	OLZ N=8	p-Values		
				Overall	OFC vs. FLX	OFC vs. OLZ
MADRS Total						
Baseline Mean (SD)	29.5 (9.2)	23.8 (8.3)	25 (3.8)			
Mean Change (SD)	-13.6 (11.9)	-1.2 (11.0)	-2.8 (6.0)	0.026	0.012	0.035
CGI-Severity						
Baseline Mean (SD)	4.6 (0.8)	4.3 (0.7)	4.3 (0.7)			
Mean Change (SD)	-2 (1.3)	-0.4 (1.2)	0 (0.9)	0.003	0.005	0.001

As discussed in 6.1.2 General Discussion of Endpoint, both HAMD and MADRS are well-validated and standard tools to assess improvement of depression. However, using MADRS as the primary analysis measure in studies that include olanzapine helps to differentiate direct effects on mood from effects on sleep and appetite. HGFR was the first TRD study and was the only TRD study that uses HAMD as the primary measure for evaluation of depression. In the rest of TRD studies, MADRS was used as the primary variable. Therefore, I would consider Study HGFR as a positive supportive study based on its positive findings in MADRS even though the study failed its primary variable.

6.1.4.6.3 Study HGIE

Study HGIE was a dose-ranging study. Four different OFC doses (6/25, 6/50, 12/25 and 12/50) were chosen to assess the efficacy of OFC against olanzapine, fluoxetine and venlafaxine in the treatment of TRD measured by mean change from baseline to endpoint (12 weeks) in MADRS total score. The OFC 6/25, OFC 6/50, OFC 12/25, and OFC 12/50 treatment groups each had statistically significantly greater mean decreases in MADRS total score compared with the OLZ treatment group. However, none of the individual OFC treatment groups were statistically significantly different from the FLX or VNL treatment groups. Examination of the mean change from baseline in MADRS suggested no evidence of dose-response. The composite OFC treatment group (composite of OFC 6/25, 6/50, 12/25 and 12/50 group) had a statistically significantly greater mean decrease in MADRS total score from baseline to endpoint compared with the OLZ treatment group. However, the composite OFC treatment group was not statistically significantly different from the FLX or VNL treatment groups. Using visit-wise analyses, the composite OFC treatment group had a statistically significantly greater mean decrease in MADRS total score for up to eight weeks of treatment compared with the FLX treatment group. The result of LOCF analysis in mean change from baseline to endpoint in MADRS total score was summarized in Table 18.

Table 18 Mean Change from Baseline to Endpoint in MADRS Total Score in Study HGIE (LOCF)

	OFC 6/25 N=59	OFC 6/50 N=61	OFC 12/25 N=55	OFC 12/50 N=56	FLX N=56	OLZ N=59	VNL N=58	OFC 1/5 N=55
Baseline (SD)	28.44 (7.24)	28.87 (7.92)	30.58 (5.85)	30.79 (6.16)	31.50 (6.22)	30.48 (6.91)	30.02 (5.18)	30.15 (7.16)
Mean Δ (SD)	-13.34 (9.87)	-11.90 (11.48)	-11.67 (9.04)	-13.09 (10.04)	-10.66 (10.88)	-7.29 (11.28)	-11.93 (9.77)	-10.69 (10.27)
					P - Values			
OFC* vs.					.271	.000	.606	.229
OFC 6/25 vs.					.168	.001	.360	.144
OFC 6/50 vs.					.613	.016	.978	.554
OFC 12/25 vs.					.644	.021	.997	.586
OFC 12/50 vs.					.250	.003	.490	.217

OFC*: composite of OFC 6/25, OFC 6/50, OFC 12/25 and OFC 12/50

Mean change in MADRS total score was also examined within the subset of patients with historical failure to SSRI treatment during their current episode of MDD (n = 334). In this subset, the composite OFC treatment group demonstrated a statistically significantly greater mean decrease in MADRS total score compared with both the FLX (p=0.021) and OLZ (p=0.003) treatment group.

The result from visitwise OC analysis on mean change from baseline to endpoint in MADRS total score in all patients was consistent with the results from LOCF analysis: OFC treatment showed statistical superiority to olanzapine monotherapy (p = 0.004), but not to fluoxetine (p = 0.35) or venlafaxine monotherapies (p = 0.88). The result from visitwise OC analysis in patients with historical failure to SSRI treatment during their current episode of MDD showed OFC treatment was statistically superior to fluoxetine treatment (p = 0.049), but not to olanzapine (p = 0.061) or venlafaxine (p = 0.754) (see Table 37 in Appendices 10.2).

Study HGIE is one of the earlier TRD studies which had relatively liberal TRD defining criteria—patients historically failed one antidepressant (not have to be in current depressive episode), plus failed lead-in treatment phase (second antidepressant). Later, the sponsor applied more restrictive inclusion criteria to TRD studies (HDAO 1&2) —patients had to fail two adequate antidepressant trials in current depressive episode to be included. The sponsor believes that patients who meet the more restrictive criteria represent a more treatment-resistant population. I agree. Therefore, I would consider Study HGIE as a positive supportive study based on its positive findings in MADRS in the subset of patients who failed two antidepressants in current depressive episode, even though the study failed its pre-specified primary variable—mean change in MADRS total score in all patients.

6.1.4.6.4 Study HGHZ

The primary efficacy analysis in Study HGHZ was mean change from baseline to endpoint for MADRS total score. Using pair-wise comparisons, the OFC treatment group had a statistically

significantly ($p = .044$) greater mean decrease at endpoint in MADRS total score compared with the OLZ treatment group. There were no statistically significant differences between the OFC and FLX treatment groups, or between the OFC and NRT treatment groups. Visitwise analyses (LOCF) revealed that The OFC treatment group had a statistically significantly greater mean decrease in MADRS total score compared with the FLX treatment group at Weeks 1, 2, 3, 4, and 5. The OFC treatment group had a statistically significantly greater mean decrease in MADRS total score compared with the OLZ treatment group at Weeks 1, 2, 4, 6, 7, and 8. Table 19 summarizes mean change from baseline to endpoint in the primary efficacy measure (MADRS total score) for all patients during the acute phase (LOCF).

Table 19 Mean Change from Baseline to Endpoint on MADRS Total Score in Study HGHZ (LOCF)

	OFC N=145	FLX N=142	OLZ N=144	NRT N=68	p-Values			
					Overall	OFC vs. FLX	OFC vs. OLZ	OFC vs. NRT
Baseline (\pm SE)	28.7 (0.6)	28.4 (0.6)	28.4 (0.6)	28.8 (0.8)				
Mean Δ (\pm SE)	-8.6 (0.8)	-7.6 (0.8)	-6.5 (0.8)	-7.2 (1.3)	0.225	0.332	0.044	0.393

Mean change in MADRS total score was also examined within the subset of patients with historical failure to SSRI treatment during their current episode of MDD. The results were consistent with the findings from all patients (OFC vs. FLX: $p = 0.106$; OFC vs. OLZ $p = 0.007$).

6.1.4.7 Subgroup Analyses

Subgroup analyses were performed evaluating change from baseline to endpoint on the MADRS within subgroups based on race, sex, age. Subgroup analysis data from Study HDAO and HGIE (positive and supportive studies) were reviewed. There were no subgroup for which there was a statistically significant therapy-by-subgroup interaction ($p < .10$). Subgroup analyses were not performed in Study HGFR (positive pilot study) due to the small sample size.

6.1.5 Clinical Microbiology

Not applicable for this submission

6.1.6 Efficacy Conclusions

Study HDAO-2

OFC was statistically significantly more effective than olanzapine or fluoxetine monotherapy in reducing depressive symptoms in TRD population over the 8-week study as assessed by the primary variable of change from baseline on MADRS total score.

Results on secondary variables of efficacy, including CGI-Severity and remission rates, paralleled results for the primary variable with OFC showing statistically significant superiority over FLX and OLZ.

Thus, this study is considered as a positive pivotal study.

Study HGFR

There was no statistically significant difference among OFC, FLX and OLZ treatment groups in treatment of TRD in the 8 week study measured by HAMD-21 total score, the primary variable. However, the OFC treatment group demonstrated statistically significantly greater decrease from baseline in MADRS total score and CGI-Severity score as compared with the FLX and OLZ treatment group. Since MADRS also is a well-validated and standard measurement to assess improvement of depression, I consider this study as a positive supportive study.

Study HGIE

The composite OFC treatment group (a pre-specified analysis approach, composite of OFC 6/25, 6/50, 12/25 and 12/50 group) had a statistically significantly greater mean decrease in MADRS total score from baseline to endpoint (12 weeks) compared with the OLZ treatment group in TRD population, but not the FLX or VNL treatment group.

In a subset of patients with historical failure to SSRI treatment during their current episode of MDD, the composite OFC treatment group demonstrated a statistically significantly greater mean decrease in MADRS total score compared with both the FLX and OLZ treatment group at the end of 12 weeks. If we agree that this subset of patients represents a more treatment-resistant population, even though data from this subset patients were post-hoc, I would consider this study a positive supportive study.

Study HGHZ

The OFC treatment group had a statistically significantly greater mean decrease at endpoint (8 weeks) in MADRS total score compared with the OLZ treatment group, but not the FLX or NRT treatment group.

Study HDAO-1

OFC was not statistically more effective than OLZ or FLX monotherapy in the treatment of TRD over the 8 week study as assessed by change from baseline on MADRS total score.

Summary

A total of 5 double-blind, placebo-controlled TRD clinical studies were conducted by Lilly. Only one study (HDAO-2) had clearly positive results on both primary and secondary variables. In Study HGFR, HAMD-21 was the pre-specified primary and the study failed HAMD-21. However, Study HGFR had positive results on MADRS (OFC separated from FLX and OLZ). In study HGIE, OFC showed statistically significantly greater reduction on the MADRS than both FLX and OLZ after 8 weeks of treatment. However the difference over FLX was only numerically superior after 12 weeks of treatment and the 12 week study is the pre-specified study design. If the more restrictive inclusion criteria (failed two antidepressants in current episode) were applied to Study HGIE, OFC was statistically superior to FLX and OLZ monotherapies at the end of 12 weeks. In Study HGHZ, OFC treatment is only superior to OLZ at the end of 8

weeks and Study HDAO-1 was a totally negative study—OFC did not separate from either FLX or OLZ.

Efficacy summary for acute treatment phase in patients with two antidepressant failures in current depressive episode by studies was presented in Table 20.

Table 20 Efficacy Summary for Acute Treatment Phase in Patients with Two Antidepressant Failures in Current Depressive Episode by Studies

Study		HDAO-2	HGFR	HGIE	HGHZ	HDAO
Sample Evaluated for Efficacy		OFC=97 FLX=101 OLZ=102	OFC=10 FLX=10 OLZ=8	OFC=163 FLX=41 OLZ=47	OFC=91 FLX=88 OLZ=90	OFC=101 FLX=102 OLZ=95
MADRS	OFC	-14.6 <u>p vs. OFC</u>	-13.6 <u>p vs. OFC</u>	-13.3 <u>p vs. OFC</u>	-9.0 <u>p vs. OFC</u>	-10.8 <u>p vs. OFC</u>
LOCF	FLX	-9.0 p<0.001	-1.2 p=0.012	-10.0 p=0.021	-7.0 p=0.106	-9.4 p=0.346
Endpoint	OLZ	-7.7 p<0.001	-2.8 p=0.035	-8.8 p=0.003	-5.1 p=0.007	-10.1 p=0.624

In summary, there are one positive pivotal study (HDAO-2) and two supportive studies (HGFR and HGIE) supporting the use of Symbyax for TRD indication. Based on FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Product, Part II C section 2, these data are felt to provide sufficient evidence of efficacy in treatment of TRD.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The integrated safety database used for this review included patients who participated in the double-blind, acute phases of 10 controlled clinical depression trials and who were randomized to either OFC, fluoxetine, olanzapine, or placebo for up to 12 weeks. These 10 clinical trials (represented by 7 clinical protocols, 3 of which involved 2 identical studies conducted under a single protocol) were conducted in patients with several forms of depression: treatment-resistant depression (5 studies), bipolar depression (2 studies), major depressive disorder (MDD) with psychotic features (2 studies), and MDD with sexual dysfunction (1 study). Table 21 summarizes studies that were included in the integrated safety database.

Table 21 Studies Included in the Integrated Safety Database

Protocol No.	Study Design
H6P-MC-HDAO (1&2)	Double-blind, multicenter, parallel, randomized studies in patients TRD, starting with fluoxetine lead-in period and ending with an OFC open-label period.
F1D-MC-HGGY (1&2)	Double-blind, multicenter, parallel, randomized studies in patients with bipolar disorder—depressed, with an olanzapine or OFC open-label period.

F1D-MC-HGHZ	Double-blind, multicenter, parallel, randomized study in patients with TRD, starting with a nortriptyline lead-in period and ending with an OFC open-label period.
F1D-MC-HGIE	Double-blind, multicenter, parallel, randomized, dose ranging, comparative study in patients with TRD, starting with a venlafaxine lead-in period and ending with an OFC open-label period.
F1D-MC-HGFR	Double-blind, multicenter, parallel, randomized studies in patients with TRD, starting with a fluoxetine lead-in period and ending with an OFC open-label period.
F1D-MC-HGGA (1&2)	Double-blind, multicenter, parallel, randomized studies in MDD patients with psychotic features, ending with an OFC open-label period.
B1Y-MC-HCKB	Double-blind, multicenter, parallel, randomized, fluoxetine-controlled studies of premenopausal women experiencing sexual dysfunction while receiving fluoxetine treatment.

Since marketing of OFC began in January 2004, its safety profile has been well established. The safety review from this submission did not detect any unexpected serious adverse events and the patterns of common adverse events of OFC remained same as its current labeling.

7.1.1 Deaths

There were 4 deaths reported in the OFC integrated safety database—one from OFC- and 3 from placebo-treated groups. None of the deaths were considered to be related to study drug or study procedures by investigators:

- Patient HGIE-641-7451 (randomized to OFC 12/25) died from an accidental gunshot wound incurred during a hunting accident.
- Patient HGGY-010-0326 (randomized to placebo) died after a stabbing incident; autopsy results gave the cause of death as blunt force trauma to the head and chest.
- Patient HGGY-403-4051 (randomized to placebo) committed suicide by hanging.
- Patient HGGY-702-7029 (randomized to placebo) committed suicide by drowning.

7.1.2 Other Serious Adverse Events

Serious adverse events (SAEs) were experienced by 4.0% of OFC-treated, 2.8% of fluoxetine-treated, 3.4% of olanzapine-treated, and 5.9% of placebo-treated patients. The only SAEs that were reported by 2 or more of the 771 OFC-treated patients were depression (8 patients), suicidal ideation (6), chest pain (2), dyspnea (2), and peripheral edema (2). The SAE of depression was statistically significantly more common in OFC-treated than in fluoxetine-treated patients. The majority of these depression events occurred in Studies HGGY and HGGA, which were studies in bipolar and psychotic depression, respectively, and did not have fluoxetine treatment arms. Given the smaller sample size for fluoxetine compared to OFC and the lack of fluoxetine arms in the studies with the highest rates of serious depression events, it is difficult to assess the potential relationship to fluoxetine. There were no other statistically significant differences between OFC and other treatment groups with respect to rates of individual SAEs.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall Profile of Dropouts

In the integrated safety database, OFC and olanzapine treatment was associated with higher dropout rate due to adverse events. 11.3% of all OFC-treated patients discontinued due to AEs compared to 3.3%, 10.9%, and 4.4% of fluoxetine-, olanzapine-, and placebo-treated patients, respectively.

7.1.3.2 Adverse Events Associated with Dropouts

Most of the adverse events that commonly led to discontinuation for OFC-treated patients were events that were common with OFC and olanzapine (weight gain, somnolence, sedation) or that were associated with the underlying disease (suicidal ideation). The only events that led to discontinuation at a statistically significantly higher rate for OFC-treated patients than for another group were increased weight (2.1%) and sedation (1.3%) (compared with fluoxetine- and placebo-treated patients). In general, rates of discontinuation due to adverse events, both overall and for individual events, were similar for OFC- and olanzapine-treated patients. Table 22 summarizes the discontinuations due to AEs in the integrated safety database.

Table 22 Discontinuations Due to Adverse Events in the Integrated Safety Database

Event ^a	OFC	FLX	OLZ	PBO
	N=771 %	N=457 %	N=884 %	N=477 %
ANY EVENT	11.3	3.3	10.9	4.4
Weight increased	2.1	0.0	1.7	0.0
Sedation	1.3	0.0	1.0	0.0
Suicidal ideation	0.6	0.0	0.5	0.4
Somnolence	0.5	0.2	0.5	0.0
Fatigue	0.4	0.0	0.1	0.0
Increased appetite	0.4	0.0	0.2	0.0
Disturbance in attention	0.3	0.0	0.1	0.0
Liver function test abnormal	0.3	0.0	0.0	0.0
Peripheral edema	0.3	0.0	0.3	0.0
Tremor	0.3	0.0	0.0	0.0
Depression	0.1	0.0	0.3	0.2
Suicide attempt	0.0	0.0	0.1	0.6

^a Event list comprises all events for which the rate for OFC was 0.3% or more in either database.

7.1.3.3 Other Significant Adverse Events

No other clinically significant adverse events were detected.

7.1.4 Other Search Strategies

Suicidality

Placebo-Controlled Suicidality Review

In response to FDA request, Lilly submitted a safety report in March 2006 (updated in June 2006) summarizing placebo-controlled data on suicidality from two study protocols (4 studies: HGGA 1&2, HGGY1&2). HGGA is a study of MDD with psychotic feature and HGGY is a study of bipolar depression.

There were no completed suicides or deaths in the OFC-treated group within the double-blind phase of the studies. Two completed suicides occurred within placebo-treated patients in the double-blind phase. No “possible suicidal behaviors (completed suicides, suicide attempts or self-injurious behaviors)” were observed in OFC-treated patients, but were observed in the placebo-treated group. A statistically significantly greater incidence of suicidal ideation events (measured by suicidal items of the HAMD-24 in Study HGGA and MADRS in HGGY) was observed in OFC-treated patients compared with placebo-treated patients when the two placebo-controlled protocols were combined, but the results varied depending on the protocol (study), and were not consistent in the analyses of scale suicide items.

In summary, Lilly concluded that this review do not indicate an increased risk of suicidality in patients treated with OFC compared with those treated with placebo.

TRD Suicidality Review

Lilly applied text string searches that potentially indicate suicide attempts to actual and preferred terms across all patients in all studies (and including all phases of each study) to produce a listing of events that might represent possible suicide attempts. (The specific text strings were provided by FDA in the 12 November 2005 suicidality request, and included: *accident, asphyxiation, attempt, burn, cut, drown, firearm, gas, gun, hang, hung, immolat, injur, jump, monoxide, mutilat, overdos, poison, self-damag, self damag, self-harm, self harm, self-inflict, self inflic, self-injur, self injur, shoot, slash, suic, and suffocation*. In addition, certain text strings were excluded through programming).

A complete list of relevant events was provided to Lilly Global Product Safety. This list was reviewed, and events that were not possible suicide attempts (or completed suicides) were removed from the list. Patient information was then reviewed for the resulting cases of possible suicide attempts and completed suicides. Based on this review, the Lilly safety physician concluded that no further evaluation was warranted at this time, because the reviewed data do not change the conclusions of the placebo-controlled suicidality review.

Treatment-Emergent Mania/Hypomania

Mania-related treatment-emergent adverse events were summarized (adjusted for exposure), and treatment groups were compared. The population evaluated for this analysis was limited to patients in TRD trials (HDAO, HGFR, HGIE, and HGHZ), since the risk for mania might differ in a TRD population versus some of the other populations in the database (in particular, a population with bipolar disorder).

In patients in TRD trials, very few patients had mania-related events (logorrhea, elevated mood, euphoric mood, hypomania, mood swings, psychomotor hyperactivity, libido increased, pressure of speech), and there were no statistically significant differences between OFC and the other treatment groups in exposure-adjusted event rates for mania-related events. Table 23 summarizes the incidence of treatment-emergent adverse events possibly related to mania in TRD studies.

Table 23 Incidence of Treatment-Emergent Adverse Events Possibly Related to Mania in TRD studies

	OFC		FLX		OLZ	
	N	n (%)	N	n (%)	N	n (%)
Patients with \geq TEAE	599	8 (1.3)	418	4 (1.0)	413	8 (1.9)

TEAE: Treatment-emergent adverse events

7.1.5 Common Adverse Events

7.1.5.1 Eliciting Adverse Events Data in the Development Program

Treatment-emergent adverse events were defined as events that first occurred or worsened after baseline. All adverse events recorded prior to the first administration of study drug, and any secondary conditions were used as baseline. Secondary conditions were defined as events occurring prior to Visit 1 (that is, pre-existing conditions that patients bring with them into a study).

7.1.5.2 Appropriateness of Adverse Event Categorization and Preferred Terms

Adverse events were coded to lower level MedDRA terms according to the MedDRA dictionary in effect at the time of processing; for analysis purposes, MedDRA version 8.0 was used to map lower-level terms to preferred terms. Analyses were then conducted at the preferred-term level.

7.1.5.3 Incidence of Common Adverse Events

OFC treated patients exhibited an overall AE rate of approximately 83%, higher than placebo treated patients (74%), but similar to olanzapine- (82.7%) and fluoxetine- treated (82.3%) patients.

The most frequently reported adverse events in the OFC treatment group (reported by $\geq 5\%$ of OFC-treated patients) were: increased weight, increased appetite, dry mouth, somnolence, fatigue, headache, peripheral edema, tremor, dizziness, sedation, diarrhea, nausea, and anxiety.

Frequently reported events for which the exposure-adjusted event rates were statistically significantly higher for OFC than for a comparator included for fluoxetine: increased weight, increased appetite, dry mouth, somnolence, fatigue, peripheral edema, tremor, and sedation; and for placebo: increased weight, increased appetite, dry mouth, somnolence, fatigue, peripheral edema, and tremor. There were no commonly reported events for which event rates were statistically significantly higher (after adjusted with exposure) for OFC than for olanzapine.

7.1.5.4 Common Adverse Event Tables

Table 24 summarizes the incidence of adverse events in the integrated safety databases for which the rate for OFC-treated patients was at least 2% and statistically significantly greater than at least one of the other treatment groups.

Two relatively common events that were reported statistically significantly more often by OFC-treated than olanzapine-treated patients were peripheral edema and tremor. For both events, the differences were not statistically significant when exposure-adjusted event rates are examined.

Table 24 Treatment-Emergent Adverse Events in the Integrated Safety Database

Event ^a	OFC N=771 %	FLX N=457 %	OLZ N=884 %	PBO N=477 %
ANY EVENT	83.1	82.3	82.7	74.6
Weight increased	24.9	6.6 ^b	23.5	2.9 ^b
Increased appetite	19.7	5.5 ^b	17.9	3.6 ^b
Dry mouth	15.2	5.3 ^b	16.1	6.3 ^b
Somnolence	13.7	6.6 ^b	12.1	6.1 ^b
Fatigue	12.5	7.9 ^b	11.3	2.3 ^b
Peripheral edema	9.3	0.9 ^b	6.0 ^b	0.4 ^b
Tremor	9.2	5.3 ^b	5.9 ^b	2.9 ^b
Sedation	8.4	2.6 ^b	11.2	3.8 ^b
Hypersomnia	4.9	1.8 ^b	5.1	0.8 ^b
Disturbance in attention	4.7	3.3	4.9	1.3 ^b
Vision blurred	4.5	2.0 ^b	4.1	2.1 ^b
Restlessness	4.3	3.1	4.2	0.6 ^b
Arthralgia	3.8	2.2	4.6	1.5 ^b
Edema	3.2	0.9 ^b	2.9	0.0 ^b
Asthenia	2.9	2.0	2.6	0.6 ^b
Flatulence	2.7	0.9 ^b	2.9	1.3
Abdominal distention	2.5	0.0 ^b	2.4	0.4 ^b
Pain	2.2	1.1	2.6	0.6 ^b
Thinking abnormal	2.2	0.2 ^b	0.6 ^b	0.6 ^b

^a Event list comprises all events for which the rate for OFC was at least 2% and statistically significantly greater than one of the comparators in the controlled database.

^b Indicates that $p < .05$ compared to OFC by Fisher's exact test.

7.1.5.5 Identifying Common and Drug-Related Adverse Events

As mentioned in 7.1.5.4 Common adverse event tables, common and drug-related adverse events were identified by 1) the rate of AEs for OFC-treated patients was at least 2%, and 2) statistically significantly greater than at least one of the other treatment groups.

Most of the events in above table were reported statistically significantly more often by OFC-treated patients than by placebo-treated patients and by fluoxetine-treated patients, but not olanzapine-treated patients. This finding confirms previous data suggesting that OFC's adverse event profile is similar to that of olanzapine.

7.1.5.6 Additional Analyses and Explorations

Extrapyramidal Symptoms

No new or clinically significant differences between OFC and comparator groups on assessments of extrapyramidal symptoms (EPS) (measured by Simpson-Angus Scale total score, the Barnes Akathisia Scale total score, and the Abnormal Involuntary Movement Scale total score) were identified. In analyses of mean change from baseline to endpoint on EPS scale scores, OFC-treated patients had a mean decrease (improvement) on the Barnes score that was statistically significantly different from a mean increase observed in patients treated with olanzapine; and a mean decrease (improvement) on the Simpson-Angus score that was significantly smaller than the mean decrease seen in patients treated with placebo.

In evaluations based on predefined changes in EPS scale scores (See 10.3 in Appendices for criteria), the incidences of treatment-emergent parkinsonism, akathisia, and dyskinesia at any time in the integrated safety database were 3.1%, 11%, and 1.2%, respectively. Furthermore, there were few statistically significant differences between OFC and comparator groups in the proportions of patients experiencing such symptoms, with no cases where OFC incidence was statistically greater than placebo incidence.

In evaluation of incidence of EPS-related adverse events, there were no statistically significant differences between OFC and olanzapine. However, OFC had statistically significantly higher exposure-adjusted event rates than fluoxetine and placebo on 3 comparisons: rates of any adverse event possibly related to EPS, rates of any parkinsonism-related adverse event, and rates of the specific parkinsonism-related event of tremor.

OFC appears to be associated with a slightly higher incidence of tremor than either of its components due to an additive effect of EPS-related tremor from olanzapine and SSRI-related tremor from fluoxetine (see Table 24).

7.1.6 Less Common Adverse Events

No less common adverse events of significant concern were identified in these studies.

7.1.7 Laboratory Findings

7.1.7.1 Overview of Laboratory Testing in the Development Program

Routine safety laboratory including hematology, clinical chemistry, lipid panel, and urinalysis testing were conducted. Mean change from baseline to endpoint, treatment-emergent abnormalities at endpoint and at any time, and treatment-emergent potentially clinically significant abnormalities for each laboratory analyte were analyzed.

7.1.7.2 Selection of Studies and Analyses for Drug-Control Comparisons of Laboratory Values

The laboratory data from 10 depression studies (5 TRD studies, 2 bipolar depression studies, 2 MDD with psychotic feature studies and 1 MDD with sexual dysfunction) were analyzed in this integrated safety database. Controlled comparison between treatment groups was applied to analyze the mean change from baseline, outliers, dropouts, and special analyses (See 7.1.7.4).

7.1.7.3 Standard Analyses and Explorations of Laboratory Data

7.1.7.3.1 Analyses Focused on Measures of Central Tendency

Statistically significant differences in mean changes at endpoint were observed between treatment groups for several laboratory measures. In general, the changes observed in OFC-treated patients were consistent with changes that have previously been observed with OFC and its component monotherapies, particularly olanzapine. This observation is supported by review of the most common treatment-emergent laboratory abnormalities seen at anytime in OFC-treated patients, which included: high prolactin (incidence rate of OFC vs. PLA: 27.6% vs. 4.8%), low total bilirubin (15.3% vs. 3.9%), low bicarbonate (14.1% vs. 8.8%), high ALT (7.8% vs. 0.5%), high fasting glucose (7.1% vs. 0%), high hemoglobin A1c (HbA1c) (5.9% vs. 0%), and high triglycerides (5.2% vs. 0%). Rates of abnormalities in OFC-treated patients tended to be similar to or lower than rates seen in olanzapine-treated patients; the only abnormalities seen statistically more often in patients treated with OFC than in patients treated with olanzapine were low erythrocytes (1.9% vs. 0.5%), high cholesterol (3.9% vs. 1.7%), and high fructosamine (4.6% vs. 1.3%). In contrast, numerous abnormalities were seen at higher rates in OFC-treated than in fluoxetine-treated or in placebo-treated patients, suggesting that OFC's safety profile with respect to treatment-emergent laboratory abnormalities is similar to that of olanzapine.

There were several analytes for which OFC had statistically significantly greater mean changes than all three of the other treatment groups that were all examined in more detail: hematocrit, hemoglobin, erythrocyte count, and albumin (all decreases); and alkaline phosphatase, urea nitrogen, creatinine, and cholesterol (all increases). For all of these analytes, further assessment of treatment-emergent high or low values and potentially clinically significant values revealed similar patterns as those seen in the original OFC safety package, and led to similar conclusions.

7.1.7.3.2 Analyses Focused on Outliers or Shifts from Normal to Abnormal

Potentially clinically significant changes were low overall. The only analytes for which statistically significantly higher proportions of OFC-treated patients had potentially clinically significant abnormalities than other treatment groups were GGT (as compared to placebo), Non-fasting glucose (compared to both fluoxetine and placebo), and glucose in the urine (compared to fluoxetine). More discussions regarding to glucose and other metabolic measures, hepatic laboratory will be found in 7.1.7.4 Additional analyses and exploration.

7.1.7.3.3 Marked Outliers and Dropouts for Laboratory Abnormalities

No any SAEs were caused by lab abnormality. Two patients in OFC treated groups were discontinued from the studies due to “liver function test abnormal”. No cases in other groups were discontinued for laboratory abnormalities.

7.1.7.4 Additional Analyses and Explorations

Hepatic Measures

Mean Change to Maximum and Categorical Analyses

Mean changes from baseline to maximum values for selected hepatic-related laboratory analytes (AST, ALT, alkaline phosphatase, and total bilirubin) were analyzed. OFC-treated patients had statistically significantly greater mean change to maximum than placebo- or fluoxetine-treated patients on AST, ALT, and alkaline phosphatase; and also had a statistically significantly greater change to maximum on alkaline phosphatase as compared to olanzapine-treated patients. There were no differences between OFC and the other groups with respect to treatment-emergent high alkaline phosphatase either at anytime or at endpoint, or potentially clinically significant high alkaline phosphatase; and overall, results for this analyte were similar in the original OFC safety package.

Proportions of patients with treatment-emergent ALT and bilirubin increases were summarized and compared across treatment groups (see Table 25). The incidence of ALT elevations in OFC-treated patients was statistically significantly greater than incidences in other groups in three instances: baseline ≤ 1 to postbaseline > 3 times the upper limit of normal, as compared to fluoxetine; and baseline ≤ 3 to postbaseline > 3 times the upper limit of normal, as compared to both fluoxetine and placebo. No patient in the integrated safety database met criteria for Hy’s rule (the combination of high liver cell damage as measured by liver enzymes and bilirubin).

Table 25 Incidence of ALT Elevations (Covance Reference Ranges) in Integrated Safety Database

Event Classification	OFC		FLX		OLZ		PLA	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Baseline $\leq 1X$ and								
Postbaseline $> 3X$	586	20 (3.4)	370	1 (0.3)	665	23 (3.5)	342	0 (0.0)
Postbaseline $> 5X$	586	7 (1.2)	370	0 (0.0)	665	9 (1.4)	342	0 (0.0)
Postbaseline $> 10X$	586	1 (0.2)	370	0 (0.0)	665	0 (0.0)	342	0 (0.0)
Postbaseline $> 20X$	586	0 (0.0)	370	0 (0.0)	665	0 (0.0)	342	0 (0.0)
Baseline $\leq 3X$ and								
Postbaseline $> 3X$	700	38 (5.4)	430	5 (1.2)	759	31 (4.1)	387	2 (0.5)

Hepatic Adverse Events

There were no statistically significant differences in exposure-adjusted rates of hepatic-related adverse events between OFC and any of the other treatment groups. A standardized MedDRA

query (SMQ) for “Possible drug related hepatic disorders (SMQ 20000006)” was used to identify relevant events.

Metabolic Measures

Abnormalities in Glucose- and Lipids-Related Analyte

Analyses of the exposure-adjusted incidence of patients with specified increases in selected metabolic analytes (fasting and nonfasting glucose, cholesterol, and triglycerides) at anytime and at endpoint were performed. Table 26 summarizes the incidence of treatment-emergent abnormalities in these selected metabolic analytes at anytime.

These analyses use cut-off points recommended by the American Diabetes Association (ADA) for glucose and by the National Cholesterol Education Program (NCEP) for lipids. There were no statistically significant differences between OFC and comparators in exposure-adjusted event rates for fasting glucose or for triglycerides; note that sample sizes for these two analytes were relatively small as compared to the total population because these analytes were not routinely collected in all of the TRD studies. For non-fasting glucose, OFC-treated patients had statistically significantly higher rates than placebo-treated patients of increases from normal to high (at anytime) or from borderline to high (at anytime and at endpoint). For cholesterol, OFC-treated patients had statistically significantly higher rates of treatment-emergent high cholesterol than both fluoxetine-treated patients (at anytime and at endpoint), and placebo-treated patients (at anytime). OFC-treated patients also had higher rates of treatment-emergent high cholesterol than olanzapine-treated patients, though the differences were not statistically significant.

Table 26 Incidence of Treatment-Emergent Abnormalities in Selected Metabolic Analytes at Anytime in the Integrated Safety Database

Event Classification	OFC		FLX		OLZ		PLA	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose Fasting								
Normal to High (<126 mg/dl to ≥ 126 mg/dl)	29	2 (6.9)	32	1 (3.1)	20	1 (5.0)	0	0 (0.0)
Glucose Non-Fasting								
Normal to High (<140 mg/dl to ≥ 200 mg/dl)	628	18 (2.9)	391	8 (2.0)	706	17 (2.4)	353	1 (0.3)
Borderline to High (≥ 140 - <200 mg/dl to ≥ 200 mg/dl)	35	16(45.7)	11	2 (18.2)	27	9 (33.3)	22	1 (4.5)
Cholesterol								
Normal to High (<200 mg/dl to ≥ 240 mg/dl)	319	31 (9.7)	171	5 (2.9)	360	19 (5.3)	207	4 (1.9)
Triglycerides								
Normal to High (<150 mg/dl to ≥ 500 mg/dl)	87	0 (0.0)	103	0 (0.0)	107	1 (0.9)	0	0 (0.0)

Furthermore, proportions of patients with treatment-emergent impaired glucose tolerance (<100 mg/dL at baseline; ≥100 and <126 mg/dL post-baseline) or potential diabetes (<100 mg/dL at baseline; ≥126 mg/dL post-baseline) based on fasting glucose values were similarly analyzed (see Table 27). Based on sponsor’s analyses, there were no statistically significant differences

between groups with respect to exposure-adjusted event rates of either type of abnormality. However, it should be noted that the sample sizes for this analysis were quite low, as fasting glucose was not collected frequently in the included database.

Table 27 Incidence of Treatment-Emergent Impaired Glucose Tolerance and Potential Diabetes in the Integrated Safety Database

Lab Test	OFC		FLX		OLZ		PLA	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Baseline \leq 100 mg/dl to any postbaseline $>$ 126	22	0 (0.0)	27	1 (3.7)	15	1 (6.7)	0	0 (0.0)
Baseline \leq 100 mg/dl to any postbaseline $>$ 100 but \leq 126	22	9 (40.9)	27	5 (18.5)	15	5 (33.3)	0	0 (0.0)

Proportions of patients with treatment-emergent glycosuria were summarized and compared across treatment groups using Fisher's exact test. A statistically significantly higher proportion of OFC-treated patients had glycosuria (4.4%) than did fluoxetine- (0.4%) or placebo-treated (1.4%) patients; the proportion in OFC-treated patients was close to statistically significantly greater than that of olanzapine-treated patients (2.3%).

7.1.7.5 Special Assessments

No special assessments were warranted in these studies.

7.1.8 Vital Signs

7.1.8.1 Overview of Vital Signs Testing in the Development Program

The potential treatment effect on mean change from baseline to endpoint and treatment-emergent potentially clinical significant abnormalities (adjusted for exposure) in vital signs (standing and supine blood pressure, standing and supine pulse, temperature, and weight) was summarized and assessed across treatment groups.

7.1.8.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The vital sign data from 10 OFC studies (5 TRD studies, 2 bipolar depression studies, 2 MDD with psychotic feature studies and 1 MDD with sexual dysfunction) were analyzed in this integrated safety database. Controlled comparison between treatment groups was applied to analyze the mean change from baseline, outliers, and dropouts.

7.1.8.3 Standard Analyses and Explorations of Vital Signs Data

7.1.8.3.1 Analyses Focused on Measures of Central Tendencies

Mean Change in Vital Signs

There were statistically significant differences between OFC and fluoxetine and between OFC and olanzapine with respect to mean change in supine and standing pulse. For both measures, OFC-treated patients had small decreases, while fluoxetine-treated patients had larger decreases, and olanzapine-treated patients had increases, suggesting that any potential effect of OFC on pulse is intermediate to those of fluoxetine and olanzapine. There were also statistically significant differences between OFC and placebo, with respect to mean change in standing pulse and supine diastolic blood pressure. For standing pulse, OFC had a larger increase than placebo; for supine diastolic blood pressure, OFC had a decrease, and placebo had a small increase.

Mean Change in Weight

OFC- and olanzapine-treated patients both had mean weight gain (3.97 kg and 3.57 kg, respectively), with corresponding increases in body mass index, while fluoxetine- and placebo-treated patients had mean weight loss of much lesser magnitude (-0.21 and -0.29 kg, respectively). The differences between OFC and other treatment groups were statistically significant in all cases, including between OFC and olanzapine. However, when adjusted with exposure, there was no statistical difference in weight gain for the two groups.

7.1.8.3.2 Analyses Focused on Outliers or Shifts from Normal to Abnormal

Potentially Clinically Significant Change in Vital Signs

The incidence of potentially clinically significant changes in vital signs for OFC-treated patients was low (with no measure having incidence greater than 4%), with no statistically significant differences in exposure-adjusted event rates between OFC and any of the other treatment groups.

Weight

Potentially clinically significant weight gain ($\geq 10\%$) at any time was more common, observed in 16.0% of OFC-treated patients, compared with 0.7% of fluoxetine-treated patients, 14.6% of olanzapine-treated patients, and 0.2% of placebo-treated patients. Exposure-adjusted rates of potentially clinically significant weight gain were statistically significantly greater for OFC as compared to both fluoxetine and placebo, and not statistically different from olanzapine.

7.1.8.3.3 Marked Outliers and Dropouts for Vital Sign Abnormalities

There were no patients discontinued studies due to abnormal vital signs. 2.1% of OFC-treated patients and 1.7% of olanzapine-treated patients discontinued due to weight gain.

7.1.8.4 Additional Analyses and Explorations

No further exploration was deemed necessary.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the Development Program, Including Brief Review of Preclinical Results

Mean change, treatment-emergent ECG abnormalities, and treatment-emergent potentially clinically significant ECG abnormalities were summarized and compared across treatment groups in the integrated safety database. QT interval was corrected by a regression-based correction formula. The details of this method were not provided.

7.1.9.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The ECG data from 10 OFC studies (5 TRD studies, 2 bipolar depression studies, 2 MDD with psychotic feature studies and 1 MDD with sexual dysfunction) were analyzed in this integrated safety database. Controlled comparison between treatment groups was applied to analyze the mean change from baseline, outliers and dropouts.

7.1.9.3 Standard Analyses and Explorations of ECG data

7.1.9.3.1 Analyses Focused on Measures of Central Tendency

Statistically significant differences in mean change at endpoint in QT interval and heart rate were observed between OFC and other treatment groups (see Table 28). Changes tended to be consistent with known safety profiles of the individual treatments. For example, heart rate decreased for fluoxetine, increased for olanzapine, and decreased only slightly for OFC, resulting in statistically significant differences between OFC and both of its component monotherapies. QT prolongation (corrected by regression) in OFC treated patients was statistically significantly different from a shortening of the QT interval seen in olanzapine- and placebo-treated patients and a slightly prolonged QT seen in fluoxetine-treated patients. However, the placebo-adjusted mean change (5.3 ms) in OFC treatment is not considered to be clinically significant.

Table 28 Mean Change from Baseline to Endpoint of QT Intervals and Heart Rate in the Integrated Safety Database

ECG Variables	Therapy	N	Baseline Mean	Δ to Endpoint Mean	P-values		
					OFC vs FLX	OFC vs. OLZ	OFC vs. PLA
Heart rate per minute	OFC	538	71.96	-0.12	0.025	<0.001	0.028
	FLX	320	70.62	-1.99			
	OLZ	578	71.35	4.5			
	PLA	305	70.74	1.73			
OTc (corrected by Regression)	OFC	538	418.19	4.42	0.026	<0.001	<0.001
	FLX	320	417.66	1.71			
	OLZ	578	416.62	-0.33			
	PLA	305	415.24	-0.84			

Intervals PR/Sec.	OFC	538	0.15	0.00	0.302	0.631	0.022
	FLX	320	0.15	0.00			
	OLZ	578	0.15	0.00			
	PLA	304	0.15	-0.00			
Intervals QRS/Sec.	OFC	538	0.09	-0.00	0.423	0.790	0.395
	FLX	320	0.09	0.00			
	OLZ	578	0.09	-0.00			
	PLA	305	0.09	0.00			
Intervals QT/Msec	OFC	538	391.11	4.20	0.48	<0.001	<0.001
	FLX	320	393.76	5.66			
	OLZ	578	391.07	-10.37			
	PLA	305	391.58	-4.85			

7.1.9.3.2 Analyses Focused on Outliers or Shifts from Normal to Abnormal

The most common treatment-emergent ECG abnormalities in OFC-treated patients were rhythm abnormalities (experienced by 8.3% of the group), morphology abnormalities (6.2%), and T-wave abnormalities (5.9%). However, there were no statistically significant differences between OFC and any of the other treatment groups for any abnormality category.

There were few patients with potentially clinically significant changes in ECG intervals and heart rate in OFC treated patients. However, the incidence of these abnormalities was not statistically significant between OFC and any of the other treatment groups. One OFC-treated and 2 olanzapine-treated patients had QTc >500 ms.

An analysis of treatment-emergent increases in QTc of 0 to 30 ms, 30 to 60 ms, or more than 60 ms from baseline to postbaseline maximums is presented in Table 29. The incidence of OFC-treated patients with QTc increases from baseline to maximum of 30 to 60 ms was statistically significantly greater than that of any of the other treatment groups, approximately twice the incidence of each of the other groups. The majority of patients with increases of 30 to 60 ms did not experience increases into clinically significantly high ranges (>470 for females; >450 for males): of the 42 OFC-treated patients who had increases of this magnitude, just 1 (a female) increased to a value >500 ms (HGIE-010-1454), 2 other females to a value >470 ms (HDAO-039-6911 and HGIE-625-6964), and 1 male to a value >450 ms (HGIE-010-1453).

Table 29 Categorical Analysis on QTc Prolongation in the Integrated Safety Database

ECG Intervals	Prolongation	Therapy	N	n	%	*P-values			
						Overall	(OFC vs FLX)	(OFC vs OLZ)	(OFC vs PLA)
QTC0413	0 - 30 msec	OFC	538	285	53.0%	0.007	0.944	0.017	0.010
		FLX	320	171	53.4%				
		OLZ	578	264	45.7%				
		PLA	305	133	43.6%				
	30 - 60 msec	OFC	538	42	7.8%	0.008	0.020	0.004	0.018
		FLX	320	12	3.8%				
		OLZ	578	22	3.8%				
		PLA	305	11	3.6%				
	> 60 msec	OFC	538	2	0.4%	0.606	1.000	0.612	0.623
		FLX	320	1	0.3%				
		OLZ	578	1	0.2%				
		PLA	305	2	0.7%				

QTC0413: QT interval corrected by regression

7.1.9.3.3 Marked Outliers and Dropouts for ECG Abnormalities

No SAEs or dropouts were due to ECG abnormalities in the integrated safety database.

7.1.9.4 Additional Analyses and Explorations

No additional analyses or exploration were warranted.

7.1.10 Immunogenicity

Immunogenicity was not studied in these studies.

7.1.11 Human Carcinogenicity

Human carcinogenicity was not studied in these studies.

7.1.12 Special Safety Studies

No special safety studies were warranted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Withdrawal phenomena and/or abuse potential were not studied in this submission. The existing OFC label addresses the risk of symptoms related to discontinuation of OFC (thought to be related to discontinuation from fluoxetine component of the medication). There are no data on this topic that are not already addressed in labeling.

7.1.14 Human Reproduction and Pregnancy Data

A total of 8 clinical trial case reports were coded as pregnancy. All 8 case reports had exposures in the first trimester. Of these 8 women, 2 were lost to follow up, 1 woman elected to have a therapeutic abortion, and 1 pregnancy is ongoing; Lilly will obtain follow-up information when available. All 4 of the remaining women delivered apparently normal babies at term. One of these 4 women discontinued OFC but was later asked by her physician to restart fluoxetine. The fluoxetine was later tapered and discontinued after the baby was born. The mother began breast-feeding and the infant experienced jaundice. At an 8-month checkup, no developmental abnormalities were noted in the infant; it was also reported that the infant did not experience any adverse events while breast-feeding. No reports of malformation were observed in any of the clinical trial case reports for which information is available. The numbers of natural outcomes were too few to draw conclusions about the effects of OFC exposure during pregnancy.

7.1.15 Assessment of Effect on Growth

No pediatric patients were enrolled in these studies. Therefore, the effect of OFC on growth was not studied.

7.1.16 Overdose Experience

A review of overdose events in the OFC clinical trial database revealed just one new overdose case that was not included in the previous submission.

Patient HDAO-610-9759 received fluoxetine during the double-blind phase, and then entered the open-label OFC treatment phase of the study. At the third visit of this phase, the patient took 1 extra capsule of OFC for a total dose of 24/100 mg in one day. New adverse events reported afterwards were arthralgia, somnolence, and vomiting, all with a moderate severity rating. The patient had experienced nausea prior to the event. The case was judged by investigator as accidental overdose.

Other than this case, information about overdose in clinical trials is the same as that provided in the original OFC submission.

7.1.17 Postmarketing Experience

There was no post-marketing experience on using OFC for an indication of TRD.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study Type and Design/Patient Enumeration

Table 30 summarized the studies included in OFC integrated safety database and their study design.

Table 30 Description of Studies Included in the Integrated Safety Database

Protocol No.	Study Design
H6P-MC-HDAO (1&2)	Double-blind, multicenter, parallel, randomized studies in patients TRD, starting with fluoxetine lead-in period and ending with an OFC open-label period.
F1D-MC-HGGY (1&2)	Double-blind, multicenter, parallel, randomized studies in patients with bipolar disorder—depressed, with an olanzapine or OFC open-label period.
F1D-MC-HGHZ	Double-blind, multicenter, parallel, randomized study in patients with TRD, starting with a nortriptyline lead-in period and ending with an OFC open-label period.
F1D-MC-HGIE	Double-blind, multicenter, parallel, randomized, dose ranging, comparative study in patients with TRD, starting with a venlafaxine lead-in period and ending with an OFC open-label period.
F1D-MC-HGFR	Double-blind, multicenter, parallel, randomized studies in patients with TRD, starting with a fluoxetine lead-in period and ending with an OFC open-label period.
F1D-MC-HGGA (1&2)	Double-blind, multicenter, parallel, randomized studies in MDD patients with psychotic features, ending with an OFC open-label period.
B1Y-MC-HCKB	Double-blind, multicenter, parallel, randomized, fluoxetine-controlled studies of premenopausal women experiencing sexual dysfunction while receiving fluoxetine treatment.

7.2.1.2 Demographics

The participating patients had a mean age of 42.8 years; 83.3% were Caucasian, and 65.2% were female. At baseline, there were statistically significant differences in the female-to-male ratios between the OFC treatment group (F:M = 70%:30%) and the olanzapine (F:M = 62%:38%) and placebo treatment groups (F:M = 65%:35%), with a higher proportion of females in the OFC treatment group as compared to the other 2 groups. There were no statistically significant treatment group differences in proportions of males and females in any of the individual TRD studies, which all included more females than males. Likewise, the distribution of patients to different race categories within the OFC treatment group (86% Caucasian) was statistically

significantly different from distributions for the olanzapine (81% Caucasian) and placebo treatment groups (78% Caucasian). Both differences are probably driven by the increased sample size after combining studies and may not be clinically significant. There were no statistically significant differences at baseline between OFC and any of the other treatment groups with respect to age or weight.

The existing OFC label addresses safety outcomes as they relate to sex, race, advanced age, renal/hepatic impairment, smoking status, and several other special groups. With respect to the current submission, subgroup analyses based on these variables have not been performed for the integrated databases.

7.2.1.3 Extent of Exposure (Dose/Duration)

During the time periods covered by this integrated safety database, 797 patients received OFC, 446 patients received fluoxetine monotherapy, and 873 patients received olanzapine monotherapy. Exposure data are based on the prescribed dose. The mean daily dose of study medication for OFC-treated patients, presented as olanzapine dose/fluoxetine dose, was 8.1/37.6 mg/day, compared to 40.5 mg/day for fluoxetine-treated patients and 8.8 mg/day for olanzapine-treated patients. Total exposure to OFC during controlled study periods was 122.3 patient-years, and the dose combinations with the longest exposure periods were 6/50 mg/day (33.4 patient-years), 6/25 mg/day (29.5 patient-years), and 12/50 mg/day (23.4 patient-years). The majority of the integrated database OFC exposure was in patients with TRD (104.4 patient-years, or 85.4% of the total exposure).

Table 31 OFC Exposure by Indication and Study in the Integrated Safety Database

TRD study			Bipolar Depression Study			Psychotic Depression Study			Sexual Dysfunction Study		
	N	Patient-year		N	Patient-year		N	Patient-year		N	Patient-year
Total	636	104.4	Total	84	10.5	Total	45	4.7	Total	32	2.7
HDAO1	100	13.2	HGGY1	42	5.2	HGGA1	22	2.3	HCKB	32	2.7
HDAO2	97	13.3	HGGY2	42	5.3	HGGA2	23	2.4			
HGFR	10	1.6									
HGIE	287	56.5									
HGHZ	142	19.9									
Total n = 797; Total exposure = 122.3 patient-year											

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other Studies

No other studies were conducted to evaluate the safety of OFC for this submission.

7.2.2.2 Postmarketing Experience

There is no OFC postmarketing experience for the indication of TRD.

7.2.2.3 Literature

Literature search information by the sponsor was not provided in the submission. I searched PubMed on Feb. 5, 2005 with key words of *Symbyax, olanzapine and fluoxetine, treatment resistant, refractory, and depression*. A total of 31 articles were found and no any unexpected SAEs were reported in these articles.

7.2.3 Adequacy of Overall Clinical Experience

Overall clinical experience was adequate to evaluate the efficacy and safety in TRD .

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No animal and/or in vitro test was conducted in this submission. Nor were such studies deemed necessary.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing in this submission was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

There were no studies addressing metabolic, clearance, or interaction issues in this submission. Such studies were not deemed necessary.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

An audit of the Case Report Forms (CRFs), Narrative Summaries, and adverse event data listings was conducted by Dr. Greg Dubisky, senior medical officer, for 18 patients (~5% of the patients with submitted CRFs) whom he randomly selected from the database for this sNDA. The consistency of adverse event data across CRF's, narrative summaries, and adverse.xpt files was examined.

The following is a list of patients selected for auditing:

HDAO-004-5176	HDAO-060-7967	HGHZ-025-2209
HDAO-018-5851	HDAO-064-8171	HGHZ-044-3151
HDAO-025-6224	HDAO-072-8572	HGIE-001-1003
HDAO-025-6225	HDAO-102-5555	HGIE-004-1180
HDAO-036-6753	HDAO-610-9477	HGIE-012-1556
HDAO-039-6914	HDAO-610-9877	HGIE-685-9206

The CRFs, data listings and Narrative Summaries were examined for every selected patient except patient HDAO-018-5851 (Narrative Summary was not provided). An examination of the adverse event information across these sources for each of the 18 patients revealed reasonable consistency and completeness.

In addition, the DSI inspected two sites from Study HDAO-2 and HGIE. The conclusion from the inspection is the data from the two sites were acceptable.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the quality and completeness of data were acceptable.

7.2.9 Additional Submissions, Including Safety Update

A 60 day safety update which summarized the safety data from one completed bipolar depression study—Study F1D-SU-HGMA (Study HGMA) conducted from 19 May 2004 to 31 March 2006, was submitted on Nov. 28, 2006 and was reviewed.

Study HGMA is a multi-center, open-label study in psychiatric care-based outpatient settings with two study periods to assess the efficacy of OFC in out-patients with bipolar depression. Patients were enrolled in a single arm and treated with OFC during Study Period I (7 weeks) and were randomized into one of 2 treatment arms (OFC or olanzapine) in Study Period II (12 weeks).

No deaths were reported during the study. Serious adverse events (SAEs) were reported in 6 patients during Study Period I and 4 patients during Study Period II. No unexpected non-fatal SAEs were reported. The majority of SAEs were not considered by the investigator to be related to study drug (see Table 32). Six patients had adverse events that led to discontinuation in Study Period I, 4 patients in Study Period II. Treatment-emergent adverse events reported were consistent with already established OFC safety profile.

Table 32 Serious Adverse Events in Study Period 1, Study HGMA

Preferred Term	Number (%) of Patients (N=161)
Adhesion	1 (0.6%)
Aggression	1 (0.6%)
Appendicectomy	1 (0.6%)
Appendicitis	1 (0.6%)
Blood triglycerides increased	1 (0.6%)
Cholelithiasis	1 (0.6%)
Hallucination, auditory	1 (0.6%)
Impulse-control disorder	1 (0.6%)
Judgement impaired	1 (0.6%)
Mania	1 (0.6%)
Pancreatitis	1 (0.6%)
Platelet count decreased	1 (0.6%)
Pregnancy test positive	1 (0.6%)
Pyrexia	1 (0.6%)
Suicidal ideation	1 (0.6%)
Viral infection	1 (0.6%)
Overall	6 (3.7%)

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The integrated safety database includes data from a variety of depression studies. However, the majority of OFC safety data (85.4% OFC exposure) were collected from TRD studies. It is unlikely that adding safety data from other depression studies will change the safety profile of OFC in TRD population. In my opinion, the integrated safety database is acceptable for this submission.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled Data vs. Individual Study Data

The safety data reviewed for this submission were a pool of 10 different depression studies which included 5 TRD studies, 2 bipolar depression studies, 2 MDD with psychotic feature studies and 1 MDD with sexual dysfunction study. A total of 2589 patients were included in the database (771 OFC-, 457 fluoxetine-, 884 olanzapine- and 477 placebo-treated patients). The safety report from each individual TRD study was not reviewed.

7.4.1.2 Combining Data

Data from the OFC, fluoxetine, olanzapine, and placebo arms of 10 different depression studies were pooled to form OFC, fluoxetine, olanzapine, and placebo treatment groups for the database as a whole. Analyses were done on an intent-to-treat (ITT) basis.

Table 33 summarizes the number of patients in the integrated safety database by study.

Table 33 Number of Patients per Treatment Arm in the Integrated Safety Database

Study	OFC	FLX	OLZ	PLA
HDAO-1	102	104	96	0
HDAO-2	98	102	103	0
HGGY-1	43	0	191	193
HGGY-2	43	0	179	184
HGGA-1	25	0	48	51
HGGA-2	23	0	53	49
HGIE	243	60	62	0
HGFR	10	10	8	0
HGHZ	146	142	144	0
HCKB	38	39	0	0
Total	771	457	884	477

7.4.2 Explorations for Predictive Factors

No further explorations for predictive factors were conducted in these studies.

7.4.3 Causality Determination

Adverse events were considered as treatment-related only if the rate for OFC-treated patients in the integrated safety database was at least 2% and statistically significant greater than at least one of the other treatment groups.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

All TRD studies were flexible dose studies except Study HGIE which was a dose ranging study. The detail dose information is summarized in Table 7 in section 6.1.3.5 Dose and Administration. All study drugs were administered orally. There are no specific concerns regarding to the study dosing regimen.

8.2 Drug-Drug Interactions

The existing OFC label addresses safety outcomes related to potential drug-drug and drug-food interactions. There have been no new data generated on these topics from this submission.

8.3 Special Populations

The existing OFC label addresses safety outcomes as they relate to sex, race, advanced age, renal/hepatic impairment, smoking status, and several other special groups. There have been no new data generated on these topics that have not already been addressed in labeling.

8.4 Pediatrics

Lilly requested a full waiver of pediatric studies for the use of Symbyax for the treatment of TRD in the pediatric population. The main reason justifying the request for waiver is that the studies of use of OFC to treat TRD in pediatric population are impossible or highly impractical, and Symbyax is not likely to be used in a substantial number of pediatric patients with TRD. Lilly provided the following points to support their request:

1. Recruitment of pediatric patients for a TRD study will be very difficult. Lilly mentioned that the NIMH-sponsored “Treatment of Resistant Depression in Adolescents (TORDIA) study, which commenced in 2001, has experienced slow recruitment, even with the more liberal definition of treatment resistant as failure of one adequate course of an SSRI.
2. The prevalence of TRD in pediatric population may be low. Base on recent literature search, MDD affects fewer than 10% of pediatric patients (cheung et al, 2006; Ryan, 2005) by estimation, and the recovery rate is high, 70~90%, with or without treatment (Birmhauer et al, 2004).
3. Symbyax is unlikely to be used in a substantial number of pediatric patients. SSRIs are current recommended treatment for children with MDD or TRD in clinical practice. Atypical antipsychotics are rarely, if ever, used to treat TRD in pediatric patients.
4. Lilly recently completed acute and long term safety studies in adolescents with schizophrenia and bipolar disorder. Lilly has also completed pediatric studies of fluoxetine in depression. Thus, even if physicians may wish to consider Symbyax as a possible treatment for adolescents with TRD, no additional studies are needed to characterize the safety and efficacy of Symbyax in adolescent patients.

I personally agree with Lilly’s arguments. In addition, Symbyax is associated with significant weight gain and potentially metabolic syndrome (appeared related to its olanzapine component) which will pose additional risk to children if pediatric OFC studies are conducted. I recommend a full waiver of pediatric study for the use of Symbyax in treatment of TRD in pediatric population.

8.5 Advisory Committee Meeting

This submission was not presented to the Psychopharmacologic Drug Advisory Committee.

8.6 Literature Review

Literature search information by the sponsor was not provided in the submission. I searched PubMed on Feb. 5, 2005 with key words of *Symbyax, olanzapine and fluoxetine, treatment resistant, refractory, depression*. A total of 31 articles were found and no any unexpected SAEs related to olanzapine or fluoxetine were reported in these articles.

8.7 Postmarketing Risk Management Plan

There are no additional recommendations regarding a postmarketing risk management plan.

8.8 Other Relevant Materials

No other relevant materials were provided.

9 OVERALL ASSESSMENT

9.1 Conclusions

Results from Study HDAO-2 demonstrated that OFC treatment was statistically significantly more effective than olanzapine or fluoxetine monotherapy in reducing depressive symptoms in adult TRD population over the 8-week study as assessed by the primary variable of change from baseline on MADRS total score.

Results from Study HGFR and Study HGIE (only results from the subset of patients who failed two adequate antidepressant trials in current depressive episode) also demonstrated that OFC treatment had a statistically significant decrease from baseline in MADRS total score compared with the fluoxetine or olanzapine monotherapy over the 8-week (Study HGFR) and 12-week (Study HGIE) periods.

The safety findings from an integrated safety database included patients who participated in the double-blind, acute phase of 10 controlled OFC depression trials, were consistent with the previously observed OFC safety profile.

9.2 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this supplement NDA be granted approvable status. There are a number of requests to which the sponsor needs to respond. Their responses will be reviewed in an addendum. Final approval is contingent on satisfactory responses to the concerns conveyed in these requests and mutual agreement on labeling.

9.3 Recommendation on Postmarketing Actions

There are no recommendations on post-marketing actions.

9.3.1 Risk Management Activity

There are no further recommendations for risk management activity at this time point.

9.3.2 Required Phase 4 Commitments

The sponsor need to conduct a phase 4 study to assess the long term efficacy and safety of OFC in the treatment of TRD in adult population after this sNDA is approved. The study should have a double blind, randomized, and controlled study design, and the study should last at least 3 months or longer after patients are fully stabilized by Symbyax. The sponsor should commit to conducting such a study prior to the final approval of this sNDA.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 Labeling Review

(b) (4)

10 APPENDICES

10.1 Investigators and Study Sites

List of Principal Investigators, HDAO Study 2

Site #	Principal Investigator	Site & Address
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6	Londborg, Peter D.	Summit Research Network (Seattle), LLC 901 Boren Avenue, Suite 1800 Seattle, WA 98104
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12	Gutierrez, Rosben	Psycare, Inc. 15525 Pomerado Road, Suite A7 Poway, CA 92064
15	Gupta, Sanjay	Global Research and Consulting 515 Main Street Olean, NY 14760
16	Nunez, Margarita	Clinical Studies, St. Petersburg 9887 4th Street N, Suite 200 St. Petersburg, FL 33702
18	Miller, Janice L.	Psychiatric Institute of Florida/ Clinical Neuroscience Solutions 5601 Corporate Way E, Suite 210 West Palm Beach, FL 33407
19	Thomas, H. Mikel	CTT Consultants 8340 Mission Road, Suite 205 Prairie Village, KS 66206
20	Alam, Mohammed	American Medical Research, Inc. 1200 Harger Road, Suite 415 Oak Brook, IL 60523
21	Isenberg, Keith E.	Washington University School of Medicine Dept of Psychiatry #1 Barnes Plaza, Suite 17301 St. Louis, MO 63110
23	Khojasteh, Saaïd	Saaïd Khojasteh and Associates, Inc. 330 First Capitol Drive, Suite 410 St. Charles, MO 63301
28	Greenberg, William M.	Nathan Kline Psychiatric Research Institute 140 Old Orangeburg Road Orangeburg, NY 10962
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42	Lowy, Adam	Psychiatric Institute of Washington, DC / Comprehensive Neuroscience (CNS), Inc. 4228 Wisconsin Avenue, NW Washington, DC 20016
44	Jaffe, Richard	Belmont Center for Comprehensive Treatment 4200 Monument Road Philadelphia, PA 19131
45	Bransfield, Robert	225 Highway 35 Red Bank, NJ 07701
47	Rosenberg, Leon I.	Center for Emotional Fitness 110 Marter Avenue, Suite 304 Moorestown, NJ 08057
53	Downs, John	Clinical Trials of Memphis, INC 707 West Brookhaven Circle Memphis, TN 38117
56	Safirstein, Beth	Baumel-Eisner Neuromedical Institute 7301 N University Drive, Suite 300 Fort Lauderdale, FL 33321
60	Beckett, Louise M.	IPS Research Company, Inc. 1111 North Lee, Suite 400 Oklahoma City, OK 73103
62	Ferguson, James M.	Radiant Research 448 East 6400 South, Suite 200 Salt Lake City, UT 84107
64	Ginsberg, Lawrence D.	Red Oak Psychiatry Associates 17115 Red Oak Drive, Suite 109 Houston, TX 77090

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75	Gillette, Patrick J.	Clinical Research Institute of Southern Oregon 3860 Crater Lake Avenue, Suite B Medford, OR 97504
76	Crabbe, Henry F.	Psychiatric Medicine Center 501 Ocean Avenue New London, CT 06320
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87	Khan, Arif	Northwest Clinical Research Center 1900 116th Avenue, NE Bellevue, WA 98004
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101	Holloway Jr., Willis	Cutting Edge Research Group 3140 West Britton Road, Suite B Oklahoma City, OK 73120
105	Pigott, Theresa	University of Florida Behavioral Health Clinic 2970 Hartley Road, Suite 202 Jacksonville, FL 32257
106	Okasha, Mahmoud	Comprehensive Psychiatric Care PC 200 West Town Street Norwich, CT 06360
601	Koka, Hanumantha R.	Neureka Research Corporation 680 Kirwood Road Sudbury, ON P3E 1X3 Canada
602	Milev, Roumen	Mental Health Services Providence Continuing Care Centre 752 King Street W Kingston, ON K7L 4X3 Canada
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Sources: RMP.H6POSTAT.HDAOOLF (FQDISO13), CT-Man.

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007	Dr. Donald L. England Radiant Research Eugene 755 E. 11th Street Eugene, OR 97401	England Donald L (b) (6)	Primary Investigator Subinvestigator Subinvestigator Subinvestigator Subinvestigator

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		(b) (6)	Subinvestigator

10.2 Appendix to Integrated Review of Efficacy

Table 34 MADRS Total Score: Visitwise Mean Change from baseline (OC), Double –Blind Treatment Phase, Study HDAO-1

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8	
	n	Mean	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
OFC	101	29.47	95	-10.19	93	-12.43	90	-12.12	84	-12.23	78	-12.94	76	-13.66	73	-14.12	74	-12.61
FLX	102	29.66	100	-6.37	100	-7.89	99	-8.02	92	-8.86	88	-8.76	87	-10.08	85	-10.29	83	-10.04
OLZ	95	29.72	94	-9.54	91	-11.19	88	-11.84	85	-11.49	80	-10.99	70	-12.14	65	-12.25	64	-12.55
Two-sided p-values																		
OFC vs. FLX			0.001		<0.001		0.002		0.021		0.006		0.024		0.015		0.104	
OFC vs. OLZ			0.583		0.325		0.836		0.620		0.204		0.362		0.262		0.971	

Table 35 MADRS Total Score: Visitwise Mean Change from baseline (OC), Double –Blind Treatment Phase, Study HDAO-2

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8	
	n	Mean	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
OFC	97	30.64	95	-12.49	92	-13.70	89	-14.21	88	-14.19	84	-14.67	78	-15.36	76	-15.50	75	-15.55
FLX	101	30.13	101	-4.68	98	-6.56	97	-7.51	94	-8.34	90	-9.38	85	-9.29	84	-10.14	83	-9.34
OLZ	102	30.08	97	-10.10	94	-12.15	88	-13.05	84	-12.10	76	-13.03	71	-11.15	67	-10.76	65	-8.95
Two-sided p-values																		
OFC vs. FLX			<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
OFC vs. OLZ			0.028		0.196		0.388		0.136		0.276		0.006		0.003		<0.001	

Table 36 MADRS Total Score: Visitwise Mean Change from baseline (OC), Double –Blind Treatment Phase, Study HGFR

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8	
	n	Mean	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
OFC	10	29.5	10	-16.70	10	-17.70	10	-16.90	9	-16.33	10	-16.88	10	-16.50	10	-15.90	9	-16.00
FLX	10	23.8	10	-5.00	9	-6.22	8	-3.38	8	-6.38	8	-7.63	7	-7.57	7	-7.57	7	-4.14
OLZ	8	25.00	8	-7.88	8	-8.13	8	-13.13	8	-7.38	7	-6.14	7	-4.14	6	-5.17	6	-2.83
Two-sided p-values																		
OFC vs. FLX			<0.001		0.011		0.003		0.018		0.040		0.090		0.119		0.016	
OFC vs. OLZ			0.012		0.036		0.362		0.031		0.023		0.023		0.059		0.011	

Table 37 MADRS Total Score: Visitwise Mean Change from baseline (OC), Double –Blind Treatment Phase, Study HGIE: Patients with SSRI Failure in Current Episode

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
OFC	163	30.10	153	-7.84	149	-10.38	144	-11.63	144	-12.33	140	-13.58	138	-13.48
FLX	41	31.07	40	-5.20	39	-7.44	39	-7.51	37	-8.38	34	-8.41	35	-9.40
OLZ	47	31.51	45	-5.87	43	-8.23	40	-8.78	37	-10.59	38	-11.03	35	-10.14
VNL	42	30.52	41	-4.98	40	-5.98	39	-7.26	36	-8.81	37	-11.41	36	-10.56
OFC 1/5	42	30.24	41	-4.39	41	-6.22	40	-9.15	40	-10.58	39	-11.36	40	-9.68
OFC vs. FLX	p-values		0.027		0.029		0.006		0.008		0.002		0.012	
OFC vs. OLZ	p-values		0.084		0.097		0.055		0.242		0.108		0.039	
OFC vs. VNL	p-values		0.016		0.001		0.004		0.019		0.176		0.067	
OFC vs. OFC 1/5	p-values		0.004		0.002		0.095		0.223		0.158		0.013	
	Baseline		Week 7		Week 8		Week 9		Week 10		Week 11		Week 12	
	n	Mean	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
OFC	163	30.10	133	-14.05	131	-14.34	129	-14.52	127	-14.69	125	-15.14	125	-15.16
FLX	41	31.07	33	-9.97	33	-9.73	34	-10.15	33	-11.39	32	-11.84	33	-11.48
OLZ	47	31.51	36	-10.86	36	-12.28	36	-11.69	34	-11.79	34	-11.71	33	-11.67
VNL	42	30.52	36	-13.86	34	-13.56	34	-14.62	33	-15.85	32	-17.13	34	-15.74
OFC 1/5	42	30.24	34	-11.71	37	-12.27	36	-12.19	35	-13.14	35	-12.86	35	-13.43
OFC vs. FLX	p-values		0.017		0.009		0.013		0.061		0.074		0.049	
OFC vs. OLZ	p-values		0.054		0.225		0.099		0.096		0.056		0.061	
OFC vs. VNL	p-values		0.911		0.654		0.955		0.511		0.279		0.754	
OFC vs. OFC 1/5	p-values		0.166		0.218		0.175		0.367		0.199		0.341	

10.3 Criteria for EPS Evaluation

Evaluation of Extrapyramidal Symptoms

Mean Change. LOCF mean changes from baseline to endpoint in total scores on the Simpson-Angus Scale, Barnes Akathisia Scale, and AIMS were summarized for both databases, and treatment groups were compared for the controlled database using an ANOVA model.

Treatment-Emergent EPS Abnormalities (Adjusted for Exposure). The proportions of patients with treatment-emergent abnormalities based on scale scores were summarized (adjusted for exposure) and compared across treatment groups where appropriate, as follows:

- To assess treatment-emergent parkinsonism, the proportion of patients with a Simpson-Angus scale total score >3 at any postbaseline visit was calculated from among those with a total score ≤ 3 at baseline.
- To assess treatment-emergent akathisia, the proportion of patients with a Barnes Akathisia Scale global score ≥ 2 at any postbaseline visit was calculated from among those with a score <2 at baseline.
- To assess treatment-emergent abnormal dyskinetic movements, the proportion of patients with a score ≥ 3 on any one of the AIMS items 1 through 7 or a score ≥ 2 on any two of the AIMS items 1 through 7 at any postbaseline visit was calculated from among those without either of these criteria at baseline. This criterion is consistent with the cross-sectional symptom severity criteria suggested by Schooler and Kane (1982) as research diagnostic criteria. Treatment-emergent dyskinetic movements at any postbaseline visit, at endpoint, and at last two consecutive visits were analyzed.

EPS-Related Treatment-Emergent Adverse Events. EPS-related adverse events were summarized (adjusted for exposure), and treatment groups were compared.

- EPS-related events: A prespecified list of events was selected from all MedDRA preferred terms (as well as a few lower level terms used in place of less-specific preferred terms) by Lilly Global Product Safety and placed into subcategories for akathisia, dyskinesia, dystonia, parkinsonism, and non-specific events. The complete list is available upon request.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-520/S-012

CHEMISTRY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
OFFICE OF NEW DRUG QUALITY ASSESSMENT
POST-MARKETING EVALUATION
CMC ASSESSMENT FORM**

APPLICANT: LILLY RES LABS	NDA NUMBER: 018936	DOC TYPE: SE1	SEQ NUMBER: 077	SUBMISSION TYPE: ORIGINAL
PROPRIETARY NAME: PROZAC		ESTABLISHED NAME: FLUOXETINE HYDROCHLORIDE		
DOSAGE FORM: CAP		STRENGTH/POTENCY: 10MG, 20MG	PHARMACOLOGICAL CATEGORY:	
LETTER DATE: 9/28/2006	STAMP DATE: 9/29/2006	PDUFA GOAL DATE: 7/5/2007	SUBMISSION (CHECK ONE) FIRM: PA FINAL: PA	
DIVISION IV BRANCH: VII	OND DIVISION: 130	MANAGED BY: OND	PAL: Brown	
			MEDIA SUBMISSION: Electronic	
SUPPLEMENT PROVIDES FOR: an indication for the use of Symbyax and the co-administration of Zyprexa and Prozac for an indication of Treatment Resistant Depression.				
BUNDLED: This bundle includes the following supplements: 18-936/S-077 (lead), 20-592/S-039, 21-086/S-021, and 21-520/S-012.				
CHANGE CATEGORY: Efficacy Supplement				
LABELING INVOLVED: No	PAT: No	COMPARABILITY PROTOCOL: No	PHASE 4 COMMITMENT:	
REVIEW PATH: 6 - OND Multi-Discipline Review				
CONSULTS:				
JUSTIFICATION/COMMENTS: 3/8/2007 - BROWNJA				
<ol style="list-style-type: none"> 1. This bundle includes the following supplements: 18-936/S-077 (lead), 20-592/S-039, 21-086/S-021, and 21-520/S-012. 2. Eli Lilly and Company has claimed a Categorical Exclusion from the requirement for an environmental assessment to support the approval of Symbyax (olanzapine and fluoxetine in combination) and the co-administration of Prozac (fluoxetine) and Zyprexa (olanzapine) for treatment resistant depression. Environmental assessments have previously been submitted to the agency for both olanzapine (NDA 20-592, 21-Sep-1995) and fluoxetine (NDA 20-187, 6-Aug-1993). In these assessments, it was concluded that given their projected use rates, neither of these compounds posed a threat to the aquatic environment. The applicant is requesting a categorical exclusion based on 21 CFR 25.31 (b). Even with the addition of the treatment resistant depression indication, the annual peak sales volumes of olanzapine will still be below 1 part per billion. The applicant's request for a categorical exclusion is granted. 3. There are no CMC changes to the approved labeling for 18-936/S-077 (lead), 20-592/S-039, 21-086/S-021, and 21-520/S-012. 4. From a CMC standpoint, these bundled supplements can be approved. 				
PAL ACTION: Recommend approval				
BRANCH CHIEF: James Vidra				

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-520/S-012

STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA/Serial Number: 21-520 (SE012)
Drug Name: Symbyax[®] (olanzapine and fluoxetine in combination)
Indication: Treatment Resistant Depression
Applicant: Eli Lilly and Company
Dates: Date of Document: 9/28/2006
PDUFA Due Date: 3/27/2007
Review Priority: Priority
Biometrics Division: Biometrics I, HFD-710
Statistical Reviewer: Yeh-Fong Chen, Ph.D.
Concurring Reviewers: Peiling Yang, Ph.D.
James Hung, Ph.D.
Medical Division: Division of Psychiatry Drug Products, HFD-130
Clinical Team: Clinical Reviewer: Jing Zhang, M.D.
Clinical Team Leader: Mitchell Mathis, M.D.
(Deputy Director and also
Acting Team Leader)
Project Manager: Renmeet Grewal

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1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Among the sponsor-submitted five efficacy studies, only one study (Study 2 of HDAO) clearly demonstrated the efficacy of olanzapine and fluoxetine combination (OFC) in treating patients with treatment resistant depression (TRD). Both HADO-1 and -2 studies had identical design and similar dropout rates. It was not clear what yielded inconsistent efficacy results between these two HDAO studies.

Although during an earlier meeting, FDA informed the sponsor that two positive studies would be required for an indication of treatment resistant depression, the sponsor argued in this NDA submission that based on the FDA Guidance (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products) one clearly positive study with multiple studies supporting the new use would be sufficient for the approval. So, they listed other significant findings from Studies HGFR, HGIE and HGHZ to support the efficacy of the OFC.

From the sponsor's listed supportive evidence from Studies HGFR, HGIE and HGHZ, this reviewer only thinks that at most the results from Study HGIE could possibly be considered if the medical division really agrees with the sponsor that the subset of patients who had failed two antidepressants in their current episode fairly represent the patients in Study HDAO and they are the most suitable patients for being determined as patients with treatment resistant depression. However, we should note that OFC was not statistically significantly different from the olanzapine at Week 8 for this subset of patients and the positive findings at Week 12 might only come from the highest olanzapine and fluoxetine combination (OFC 12/50). In addition, the quality of data for identifying the subset of patients appeared questionable.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this NDA submission, the sponsor included five efficacy double-blind active controlled clinical studies: H6P-MC-HDAO Study 1, H6P-MC-HDAO Study 2, F1D-MC-HGFR, F1D-MC-HGIE and F1D-MC-HGHZ to seek the approval of the OFC in the treatment of patients with TRD. Of these five studies, two had an identical design (Studies 1 and 2 of HDAO) with patient who had failure of two antidepressants at an adequate dose and duration during the current depressive episode, one was a small pilot study (HGFR) with the same type of patients recruited as HDAO, and the other two were designed to require only the patients who had a failure of one antidepressant during the current depressive episode.

Study HGFR had the protocol pre-specified primary endpoint based on HAMD-21 total scores, but for the other four studies, the protocol pre-specified primary endpoint was based on MADRS total scores. Regarding the study duration, only Study HGIE was designed to have the 12 weeks of the acute phase, others had the 8 weeks of the acute phase. Of these five studies, it is actually only one positive study (HDAO Study 2); the sponsor used three other studies to support the use of OFC in TRD and determined that one study (HDAO-Study 1) was inconclusive. The sponsor believed that these studies exhibited a clear pattern in the behavior of OFC in the treatment of patients with TRD.

1.3 STATISTICAL ISSUES AND FINDINGS

Basically, this reviewer confirmed the sponsor's analysis results for the primary endpoint, commonly proposed secondary endpoints and the subgroup analyses for all studies. Of the five efficacy studies (Studies HDAO-1, HDAO-2, HGFR, HGIE and HGHZ), Study HDAO-2 was the only one that clearly demonstrated the efficacy of OFC in the treatment of patients with TRD. Although Study HDAO-1 was an identical study with Study HDAO-2, it was a negative study, which did not show any supportive evidence for OFC's efficacy at the endpoint visit, or even any earlier visit.

According to the meeting minutes dated January 16, 2002, the FDA clearly informed the sponsor that because studies HGIE, HGHZ, and HGFR did not meet their primary endpoints, two additional positive studies would be required for an indication of TRD. Using the FDA Guidance on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, the sponsor argued that in this NDA submission that a single adequate and well-controlled study demonstrating effectiveness of a new use can be used to support consideration of a new indication when there are "multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness." Two strong supportive evidence that the sponsor listed are as follows.

- *For Study HGFR, the OFC showed statistically significantly greater reduction than both fluoxetine ($p=0.012$) and olanzapine ($p=0.035$) on the MADRS after 8 weeks of treatment. This was a small, pilot study ($n=28$) and therefore may not be readily generalizable, but it is noteworthy that treatment differences showed statistical separation despite the low power from a small sample size.*
- *For Study HGIE, OFC showed statistically significantly greater reduction on the MADRS than both fluoxetine ($p=.010$) and olanzapine ($p=.006$) after 8 weeks of treatment, although the difference over fluoxetine was only numerically superior after 12 weeks of treatment. In the subgroup of patients in Study HGIE who had failed two antidepressants in their current episode (that is, those who most closely resemble patients in Study HDAO and Study HGFR), OFC showed statistically significantly greater reduction on the MADRS than did fluoxetine ($p=.021$) or olanzapine ($p=.003$) after 12 weeks of treatment.*

Regarding the sponsor's supportive evidence listed above, this reviewer agreed with the sponsor's numerical findings. However, this reviewer would like to emphasize that these analysis results were indeed based on **post-hoc analyses**. In addition, for Study HGFR, since this was a small pilot study with only 28 randomized patients, this reviewer has reservation to accept the significant results for the MADRS total score. This reviewer found that the data from this study was actually not very stable. When one of many selected patients was removed from the analysis, the p-value would be greater than 0.05, and also the sponsor's ANOVA model did not adjust for any other factors or covariates, although the primary analysis in such a setting is most commonly based on ANCOVA by including baseline value as a covariate in the model to adjust for potential differences in baseline scores. When the MADRS change from baseline to endpoint LOCF data were analyzed by the aforementioned ANCOVA model, it was found that the statistically significant differences between the OFC and each monotherapy were inconclusive (p-values=0.0503 and 0.0848, respectively) at the 0.05 significance level.

For Study HGIE, this reviewer agreed with the sponsor that OFC showed statistically significant differences in comparison with both individual components at Week 8 and the significant findings at Week 12 for the subset of patients who had failed two antidepressants in their current episode. However, this reviewer is concerned about the quality of data for identifying this subset of patients and also would like to further point out that the significant findings for this subset of patients were found to be driven by the highest olanzapine and fluoxetine combination group, and at Week 8 the OFC did not show statistically significant difference in comparison with olanzapine although it did for the whole study population. These inconsistencies suggest the weakness of data in support of efficacy.

To sum up, from the statistical perspective, OFC's efficacy in treating patients with TRD was only supported by one clearly positive study. Data from those seemingly positive studies do not provide clearly supportive efficacy evidence and certainly do not add up to one positive study.

2. INTRODUCTION

2.1 OVERVIEW

According to the sponsor, patients with treatment-resistant depression (TRD) continue to fail to achieve acceptable levels of functioning and well-being although some depressed patients improve significantly with antidepressant treatment. Currently, the pharmacological options for treatment of TRD includes titration to higher doses of the initial agent, change to an alternative agent within or outside of the same class of

antidepressants as the initial agent, augmentation, and combination therapy. Preclinical studies of olanzapine plus fluoxetine hydrochloride in combination (OFC) showed a synergistic effect that produced a sustained elevation of serotonin, dopamine, and norepinephrine monoamine levels in the prefrontal cortex.

In January 2002, Lilly discussed with FDA the efficacy and safety results of completed clinical studies in TRD. FDA stated that because studies HGIE, HGHZ, and HGFR did not meet their primary endpoints, two additional positive studies would be required for an indication of TRD. As a result of that discussion, Lilly designed and conducted Study H6P-MC-HDAO (HDAO), a new TRD protocol that comprised two identical studies (HDAO Study 1 and HDAO Study 2). Lilly had a pre-NDA discussion with FDA on 14 April 2005, and during that discussion FDA indicated both HDAO Study 1 and HDAO Study 2 were needed in order to support the registration of OFC in this indication.

In this NDA submission, the sponsor included the aforementioned five double-blind active controlled clinical studies: H6P-MC-HDAO Study 1, H6P-MC-HDAO Study 2, F1D-MC-HGFR, F1D-MC-HGIE and F1D-MC-HGHZ to seek the approval of OFC in the treatment of patients with TRD. Of these five studies, two had an identical design (Studies 1 and 2 of HDAO) with patients who had failure of two antidepressants at an adequate dose and duration during the current depressive episode, one was a small pilot study (HGFR) with the same type of patients recruited as in HDAO, and the other two studies were designed to require only the patients who had a failure of one antidepressant during the current depressive episode.

The protocol-prespecified primary endpoint was based on HAM-D-21 total scores for Study HGFR, but it was based on MADRS total scores for the other four studies. Regarding the duration of the acute-phase, only Study HGIE was designed to have the 12 weeks of the acute phase; others had the 8 weeks.

Table 1 summarizes the sponsor's analysis results for these five studies. The sponsor concluded that there was only one positive study (HDAO Study 2), three other studies supported the use of OFC in TRD and one (HDAO-Study 1) was inconclusive. However, the sponsor believed that these studies exhibited a clear pattern in the behavior of OFC in the treatment of patients with TRD. Since Study HGHZ did not show any supportive evidence to demonstrate the efficacy of OFC, it was not included in this review. Although Study 1 of HDAO showed inconclusive results, it was included in this review for the purpose of comparison due to the same design as in Study 2 of HDAO.

Table 1 Efficacy Summary for Five Studies to Provide Efficacy Evidence of the OFC
As Treatment for TRD Indication (Based on Sponsor's Analysis Results)

Efficacy Measure	HDAO Study 1			HDAO Study 2		
MADRS,LOCF (8 weeks)	N	Mean Change	P* v.s. OFC	N	Mean Change	P* v.s. OFC
OFC	101	-10.8		97	-14.6	
Fluoxetine	102	-9.4	P=0.346	101	-9.0	P<0.001
Olanzapine	95	-10.1	P=0.624	102	-7.7	P<0.001

Efficacy Measure	Study HGFR			Study HGIE			Study HGHZ		
MADRS,LOCF (8 weeks)	N	Mean Change	P v.s. OFC	N	Mean Change	P v.s. OFC	N	Mean Change	P* v.s. OFC
OFC	10	-13.6		231	-12.2		142	-8.6	
Fluoxetine	10	-1.2	0.012	56	-8.5	0.010	135	-7.6	0.345
Olanzapine	8	-2.8	0.035	59	-8.3	0.006	140	-6.5	0.047
MADRS,LOCF (12 weeks)				N	Mean Change	P* v.s. OFC			
OFC				231	-12.5				
Fluoxetine				56	-10.7	P=0.27			
Olanzapine				59	-7.3	P<0.001			
HAMD-21, LOCF (8 weeks)	N	Mean Change	P* v.s. OFC						
OFC	10	-11.7							
Fluoxetine	10	-3.8	P=0.061						
Olanzapine	8	-5.9	p=0.185						

Efficacy Measure	Study HGIE			Study HGHZ		
MADRS,LOCF Patients with two failures in current episode (8 weeks)	N	Mean Change	P v.s. OFC	N	Mean Change	P v.s. OFC
OFC	163	-12.8		91	-9.0	
Fluoxetine	41	-8.6	P=0.003	88	-7.0	P=0.106
Olanzapine	47	-9.9	P=0.063	90	-5.1	P=0.007
MADRS,LOCF Patients with two failures in current episode (12 weeks)	N	Mean Change	P v.s. OFC			
OFC	163	-13.3				
Fluoxetine	41	-10.0	0.021			
Olanzapine	47	-8.8	0.003			

* The primary analysis for the primary endpoint.

Note that the reported mean changes were based on the raw data.

2.2 DATA SOURCES

The sponsor's electronic submission was stored in the FDA network with the following link: "\\CDSESUB1\N21520\S 012\2006-09-28."

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

The following description is based on the sponsor's clinical study report. Any discrepancy between the study report and study protocol will be discussed in the section of statistical reviewer's comments.

3.1.1 Description of Study HDAO (Studies 1 and 2)

Study HDAO was titled as "The Study of Olanzapine plus Fluoxetine in Combination for Treatment-Resistant Depression without Psychotic Features (Double-Blind Treatment Phase)". There were total 101 principal investigators in the United States and Canada involved in the two identical studies (Study 1 has 49 centers and Study 2 has 52 centers).

3.1.1.1 Study Objective

The sponsor included two identical, phase 3, randomized, double-blind, parallel-group, multicenter, outpatient studies (named Study 1 and Study 2) inside the folder of this Study HDAO. The primary objective for both studies was to assess the efficacy of up to 8 weeks of treatment with olanzapine plus fluoxetine in combination (OFC) versus fluoxetine and olanzapine monotherapies in patients with recurrent major depressive disorder (MDD) without psychotic features who met study criteria for treatment-resistant depression (TRD), as measured by last-observation-carried-forward (LOCF) mean change from baseline to endpoint visit in the Montgomery-Asberg Depression Rating Scale (MADRS) total score.

3.1.1.2 Study Design

For both studies, after screening, patients entered an 8-week fluoxetine lead-in phase, followed by an 8-week double-blind treatment phase and an additional 8 weeks of open-label therapy. The following Figure 1 shows the detailed design. Note that for the olanzapine component, patients could take 6 mg/day, 12 mg/day or 18 mg/day.

In order to increase the potential for reproducing results from two separate but identical trials, the sponsor incorporated the same design in these two studies.

The diagram illustrates the study timeline across four periods:

- Study Period I: Screening Phase** (Visits 1-2)
- Study Period II: Lead-in Phase** (Visits 2-7)
- Study Period III: Treatment Phase** (Visits 7-16)
- Study Period IV: Open-label Phase** (Visits 16-305)

Drug Regimens:

- Study Period II:** FLX 25 mg/day (Visits 2-3), FLX 50 mg/day (Visits 3-7).
- Study Period III:** OLZ 6 mg/day (Visits 7-16), OLZ 12 mg/day (Visits 9-14), OLZ 18 mg/day (Visits 11-15), OFC 6/50 (Visits 7-11), OFC 12/50 (Visits 11-14), OFC 18/50 (Visits 14-15).
- Study Period IV:** OFC 6/50 (Visits 16-302), OFC 12/50 (Visits 302-304), OFC 18/50 (Visits 304-305).

Intervals and Visits:

- Interval 1:** 3-14 Days (Visits 1-2)
- Interval 2:** 5-9 Days (Visits 2-3)
- Interval 3:** 5-9 Days (Visits 3-4)
- Interval 4:** 14-16 Days (Visits 4-5)
- Interval 5:** 21-24 Days (Visits 5-6)
- Interval 6:** 7-9 Days (Visits 6-7)
- Interval 7:** 3-5 Days (Visits 7-8)
- Interval 8:** 3-5 Days (Visits 8-9)
- Interval 9:** Weekly (5-9 Days) (Visits 9-16)
- Interval 10:** 5-9 Days (Visits 16-301)
- Interval 11:** 5-9 Days (Visits 301-302)
- Interval 12:** Every 2 Weeks (12-16 Days) (Visits 302-305)

Randomization: Occurs at Visit 7.

3.1.1.3 Efficacy Variables and Analyses

The primary efficacy endpoint was the change from baseline to endpoint visit in MADRS total score. The secondary efficacy variables were based on the HAM-A total score, CGI-Severity of Depression score, the BPRS total score and the BPRS positive item. The response and remission rates based on MADRS total score were also considered as secondary efficacy endpoints by the sponsor. A patient was considered a responder if he or she had a $\geq 50\%$ LOCF mean decrease from baseline to endpoint visit in MADRS total score. On the other hand, remission was defined as a patient having MADRS total score ≤ 10 at endpoint visit. Sustained response and sustained remission were defined as meeting these criteria over at least two consecutive assessment periods, one of which was the endpoint visit.

The primary endpoint, the LOCF change from baseline (Visit 7) to endpoint visit in the MADRS total score was analyzed using **ANOVA**. The ANOVA model contained effects for investigator, treatment, and investigator-by treatment interaction (provided the interaction effect was statistically significant). Pair-wise comparisons of OFC to fluoxetine and to olanzapine were assessed using the least square means from this

ANOVA model. As requested by FDA, the primary variable was also assessed using the baseline MADRS score as a covariate. This analysis was done using analysis of covariance (ANCOVA) and contained effects for investigator, treatment, and baseline MADRS score in the model. Pair-wise comparisons of OFC to fluoxetine and to olanzapine were assessed using the least-square means from this ANCOVA model.

In order to assess longitudinal effects, a likelihood-based repeated measures analysis (SAS PROC MIXED) was conducted on the post-baseline changes in MADRS total score and changes in HAM-A total score in the double-blind treatment phase. The linear model for this analysis included effects for baseline, treatment, investigator, visit, and treatment-by-visit interaction. All of these effects were considered fixed effects in the model. The estimates of effects were assessed by the method of restricted maximum likelihood using an unstructured covariance matrix for the within-patient error.

Response rates were analyzed using Fisher's exact test. A patient was considered to have responded if MADRS total score decreased by $\geq 50\%$ from baseline to endpoint visit. Response was also evaluated using a different definition: a decrease in MADRS by $\geq 50\%$ from baseline to anytime. A patient with an endpoint MADRS total score of ≤ 10 was considered to be in remission. A patient with at least two consecutive visits (including endpoint visit) meeting response criteria was considered a sustained responder. Similarly, a patient with at least two consecutive MADRS total scores of ≤ 10 , one of which was at the endpoint visit, was considered to be in sustained remission. Kaplan-Meier survival curves for time to response, time to sustained response, time to remission, and time to sustained remission were created for the double-blind treatment phase.

Reviewer's Note:

(b) (4)



3.1.2 Efficacy Results for Study HDAO (Studies 1 and 2)

3.1.2.1 Patient Population and Baseline Demographic Characteristics

Table 3.1 shows patient disposition for both studies 1 and 2. For Study 1, a total of 638 patients received open-label fluoxetine during Study Period II, and 302 eligible patients were randomized in a 1:1:1 ratio to receive double-blind olanzapine plus

fluoxetine in combination (OFC), fluoxetine, or olanzapine in Study Period III. There were 4 patients without post-baseline measurement; therefore the total number of patients in the ITT population became 298. A total of 220 patients completed the double-blind treatment phase and were followed in the open-label extension phase; an additional 9 patients were bridged from the fluoxetine lead-in to the open-label extension phase. For Study 2, a total of 675 patients received open-label fluoxetine during Study Period II, and 303 eligible patients were randomized in a 1:1:1 ratio to receive double-blind OFC, fluoxetine, or olanzapine in Study Period III. Three patients did not have any post-baseline measure, so the total number of ITT population was 300. A total of 221 patients completed the double-blind treatment phase and were followed in the open-label extension phase; an additional 10 patients were bridged from the fluoxetine lead-in to the open-label extension phase.

Table 3.1 Patient Disposition for Study HDAO

Study 1				
Variable	OFC	Fluoxetine	Olanzapine	Total
Randomized	102	104	96	302
ITT Population	101	102	95	298
Discontinued	29 (28.43)	21 (20.19)	32 (33.33)	82 (27.15)
Adverse Event	15 (14.71)	3 (2.88)	10 (10.42)	28 (9.27)
Lack of Efficacy	6 (5.88)	8 (7.69)	11 (11.46)	25 (8.28)
Lost to Follow-Up	3 (2.94)	5 (4.81)	3 (3.13)	11 (3.64)
Patient Moved		1 (0.96)	1 (1.04)	2 (0.66)
Personal Conflict or Other Pat Decision	1 (0.98)	1 (0.96)	4 (4.17)	6 (1.99)
Physician Decision		2 (1.92)	2 (2.08)	4 (1.32)
Protocol Violation	4 (3.92)	1 (0.96)	1 (1.04)	6 (1.99)
Study 2				
Variable	OFC	Fluoxetine	Olanzapine	Total
Randomized	98	102	103	303
ITT Population	97	101	102	300
Discontinued	23 (23.47)	19 (18.63)	40 (38.83)	82 (27.06)
Adverse Event	12 (12.24)	2 (1.96)	22 (21.36)	36 (11.88)
Lack of Efficacy	1 (1.02)	5 (4.90)	8 (7.77)	14 (4.62)
Lost to Follow-Up	3 (3.06)	3 (2.94)	1 (0.97)	7 (2.31)
Patient Moved	1 (1.02)	1 (0.98)	3 (2.91)	5 (1.65)
Personal Conflict or Other Pat Decision	3 (3.06)	5 (4.90)	3 (2.91)	11 (3.63)
Sponsor's decision	1 (1.02)			1 (0.33)
Physician Decision	2 (2.04)			2 (0.66)
Protocol Violation		3 (2.94)	3 (2.91)	6 (1.98)

Note: Reported values are numbers and percentages. OFC = olanzapine + fluoxetine

Source: Sponsor's Tables HDAO.10a.2 and HDAO.10b.2.

Table 3.2 summarizes patient demographic characteristics at baseline for patients who participated in the double-blind treatment phase. For both studies, the treatment groups appeared comparable with respect to age, racial origin, and sex.

Table 3.2 Patient Demographic Characteristics at Baseline for Study HDAO

Study 1				
Variable	OFC (N=102)	Fluoxetine (N=104)	Olanzapine (N=96)	Total (N=302)
Gender (n and %)				
Female	63 (61.8)	61 (58.7)	56 (58.3)	180 (59.6)
Male	39 (38.2)	43 (41.3)	40 (41.7)	122 (40.4)
Origin (n and %)				
African Descent	6 (5.9)	4 (3.8)	11 (11.5)	21 (7.0)
Caucasian	87 (85.3)	87 (83.7)	73 (76.0)	247 (81.8)
East/Southeast A	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Hispanic	7 (6.9)	11 (10.6)	9 (9.4)	27 (8.9)
Other	2 (2.0)	2 (1.9)	2 (2.1)	6 (2.0)
Age (yrs)				
Mean (SD)	43.33 (10.78)	44.83 (10.04)	45.67 (11.06)	44.59 (10.63)
Height (cm)				
Mean (SD)	169.65 (10.67)	170.37 (10.06)	168.80 (9.96)	169.63 (10.23)
Weight (kg)				
Mean (SD)	90.28 (23.30)	86.76 (19.73)	85.79 (21.07)	87.64 (21.43)
BMI				
Mean (SD)	31.31 (7.54)	29.90 (6.74)	30.13 (7.11)	30.45 (7.14)
Study 2				
Variable	OFC (N=98)	Fluoxetine (N=102)	Olanzapine (N=103)	Total (N=303)
Gender (n and %)				
Female	69 (70.4)	67 (65.7)	67 (65.0)	203 (67.0)
Male	29 (29.6)	35 (34.3)	36 (35.0)	100 (33.0)
Origin (n and %)				
African Descent	3 (3.1)	5 (4.9)	8 (7.8)	16 (5.3)
Caucasian	90 (91.8)	90 (88.2)	91 (88.3)	271 (89.4)
East/Southeast A	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Hispanic	3 (3.1)	5 (4.9)	3 (2.9)	11 (3.6)
Other	2 (2.0)	0 (0.0)	1 (1.0)	3 (1.0)
Western Asian	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Age (yrs)				
Mean (SD)	45.28 (9.49)	44.45 (9.89)	42.97 (10.44)	44.22 (9.97)
Height (cm)				
Mean (SD)	166.90 (9.13)	168.20 (10.34)	167.65 (9.02)	167.59 (9.50)
Weight (kg)				
Mean (SD)	82.78 (22.11)	82.70 (26.14)	86.51 (22.59)	84.02 (23.69)
BMI				
Mean (SD)	29.65 (7.54)	28.98 (7.54)	30.66 (7.17)	29.77 (7.43)

Source: Sponsor's Tables HDAO.11a.1 and HDAO.11b.1.

3.1.2.2 Sponsor's Efficacy Analysis Results for Primary Endpoint

As requested by FDA, the sponsor analyzed the primary endpoint, the mean change from baseline to endpoint visit(at 8 weeks) in the MADRS total score, by the ANCOVA with therapy and pooled investigator as effects and the baseline MADRS total score as a covariate. Table 3.3 shows the sponsor's LOCF analysis results for the primary endpoint for both studies. As shown in the table, for Study 1, OFC did not separate from fluoxetine or olanzapine, but for Study 2, OFC showed a statistically

significantly greater mean decrease on the MADRS than both fluoxetine and olanzapine. The sponsor's LOCF and OC analysis results for change from baseline to each visit on the MADRS total score are shown in Tables 6.1 to 6.4 of the Appendices. The conclusions made based on both LOCF and OC data seem to be very consistent.

Table 3.3 Efficacy Analysis Results for the Primary Endpoint, Change from Baseline to Endpoint Visit on MADRS Total Score by LOCF Data for Study HDAO

Study 1				
Type of Treatment & Comparison	Statistic	Baseline	Raw Mean Change	LS Mean Change*
OFC	n	102	101	101
	Mean (SE)	29.60 (0.71)	-10.75 (1.0)	-10.83 (0.95)
Fluoxetine	n	104	102	102
	Mean (SE)	29.67 (0.68)	-9.42 (0.98)	-9.47 (0.95)
Olanzapine	n	96	95	95
	Mean (SE)	29.72 (0.72)	-10.14 (0.98)	-10.02 (0.99)
OFC vs. Fluoxetine	p-value	0.89	0.29	
OFC vs. Olanzapine	p-value	0.73	0.53	
Study 2				
Type of Treatment & Comparison	Statistic	Baseline	Raw Mean Change	LS Mean Change
OFC	n	98	97	97
	Mean (SE)	30.52 (0.63)	-14.62 (1.04)	-14.07 (1.02)
Fluoxetine	n	102	101	101
	Mean (SE)	30.14 (0.58)	-8.96 (0.95)	-8.31 (1.06)
Olanzapine	n	103	102	102
	Mean (SE)	30.12 (0.62)	-7.71 (0.81)	-7.14 (1.04)
OFC vs. Fluoxetine	p-value	0.72	<0.001	
OFC vs. Olanzapine	p-value	0.60	<0.001	

Note: The sponsor only reported raw mean changes. The reported LS mean changes are from this reviewer's analysis results based on the ANCOVA model with therapy, poolinv and baseline.
Source: Sponsor's Tables HDAO.11a.10. and HDAO.11.b.10.


3.1.2.3 Sponsor's Efficacy Analysis Results for Secondary Endpoints

Analyses Based on Efficacy Rating Scales

Tables 6.1 and 6.2 of the Appendices summarize the sponsor's LOCF analysis results for mean change from baseline to each visit on the MADRS total score. Tables 6.5 and 6.6 of the Appendices summarize the sponsor's LOCF analysis results for mean change from baseline to each visit on the HAM-A total score using the LOCF data. Tables 6.7 and 6.8 of the Appendices summarizes the sponsor's LOCF analysis results for mean change from baseline to each visit on the CGI-Severity Scale using LOCF data. As shown in the tables, based on the nominal significance level $\alpha=0.05$ (i.e., not adjusted for multiplicity), in Study 1 the OFC treatment group had statistically significantly greater decreases on the MADRS total score, the HAM-A total score, and CGI-S scale than did the fluoxetine treatment group at Weeks 1 through 5, at Week 1 through 3, and at Weeks 2 and 3, respectively, though not at later points.

Likewise, in Study 2 patients treated with OFC had statistically significantly greater decreases on all the three scores than did the fluoxetine-treated patients at every week of the study, including endpoint visit, and had statistically significantly greater decreases than did olanzapine-treated patients at Week 1 and from Week 4 through endpoint visit(Week 8). For the change from baseline to end point (LOCF) on the BPRS total and positive score, Study 1 did not show any statistically significant differences across treatment groups. For Study 2, there were statistically significant differences between treatment groups on the total score, with OFC-treated patients demonstrating a significantly greater mean decrease than olanzapine-treated patients. The sponsor's analysis results are shown in Tables 6.9 and 6.10 of the Appendices.

Reviewer's Note:

 (b) (4)
Accordingly, those "significant" findings should be considered exploratory only.

Analyses of Response Rate and Remission Rate

Tables 6.11 and 6.12 of the Appendices summarize the sponsor's analysis results for partial response, response, sustained response, remission and sustained remission based on MADRS total score for Study 1 and Study 2 respectively. As shown in the table, based on the nominal significance level $\alpha=0.05$, in Study 1, OFC generally did not show statistically significant difference from either fluoxetine or olanzapine (except a couple of exceptions), but in Study 2, OFC showed statistically significant difference from both fluoxetine and olanzapine for all endpoints except time to partial response on the comparison between OFC and olanzapine. Note that these significant results were again based on $\alpha=0.05$, which were not adjusted for controlling the overall study type I error rate.

Reviewer's Note:

Those "significant" results should be considered exploratory only because they did not adjust for multiplicity to control the study-wise type I error rate.

3.1.2.4 Statistical Reviewer's Findings and Comments

1. This reviewer confirmed the sponsor's analysis results for the primary endpoint. No major inconsistency was found. Based on the analysis results, Study 1 was a negative study but Study 2 was a positive study. Only data from Study 2 of HDAO supported the efficacy of the olanzapine plus fluoxetine in combination (OFC) for treatment-resistant depression (TRD) without psychotic features. Note that although Study 1 had an identical design with Study 2, the OFC did not show any trend of significant separation from olanzapine starting from visit 1 to the endpoint visit.

2. Since both studies had an identical design and also similar dropout rates, this reviewer was curious to know whether the main reason for the extremely different analysis results between these two studies was due to different doses taken among different patients in these two studies. At the same time, if the doses of olanzapine used in the OFC was very different from that used in the olanzapine arm, this reviewer questioned about the validity of the comparison between the OFC and olanzapine.

After calculating the average dose-use in different treatment arms for these two studies, this reviewer found that for these two studies, the mean dose used in the OFC, fluoxetine and olanzapine are indeed quite similar and also the mean dose of olanzapine used in the OFC were quite close to that for the mono-olanzapine. Therefore, the dose-use does not seem to be the reason for resulting different analysis results. This reviewer also agreed that data of Study 2 indeed supported the OFC's efficacy in treating patients with TRD.

3.1.3 Description of Study HGIE

Study HGIE was titled as "Olanzapine Plus Fluoxetine Combination Therapy in Treatment-Resistant Depression: A Dose Ranging Study". The study was conducted at 90 study centers in 16 countries, including the United States.

3.1.3.1 Study Objective

The primary objective of this study was to assess the efficacy of OFC (composite of the combination dosing groups excluding OFC 1/5) versus treatment with fluoxetine, olanzapine, and venlafaxine monotherapies. The patient population consisted of patients with MDD without psychotic features who met criteria for treatment resistant depression (TRD).

Treatment resistant depression was defined as:

- a failure to achieve satisfactory antidepressant response to an SSRI for at least 6 weeks at an acceptable dose
and,
- prospective failure to achieve satisfactory antidepressant response to the SNRI venlafaxine, as defined by a <30% improvement on the MADRS during the 7-week venlafaxine lead-in phase.

The secondary objectives of the study were as follows:

- To assess the differences in safety and efficacy of the individual OFC treatment groups.
- Within the four combination treatment groups (OFC 6/25, OFC 6/50, OFC 12/25, and OFC 12/50), to assess the linear and interaction effects of olanzapine and fluoxetine in MADRS total scores.

- To assess the superiority in efficacy of OFC versus treatment with olanzapine, fluoxetine, or venlafaxine monotherapies as measured by the CGI-Severity of Depression rating scale.
- To assess co-morbid anxiety symptoms of patients receiving OFC treatment versus treatment with olanzapine, fluoxetine, or venlafaxine monotherapies as measured by HAM-A.
- To assess the safety of OFC treatment versus treatment with olanzapine, fluoxetine, or venlafaxine monotherapies as measured by the frequency and severity of treatment-emergent adverse events, changes in vital signs, laboratory analytes, or ECGs, and severity of EPS. The Simpson-Angus Scale, the Barnes Akathisia Scale, and the AIMS were used to measure extrapyramidal symptoms. Adverse events were solicited using the Udvalg for Kliniske Undersøgelser (UKU) side effect rating scale. The Arizona Sexual Dysfunction Scale (ASEX) monitored sexual function.
- To assess the direct and indirect costs associated with treatment and the health-related quality of life of patients on OFC versus treatment with olanzapine, fluoxetine, or venlafaxine monotherapies as measured by the Short Form 36 Health Survey (SF-36) and Quality of Life and Depression Scale (QLDS).

3.1.3.2 Study Design

This was a randomized, double-blind, multicenter study of patients meeting DSM-IV criteria for MDD without psychotic features as determined by clinical assessment and confirmed by diagnostic interview, and also met the treatment resistant depression criteria.

The study consisted of five phases. After a 2- to 7-day screening phase (Study Period I), patients began a 7-week venlafaxine lead-in phase (Study Period II). Patients received venlafaxine 75 to 375 mg/day during this phase.

During the taper phase (Study Period III), patients were assigned randomly (in equal allocation) to one of eight treatment groups:

- olanzapine 1 mg/day plus fluoxetine 5 mg/day (OFC 1/5)
- olanzapine 6 mg/day plus fluoxetine 25 mg/day (OFC 6/25)
- olanzapine 6 mg/day plus fluoxetine 50 mg/day (OFC 6/50)
- olanzapine 12 mg/day plus fluoxetine 25 mg/day (OFC 12/25)
- olanzapine 12 mg/day plus fluoxetine 50 mg/day (OFC 12/50)
- olanzapine 6 or 12 mg/day (OLZ)
- fluoxetine 25 or 50 mg/day (FLX)
- venlafaxine 75 to 375 mg/day (VNL)

For patients assigned to any other treatment group than venlafaxine, the venlafaxine dose were tapered off over a 5- to 9- day period. Patients assigned to venlafaxine maintained the dose attained at the end of the venlafaxine lead-in phase.

The acute phase (Study Period IV) was the 12-week, double-blind treatment period of the study, and the open-label phase (Study Period V) was the 52-week open-label OFC treatment period of the study.

3.1.3.3 Efficacy Endpoints and Analyses

Efficacy Endpoints

The primary endpoint was the change from baseline to endpoint visit in MADRS total score. The MADRS total score was also used to determine response, remission, and relapse.

- A responder was defined as any patient who demonstrated a 50% or greater decrease in MADRS total score from baseline to the last value of the acute phase.
- A patient with two consecutive MADRS total scores of ≤ 8 in the acute phase was defined to be in remission.
- A patient in remission with MADRS total scores ≥ 16 at two subsequent visits was defined to have relapsed.

Secondary efficacy measures included change from baseline to endpoint visit in CGI-Severity of Depression, HAM-A total, and BPRS total scores.

Efficacy Analyses

The hypothesis of principal interest was that OFC was superior to olanzapine, fluoxetine, and venlafaxine as measured by LOCF mean change in MADRS total scores after up to 12 weeks of double-blind therapy (acute phase).

The analysis of variance (ANOVA) model was used to evaluate continuous data. The model included effects for treatment, geographic location, and treatment-by-geographic location interaction. Treatment-by-geographic location tested at $\alpha=0.10$ and found not to be significant were dropped from the model. All other tests of hypotheses were tested at a two-tailed α level of 0.05.

Primary analyses were done on an intent-to-treat basis. When LOCF mean change from baseline to endpoint visit was assessed, patients were included in the analysis only if the patient had a baseline and a post-baseline measure. For the analysis of the acute phase, unless otherwise defined, a baseline measure was the Visit 8 observation; if it was missing, then the baseline measure was the last observation available in the lead-in or taper phases. A patient's endpoint measure was defined as his/her last measure in the appropriate study period.

All total scores from rating scales and subscales were derived from individual items. If any of the individual items were missing, the total score was treated as missing.

All analyses were performed on the original scale data unless the assumptions of the ANOVA appeared to be violated, in which case results from the rank-transformed data were reported. All analyses were conducted with SAS PROC GLM using Type III sums of squares.

In order to assess longitudinal effects, a likelihood-based repeated measures analysis (SAS PROC MIXED) was conducted on the post-baseline MADRS total score in the acute phase. The linear model for this analysis included effects for the baseline, treatment, geographic location, treatment-by-geographic location interaction, visit, and treatment-by-visit interaction. All of these effects were considered fixed effects in the model. The estimates of effects were assessed by the method of restricted maximum likelihood using an unstructured covariance matrix for the within-patient error.

Observed case (OC) and LOCF visit-wise analyses of MADRS total, HAM-A total, and CGI-Severity of Depression scores were performed for the acute phase. An OC visit-wise analysis evaluates change from baseline at each visit for all patients who were active in the study at that visit. An LOCF visit-wise analysis evaluates change from baseline at each visit using that patient's score at that visit or the patient's last available score prior to that visit. Response, remission, and relapse rates were analyzed using Fisher's exact test.

Reviewer's Note:

In addition to the analysis for the change from baseline to Week 12 in the MADRS total score, the sponsor also performed the visit-wise change analysis and specifically emphasized the results for the change from baseline to Week 8 since the study duration for the other pivotal studies (Studies HDAO-1 and -2) only had the double blind period of 8 weeks.

3.1.4 Efficacy Results for Study HGIE

3.1.4.1 Patient Population and Baseline Demographic Characteristics

Table 3.4 shows a summary table of patient population for Study HGIE. As shown in the table, 483 patients were randomized to the acute phase of the study. There was an overall statistically significant difference among treatment groups for discontinuation because of an adverse event. More patients in the OFC 12/25 and OFC 12/50 treatment groups discontinued for an adverse event compared with the other treatment groups. It should be noted that patients in the venlafaxine treatment group had been receiving venlafaxine for seven weeks prior to randomization, so this factor may have contributed to the lower rate of discontinuation for adverse events among these patients during the acute phase.

Table 3.5 shows the baseline demographic characteristics for Study HGIE. As shown in the table, the treatment groups appeared comparable for these baseline demographic characteristics.

Table 3.4 Patient Disposition for Study HGIE

Variable	OFC 6/25	OFC 6/50	OFC 12/25	OFC 12/50
Randomized	63	63	60	57
ITT Population	59	61	55	56
Discontinued	12	15	14	19
Adverse Event*	2	3	11	13
Death	0	0	1	0
Satisfactory Response	1	0	0	0
Lack of Efficacy	6	5	1	1
Lost to Follow-up	0	2	1	1
Personal Conflict	2	3	0	4
Entry Criteria Not Met	0	0	0	0
Sponsor's Decision	1	2	0	0
Physician Decision	0	0	0	0
Protocol Violation	0	0	0	0
Variable	Fluoxetine	Olanzapine	Venlafexine	OFC 1/5
Randomized	60	62	59	59
ITT Population	56	59	58	55
Discontinued	12	18	15	13
Adverse Event	3	5	1	2
Death	0	0	0	0
Satisfactory Response	0	0	0	0
Lack of Efficacy	4	5	7	4
Lost to Follow-up	1	2	2	1
Personal Conflict	1	5	3	4
Entry Criteria Not Met	1	0	0	0
Sponsor's Decision	1	0	0	0
Physician Decision	1	0	1	1
Protocol Violation	0	1	1	1

* p-value by Chi-Square test <0.001. Source: Sponsor's Table HGIE.10.4.

Table 3.5 Patients' Baseline Demographic Characteristics for Study HGIE

Variable	OFC 6/25 (N=63)	OFC 6/50 (N=63)	OFC 12/25 (N=60)	OFC 12/50 (N=57)
Gender (n and %)				
Female	45 (71.4%)	47 (74.6%)	42 (70%)	39 (68.4%)
Male	18 (28.6%)	16 (25.4%)	18 (30%)	18 (31.6%)
Origin (n and %)				
African Descent	1 (1.6%)	2 (3.2%)	3 (5.0%)	0
Western Asian	0	0	0	0
Caucasian	56 (88.9%)	57 (90.5%)	51 (85.0%)	52 (91.2%)
East/Southeast A	2 (3.2%)	2 (3.2%)	2 (3.3%)	2 (3.5%)
Hispanic	4 (6.3%)	1 (1.6%)	3 (5.0%)	1 (1.8%)
Other	0	1 (1.6%)	1 (1.7%)	2 (3.5%)
Age (yrs)				
Mean (SD)	44.84 (10.73)	45.69 (12.09)	46.00 (10.56)	46.82 (10.46)
Height (cm)				
Mean (SD)	166.15 (8.44)	165.91 (10.19)	166.55 (9.76)	167.43 (8.40)
Weight (kg)				
Mean (SD)	78.10 (21.63)	78.49 (21.63)	80.60 (23.33)	83.66 (22.71)
BMI				
Mean (SD)	28.24 (6.94)	28.45 (7.37)	28.93 (7.51)	29.81 (7.80)

Variable	Fluoxetine (N=60)	Olanzapine (N=62)	Venlafaxine (N=59)	OFC 1/5 (N=59)
Gender (n and %)				
Female	43 (71.7%)	44 (71.0%)	46 (78.0%)	44 (74.6%)
Male	17 (28.3%)	18 (29.0%)	13 (22.0%)	15 (25.4%)
Origin (n and %)				
African Descent	2 (3.3%)	2 (3.2%)	4 (6.8%)	0
Western Asian	0	0	1 (1.7%)	0
Caucasian	53 (88.3%)	55 (88.7%)	52 (88.1%)	58 (98.3%)
East/Southeast A	2 (3.3%)	2 (3.2%)	1 (1.7%)	0
Hispanic	2 (3.3%)	2 (3.2%)	1 (1.7%)	0
Other	1 (1.7%)	1 (1.6%)	0	1 (1.7%)
Age (yrs)				
Mean (SD)	45.15 (10.31)	47.14 (9.87)	44.22 (11.26)	45.70 (11.38)
Height (cm)				
Mean (SD)	167.21 (9.48)	166.28 (9.60)	166.44 (8.51)	167.09 (9.27)
Weight (kg)				
Mean (SD)	79.39 (23.65)	79.94 (20.95)	79.05 (22.04)	77.00 (20.70)
BMI				
Mean (SD)	28.30 (7.24)	28.58 (6.16)	28.52 (7.87)	27.50 (6.57)

Source: Sponsor's Table HGIE.11.2.

3.1.4.2 Sponsor's Efficacy Analysis Results for Primary Endpoint

The sponsor's analysis results for the mean change from baseline to Week 12 in the MADRS total score are shown in Table 3.6. Patients in the composite OFC treatment group (composite of OFC 6/25, OFC 6/50, OFC 12/25, and OFC 12/50) demonstrated a statistically significantly greater mean decrease in MADRS total score from baseline to Week 12 compared with the OLZ treatment group but not compared with either fluoxetine or venlafaxine treatment group.

Based on the pre-specified primary endpoint, i.e., the change from baseline to Week 12 of MADRS total score, the data did not support the OFC's efficacy. However, the sponsor argued that the data indeed supported the OFC's efficacy at Week 8, the pre-specified endpoint visit for the other pivotal studies. The sponsor's analysis results for the mean change from baseline to Week 8, and to the other weeks in the MADRS total score are shown in Table 3.7 and Table 6.13 of the Appendices, respectively.

Table 3.6 LOCF Analysis Results for the Change from Baseline to **Week 12** on the MADRS Total Score for Study HGIE

Therapy	Baseline Mean (SD)	LS Mean of Change (SE)*	p-values		
			v.s. OFC (composite)	v.s. Fluoxetine	v.s. Olanzapine
OFC 6/25 (n=59)	28.44 (7.24)	-13.05 (1.29)		0.168	0.001
OFC 6/50 (n=61)	28.87 (7.93)	-11.46 (1.27)		0.613	0.016
OFC 12/25 (n=55)	30.58 (5.85)	-11.40 (1.33)		0.644	0.021
OFC 12/50 (n=56)	30.79(6.16)	-12.66 (1.33)		0.250	0.003

Therapy	Baseline Mean (SD)	LS Mean of Change (SE)*	p-values		
			v.s. OFC (composite)	v.s. Fluoxetine	v.s. Olanzapine
Fluoxetine (n=56)	31.50 (6.22)	-10.55 (1.33)	0.271		
Olanzapine (n=59)	30.48 (6.91)	-7.18 (1.30)	0.000		
Venlafaxine (n=58)	30.02 (5.18)	-11.39 (1.32)	0.606		
OFC 1/5 (n=55)	30.15 (7.16)	-10.39 (1.34)		0.931	0.077

* The sponsor only reported raw mean change from baseline and standard deviations in the CSR. This column of LS means and standard errors is based on this reviewer's analysis results.

Table 3.7 LOCF Analysis Results for the Change from Baseline to **Week 8** on the MADRS Total Score for Study HGIE

Therapy	Baseline Mean (SD)	LS Mean of Change (SE)*	p-values		
			v.s. OFC (composite)	v.s. Fluoxetine	v.s. Olanzapine
OFC 6/25 (n=59)	28.44 (7.24)	-12.96 (1.20)		0.10	0.006
OFC 6/50 (n=61)	28.87 (7.93)	-11.50 (1.18)		0.086	0.066
OFC 12/25 (n=55)	30.58 (5.85)	-11.01 (1.24)		0.166	0.133
OFC 12/50 (n=56)	30.79(6.16)	-12.92 (1.24)		0.012	0.008
Fluoxetine (n=56)	31.50 (6.22)	-8.64 (1.23)	0.010		
Olanzapine (n=59)	30.48 (6.91)	-8.47 (1.21)	0.006		
Venlafaxine (n=58)	30.02 (5.18)	-10.73 (1.23)	0.3		
OFC 1/5 (n=55)	30.15 (7.16)	-10.15 (1.25)		0.377	0.320

* The sponsor only reported raw mean change from baseline and standard deviations in the CSR. This column of LS means and standard errors is based on this reviewer's analysis results.

3.1.4.3 Sponsor's Efficacy Analysis Results for Secondary Endpoints

Since OFC did not show significant differences when compared with fluoxetine based on Week 12 data for the pre-specified primary endpoint and for all secondary endpoints, for the purpose of finding supportive evidences in conjunction with the only positive study (Study 1 of HDAO) only analysis results for the secondary endpoints based on Week 8 data are presented and discussed in this section. According to Table 3.8 which summarizes the sponsor's analysis results for the mean change from baseline to Week 8 in MADRS total score (by the likelihood based repeated measure) and CGI-S (based on LOCF data), the previous significant findings based on the LOCF data for the comparisons between the composite OFC arm and the fluoxetine arm at Week 8 are also supported by the likelihood based repeated measure analysis. In addition, the composite OFC arm also won on the comparisons with both fluoxetine and olanzapine arms individually on the CGI-S scales.

Table 3.8 Sponsor's Analysis Results for the Change from Baseline to Week 8
Secondary Endpoints for Study HGIE

Therapy	Baseline Mean (SD)	Mean of Change* (SE)	p-values		
			v.s. OFC (composite)	v.s. Fluoxetine	v.s. Olanzapine
MADRS Total Score (by the likelihood based repeated measure)					
OFC 6/25 (n=50)	28.44 (7.24)	-14.79 (1.07)		<0.001	<0.001
OFC 6/50 (n=51)	28.87 (7.93)	-12.70 (1.05)		0.007	0.005
OFC 12/25 (n=45)	30.58 (5.85)	-11.45 (1.12)		0.066	0.058
OFC 12/50 (n=38)	30.79(6.16)	-13.26 (1.17)		0.003	0.003
Fluoxetine (n=45)	31.50 (6.22)	-8.57 (1.12)	<0.001		
Olanzapine (n=46)	30.48 (6.91)	-8.49 (1.11)	<0.001		
Venlafaxine (n=46)	30.02 (5.18)	-11.60 (1.1)	0.231		
OFC 1/5 (n=48)	30.15 (7.16)	-10.39 (1.08)			
CGI-S (based on LOCF data and ANOVA model)					
OFC 6/25 (n=59)	4.37 (0.09)	-1.41 (0.15)		0.002	0.008
OFC 6/50 (n=61)	4.43 (0.10)	-1.26 (0.16)		0.017	0.057
OFC 12/25 (n=55)	4.47 (0.09)	-1.00 (0.15)		0.249	0.497
OFC 12/50 (n=56)	4.45 (0.09)	-1.13 (0.16)		0.080	0.198
Fluoxetine (n=56)	4.46 (0.10)	-0.75 (0.13)	0.008		
Olanzapine (n=59)	4.58 (0.13)	-0.85 (0.16)	0.039		
Venlafaxine (n=58)	4.38 (0.10)	-0.90 (0.15)	0.049		
OFC 1/5 (n=55)	4.35 (0.11)	-0.91 (0.15)		0.463	0.799

* For MADRS total score, the reported means of changes were from the LS means, but for CGI-S, they were from raw data means. Source: Sponsor's Tables HGIE.11.18 and 11.26.

3.1.4.4 Statistical Reviewer's Findings and Comments

1. The primary endpoint for this study was the change from baseline to endpoint, i.e., Week 12 in MADRS total score. This reviewer confirmed the sponsor's analysis results for the primary endpoint and those commonly proposed secondary endpoints. Since the OFC did not show statistically significant difference from the fluoxetine in the primary endpoint based on the ITT population at Week 12, according to the protocol, Study HGIE is a negative study.

The sponsor, however, argued that although the OFC did not show statistically significant difference in comparison with fluoxetine at Week 12, it showed significant results up to Week 8. In addition, for the subgroup of patients who had historical failure to the SSRI treatment during the current episode of MDD, OFC showed statistically significant difference in comparison with both fluoxetine and olanzapine individually at Week 12. The sponsor believed that this subset is a more treatment-resistant subset of the study population.

Regarding the sponsor's argument, if it is determined that the subset of patients with historical failure to SSRI treatment during the current episode is indeed to be a more appropriate treatment-resistant subset of the study population, the OFC did show statistically significantly better efficacy than both olanzapine and fluoxetine individually at Week 12. However, one should realize that the above subset analysis was not the pre-specified primary analysis and also note that the sponsor's efficacy conclusion for the OFC was based on the combined dose arms from four different combinations of olanzapine and fluoxetine (OFC 6/25, OFC 6/50, OFC 12/25 and OFC 12/50). When the comparisons between the specific dose combination and individual mono-therapies were further studied, it was found that only OFC 12/50 showed statistically significant difference in comparisons with olanzapine and fluoxetine individually.

2. This reviewer wishes to emphasize that as mentioned earlier, the OFC was not statistically significantly separated from the fluoxetine alone at Week 12 at the primary endpoint and most secondary endpoints. Although at Week 8, the OFC showed statistically significant differences in comparison with the fluoxetine and olanzapine individually for the primary endpoint, it did not at the comparison with the olanzapine based on the subset of patients with historical failure to SSRI treatment during the current episode of MDD. These inconsistencies suggest the weakness of data in support of efficacy. The detailed analysis results are shown in Table 6.14 of the Appendices.
3. The sponsor did not include the variable for identifying patients with historical failure to SSRI treatment during the current episode of MDD in the original submission. Before the sponsor sent in the requested variable, this reviewer tried to use the available data to identify the subset of patients.

Although this reviewer was later able to identify those subset patients and verify the sponsor's analysis results, it was found that patients' onset dates of current episode and dates of any previous therapy use were not well recorded. There were quite amount of dates only recorded by years. For patients' onset date of current episode, there were quite many of them being recorded over 10 or 20 years ago. For patients' starting date and stopping date of previous drug use, even some of them had the same year only recorded for both. So, it appears that reliability of data is questionable.

Although the plan of analysis of this subset of patients was included in the SAP, it was not pre-specified in the original protocol. It is to be noted that the sponsor's SAP was dated "16-10-01", but the study duration was dated "March 2000-Sep 24, 2001". The analysis of this subset patients appeared to be a post-hoc analysis and the results could mainly be hypothesis-generated.

3.1.5 Description of Study HGFR

This study titled as "Study of Olanzapine in Treatment Resistant Major Depressive Disorder Without Psychotic Features." The study was conducted in 2 study centers.

3.1.5.1 Study Objective

The objective of this study was to assess the combination treatment of olanzapine (5 to 20 mg/day) plus fluoxetine (20 to 60 mg/day) versus treatment with olanzapine (5 to 20 mg/day) or fluoxetine (20 to 60 mg/day) alone in outpatients who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for recurrent major depressive disorder (MDD) without psychotic features and who were nonresponsive to conventional therapy.

3.1.5.2 Study Design

This was a randomized, double-blind, multi-center study of patients meeting diagnostic criteria for MDD according to the DSM-IV and who were nonresponsive to conventional therapy.

The study consisted of three treatment phases. The fluoxetine lead-in phase (Study Period I) lasted for 6 weeks. All patients received open-label treatment with fluoxetine (20 to 60 mg/day, 1 capsule = 20 mg) during this phase. For the 8-week acute phase (Study Period II), patients were randomized to double-blind treatment with olanzapine (5 to 20 mg/day, 1 capsule = 5 mg) and fluoxetine (20 to 60 mg/day) in combination (OFC treatment group), fluoxetine 20 to 60 mg/day monotherapy, or olanzapine 5 to 20 mg/day monotherapy. During the 8-week open-label phase, all patients received open-label treatment with OFC using the same dose ranges used for the acute phase. Throughout the study, fluoxetine was administered in the morning (AM dose) and olanzapine in the evening (PM dose).

3.1.5.3 Efficacy Variables and Analyses

The primary efficacy measure was LOCF change from baseline (Visit 4) to endpoint visit (Visit 12) in HAMD-21 total score during the acute phase. If the baseline HAMD-21 observation was missing, then the patient was unevaluable for LOCF analysis.

Treatment groups were also compared with respect to LOCF change from baseline to endpoint visit in the secondary efficacy rating scales and subscales (MADRS and CGI-Severity) during the acute phase. ANOVA models were used to evaluate these continuous efficacy data; these models included a effect for treatment only. In the open-label phase, the LOCF change from baseline to endpoint visit was also analyzed for the same efficacy measures.

Observed-case and LOCF visitwise analyses of HAMD-21 total score, MADRS total score, and CGI-Severity score were performed for the acute phase. An observed case visitwise analysis evaluates change from baseline to each visit for all patients who were active in the study at that visit. A LOCF visitwise analysis evaluates change from baseline to each visit using that patient's score at that visit or the patient's last available score prior to that visit. Similar analyses were performed for the open-label phase.

Response rates were compared among treatment groups for the acute phase. Response was defined as a $\geq 30\%$ decrease from baseline to endpoint in HAMD-21 total score. Response rates were analyzed using Pearson's chi-square test.

3.1.6 Efficacy Results for Study HGFR

3.1.6.1 Patient Population and Baseline Demographic Characteristics

Table 3.9 shows patient disposition during the acute phase. One patient from the olanzapine treatment group discontinued due to an adverse event (ataxia) at Visit 8. No patients in the OFC treatment group discontinued because of adverse event or lack of efficacy.

Table 3.9 Patient Disposition for Acute Phase for Study HGFR

Variable	OFC	Fluoxetine	Olanzapine	Total
Randomized	10	10	8	28
Discontinued	1 (10.0%)	3 (30.0%)	2 (25%)	6 (21.4%)
Adverse Event	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (3.6%)
Lack of Efficacy	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (3.6%)
Personal Conflict	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (3.6%)
Protocol Violation	1 (10.0%)	1 (10.0%)	1 (12.5%)	3 (10.7%)

Source: Sponsor's Table HGFR.10.4 of CSR.

Table 3.10 summarizes patients baseline demographic characteristics for the 28 patients randomized into the acute phase. Patients had a mean age of 42 years, 96% were Caucasian, and 75% were female. As seen in the table, the treatment groups appeared comparable at baseline with respect to age, racial origin, and gender.

Table 3.10 Patient Baseline Demographic Characteristics for Acute Phase for Study HGFR

Variable	OFC (N=10)	Fluoxetine (N=10)	Olanzapine (N=8)	Total (N=28)
Gender (n and %)				
Female	8 (80.0%)	7 (70.0%)	6 (75.0%)	21 (75.0%)
Male	2 (20.0%)	3 (30.0%)	2 (25.0%)	7 (25.0%)
Origin (n and %)				
African Descent	0	1 (10.0%)	0	1 (3.6%)
Caucasian	10 (100%)	9 (90.0%)	8 (100%)	27 (96.4%)
Age (yrs)				
Mean (SD)	45.77 (8.23)	38.15 (11.31)	40.99 (11.61)	41.68 (10.54)
Height (cm)				
Mean (SD)	169.67 (11.72)	169.16 (10.59)	170.50 (10.02)	169.73 (10.46)
Weight (kg)				
Mean (SD)	74.46 (14.06)	81.42 (21.97)	76.38 (17.52)	77.49 (17.77)
BMI				
Mean (SD)	25.87 (4.08)	28.41 (6.97)	26.24 (5.22)	26.88 (5.49)

Source: Sponsor's Table HGFR.11.2 of CSR.

3.1.6.2 Sponsor's Efficacy Analysis Results

Table 3.11 summarizes the sponsor's analysis results for mean change from baseline to endpoint visit in the primary efficacy measure (HAMD-21 total score) and secondary efficacy measures (MADRS total and CGI-Severity scores) for all patients during the acute phase.

Table 3.11 Sponsor's Analysis Results for Study HGFR

Variable	OFC (N=10)	Fluoxetine (N=10)	Olanzapine (N=8)	P-Value		
				Overall	OFC v.s. Fluoxetine	OFC v.s. Olanzapine
HAMD-21						
Baseline Mean (SD)	26.4 (7.5)	23.5 (6.0)	24.5 (5.2)	0.594	0.319	0.535
Mean Change* (SD)	-11.7 (10.6)	-3.8 (9.6)	-5.9 (5.2)	0.151	0.061	0.185
MADRS						
Baseline Mean (SD)	29.5 (9.2)	23.8 (8.3)	25.0 (3.8)	0.240	0.109	0.228
Mean Change* (SD)	-13.6 (11.9)	-1.2 (11.0)	-2.8 (6.0)	0.026	0.012	0.035
CGI-Severity						
Baseline Mean (SD)	4.6 (0.8)	4.3 (0.7)	4.3 (0.7)	0.553	0.379	0.334
Mean Change* (SD)	-2.0 (1.3)	-0.4 (1.2)	0.0 (0.9)	0.003	0.005	0.001

Source: Sponsor's Table HGFR.11.12 of CSR. *Note: Since the ANOVA model only included treatment, this reported mean was the raw mean and also was the LS means.

As shown in the table, there was no overall statistically significant difference in LOCF mean change from baseline to endpoint for the HAMD-21 total score among the treatment groups during the acute phase. However, an overall statistically significant difference ($p=0.026$) in mean change from baseline to endpoint for MADRS total score was observed among the treatment groups. OFC yielded a statistically significantly

greater mean decrease in MADRS total score when compared with both monotherapies. There was also an overall statistically significant difference ($p=.003$) in mean change from baseline to endpoint visit for CGI-Severity score among the treatment groups. The OFC yielded a statistically significantly greater mean decrease in CGI-Severity score when compared with both monotherapies ($p=.005$ and $p=.001$, respectively).

3.1.6.3 Statistical Reviewer's Findings and Comments

1. This reviewer has a reservation to accept Study HGFR as a positive study. The reasons are as follows:
 - (a) The primary endpoint of this study was the change from baseline to endpoint in HAMD-21 total score during the acute phase. This reviewer confirmed the sponsor's analysis results that OFC failed to demonstrate statistical significant difference when compared with each monotherapy.
 - (b) Although the sponsor pointed out that OFC demonstrated a statistically significant greater decrease in MADRS total score (the primary efficacy measure for other pivotal studies) from baseline to endpoint visit when compared with each monotherapy, it was based on a post-hoc analysis. In addition, with any of several selected patients deleted from the analysis, the statistical significance disappeared at nominal significance level of 0.05. This suggests that even the strength of evidence based on the post-hoc analysis (analysis of MADRS total score) is not strong.
 - (c) Although the differences in treatment effects between OFC and each monotherapy seem to be large, the baseline differences between treatment groups appeared large, too. This reviewer noticed that the sponsor's ANOVA did not adjust for any other factors or covariates, although the primary analysis in such a setting is most commonly based on ANCOVA by including baseline value as a covariate in the model to adjust for potential differences in baseline scores. When the MADRS change from baseline to endpoint LOCF data were analyzed by the aforementioned ANCOVA model, it was found that the statistically significant differences between the OFC and each monotherapy do not exist anymore at 0.05 significance level (p -values=0.0503 and 0.0848, respectively).
2. Since this study was a pilot study with only 28 randomized patients, this reviewer carefully checked the normality assumption required for ANCOVA analysis. It was found that the data were fairly normally distributed.

3.2 EVALUATION OF SAFETY

The evaluation of safety was not performed in this review. Please see the clinical review for this evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

For the pivotal studies, Studies 1, 2 of HDAO and Study HGIE, for the MADRS total score the sponsor performed the subgroup analyses based on origin, sex, age, baseline BMI, and certain illness characteristics whenever there were at least 10 patients in each treatment-subgroup permutation. The certain illness characteristics consisted of age of onset of depression, number of previous episodes of depression, number of previous depressive episodes in the last 36 months, historical failure to respond to an SSRI in the current episode, historical failure to two antidepressants in the current episode, and family history of MDD.

In this section, only the subgroup analysis by gender, race, age for all reviewed pivotal studies and for Study HGIE, also the analysis for patients with historical failure to SSRI treatment during the current episode of MDD are presented and discussed. Since Study HGFR is a small study with only 28 randomized patients, none of subgroup analysis is presented in this review. This reviewer confirmed the sponsor's analysis results for these subgroup analyses.

4.1 GENDER, RACE AND AGE

Study HDAO

Table 3.12 summarizes the sponsor's subgroup analysis results by gender, race and age in MADRS total score for combined Studies 1 and 2 of Study HDAO. As shown in the table, OFC seems to perform better in female, Caucasian and older patients than their counterparts, respectively.

Table 3.12 Sponsor's Analysis Results for Subgroup Analysis by Gender, Race and Age for Study HDAO in Combined Data of Studies 1 and 2

Subgroup	Therapy	Baseline Mean (SD)	Raw Mean Change to the Endpoint (SD)	P-Value v.s OFC
Gender				
Female	OFC (N=131)	29.33 (6.23)	-13.54 (10.09)	
	Fluoxetine (N=126)	30.02 (6.14)	-10.10 (10.12)	0.030
	Olanzapine (N=122)	29.83 (6.19)	-8.43 (9.24)	<0.001
Male	OFC (N=67)	31.43 (7.26)	-10.90 (10.51)	
	Fluoxetine (N=77)	29.68 (6.88)	-7.70 (8.83)	0.022
	Olanzapine (N=75)	30.03 (7.45)	-9.60 (8.50)	0.414
Race				
Caucasian	OFC (N=177)	30.05 (6.37)	-12.66 (10.15)	
	Fluoxetine (N=175)	30.00 (6.38)	-8.93 (9.17)	<0.001
	Olanzapine (N=163)	30.10 (6.60)	-8.49 (8.81)	<0.001
Other	OFC (N=21)	29.95 (8.86)	-12.52 (11.60)	
	Fluoxetine (N=28)	29.21 (6.69)	-10.82 (12.60)	0.41
	Olanzapine (N=34)	28.97 (7.06)	-10.77 (9.55)	0.96

Subgroup	Therapy	Baseline Mean (SD)	Raw Mean Change to the Endpoint (SD)	P-Value v.s OFC
Age				
<40	OFC (N=66)	30.03 (6.33)	-11.44 (10.57)	
	Fluoxetine (N=64)	30.88 (5.62)	-9.95 (9.57)	0.69
	Olanzapine (N=67)	29.46 (6.49)	-9.70 (10.43)	0.37
≥ 40	OFC (N=132)	30.05 (6.83)	-13.25 (10.13)	
	Fluoxetine (N=139)	29.44 (6.72)	-8.84 (9.77)	<0.001
	Olanzapine (N=130)	30.13 (6.79)	-8.45 (8.11)	<0.001

Source: Sponsor's Table HDAO.14c.11.

Study HGIE

Table 3.13 shows the sponsor's subgroup analysis results by gender, race and age in MADRS total score for Study HGIE. Similar to the results based on Study HDAO, the OFC seems to perform better in female, Caucasian and older patients than their counterparts, respectively.

Table 3.13 Sponsor's Analysis Results for Subgroup Analysis by Gender, Race and Age for Study HGIE

Subgroup	Therapy	Baseline Mean (SD)	Raw Mean Change to the Endpoint (SD)	P-Value v.s OFC
Gender				
Female	OFC 6/25 (N=42)	28.00 (7.53)	-13.64 (9.89)	
	OFC 6/50 (N=45)	30.91 (6.92)	-13.56 (12.03)	
	OFC 12/25 (N=38)	29.82 (5.41)	-12.39 (8.88)	
	OFC 12/50 (N=39)	31.26 (5.92)	-13.41 (10.55)	
	Fluoxetine (N=40)	31.73 (5.61)	-11.65 (10.64)	0.414
	Olanzapine (N=42)	31.40 (6.89)	-8.33 (11.30)	0.007
Male	OFC 6/25 (N=17)	29.53 (6.57)	-12.59 (10.09)	
	OFC 6/50 (N=16)	23.13 (7.96)	-7.25 (8.42)	
	OFC 12/25 (N=17)	32.29 (6.56)	-10.06 (9.44)	
	OFC 12/50 (N=17)	29.71 (6.72)	-12.35 (9.02)	
	Fluoxetine (N=16)	30.94 (7.71)	-8.19 (11.44)	0.494
	Olanzapine (N=17)	28.18 (6.60)	-4.71 (11.14)	0.014

Subgroup	Therapy	Baseline Mean (SD)	Raw Mean Change to the Endpoint (SD)	P-Value v.s OFC
Race				
Caucasian	OFC 6/25 (N=52)	27.90 (7.13)	-13.23 (8.94)	
	OFC 6/50 (N=55)	28.47 (7.80)	-10.98 (10.13)	
	OFC 12/25 (N=46)	30.63 (5.99)	-11.96 (9.10)	
	OFC 12/50 (N=51)	30.71 (6.33)	-13.16 (10.47)	
	Fluoxetine (N=49)	31.08 (6.44)	-10.35 (10.91)	0.230
	Olanzapine (N=54)	30.63 (7.05)	-7.13 (11.36)	0.000
Other	OFC 6/25 (N=7)	32.43 (7.32)	-14.14 (16.17)	
	OFC 6/50 (N=6)	32.50 (8.96)	-20.33 (19.46)	
	OFC 12/25 (N=9)	30.33 (5.36)	-10.22 (9.08)	
	OFC 12/50 (N=5)	31.60 (4.34)	-12.40 (3.91)	
	Fluoxetine (N=7)	34.43 (3.41)	-12.86 (11.22)	0.827
	Olanzapine (N=5)	28.80 (5.45)	-9.00 (11.42)	0.712
Age				
<50	OFC 6/25 (N=37)	29.03 (6.82)	-13.19 (11.04)	
	OFC 6/50 (N=39)	28.56 (6.97)	-10.41 (9.22)	
	OFC 12/25 (N=38)	29.82 (5.59)	-10.24 (8.45)	
	OFC 12/50 (N=33)	30.61 (5.68)	-12.24 (9.41)	
	Fluoxetine (N=39)	31.51 (6.45)	-11.00 (11.39)	0.801
	Olanzapine (N=41)	30.10 (7.07)	-7.32 (12.52)	0.058
≥ 50	OFC 6/25 (N=22)	27.45 (7.97)	-13.59 (7.76)	
	OFC 6/50 (N=22)	29.41 (9.56)	-14.55 (14.53)	
	OFC 12/25 (N=17)	32.29 (6.21)	-14.88 (9.74)	
	OFC 12/50 (N=23)	31.04 (6.91)	-14.30 (10.98)	
	Fluoxetine (N=17)	31.47 (5.84)	-9.88 (9.91)	0.011
	Olanzapine (N=18)	31.33 (6.65)	-7.22 (8.07)	0.003

Source: Sponsor's Table HGIE.14.15

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

Study HGIE

For Study HGIE, the sponsor also performed the analyses for the mean change from baseline to each visit in MADRS total score for the subset of patients with historical failure to SSRI treatment during their current episode of MDD. The sponsor believed that patients in this subset were more closely resemble patients in Study HDAO. Table 3.15 shows the sponsor's analysis results for this subset of patients at Week 12. The by-visit analysis results for this subset of patients are shown in Table 6.14 of the Appendices.

For this subset of patients, the composite OFC treatment group demonstrated a statistically significantly greater mean decrease in MADRS total score compared with both the fluoxetine and the olanzapine treatment groups at endpoint visit, i.e., Week 12. Note that although the OFC showed statistically significant results in comparison

with fluoxetine and olanzapine at Week 12, the OFC did not show significant results in comparison with olanzapine at Week 8, at which visit the primary endpoint showed statistically significant results based on the whole study population. Moreover, as mentioned in Comment #3 of Section 3.1.4.4, this reviewer had a concern about the quality of data. Consequently, the interpretation of the post-hoc analysis results of this subgroup is questionable.

Table 3.15 Sponsor's LOCF Analysis Results for Patients with Historical Failure to SSRI Treatment During the Current Episode of MDD in MADRS Total Score at Week 12 for Study HGIE

Therapy	Baseline Mean (SE)	Raw Mean of Change (SE)	LS Mean Change (SE)	p-values		
				v.s. OFC (composite)	v.s. Fluoxetine	v.s. Olanzapine
OFC 6/25 (n=38)	29.34 (1.00)	-12.71 (1.52)	-13.24 (1.53)		0.061	0.020
OFC 6/50 (n=45)	29.13 (1.20)	-13.42 (1.58)	-13.08 (1.43)		0.060	0.019
OFC 12/25 (n=39)	31.08 (0.94)	-11.95 (1.46)	-11.92 (1.50)		0.209	0.095
OFC 12/50 (n=41)	30.95 (0.98)	-15.02 (1.56)	-14.02 (1.49)		0.022	0.006
Fluoxetine (n=41)	31.07 (0.88)	-9.98 (1.42)	-9.31 (1.48)	0.021		
Olanzapine (n=47)	31.51 (0.99)	-8.81 (1.69)	-8.54 (1.38)	0.003		
Venlafaxine (n=41)	30.39 (0.84)	-13.12 (1.52)	-12.50 (1.49)	0.713		
OFC 1/5 (n=42)	30.24 (1.03)	-11.12 (1.65)	-10.94 (1.48)		0.430	0.226

Source: Sponsor's Table HGIE.11.20.

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Basically, this reviewer confirmed the sponsor's analysis results for the primary endpoint, commonly proposed secondary endpoints and the subgroup analyses for all studies. Of the five efficacy studies (Studies HDAO-1, HDAO-2, HGFR, HGIE and HGHZ), Study HDAO-2 was the only one that clearly demonstrated the efficacy of OFC in the treatment of patients with TRD. Although Study HDAO-1 was an identical study with Study HDAO-2, it was a negative study, which did not show any supportive evidence for the OFC's efficacy at the endpoint visit, or even any earlier visit.

According to the meeting minutes dated January 16, 2002, the FDA clearly informed the sponsor that because studies HGIE, HGHZ, and HGFR did not meet their primary endpoints, two additional positive studies would be required for an indication of TRD. Using the FDA Guidance on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, the sponsor argued (in this NDA submission) that a single adequate and well-controlled study demonstrating effectiveness of a new use

can be used to support consideration of a new indication when there are “multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness.” Two strong supportive evidence that the sponsor listed are as follows.

- *For Study HGFR, the OFC showed statistically significantly greater reduction than both fluoxetine ($p=0.012$) and olanzapine ($p=0.035$) on the MADRS after 8 weeks of treatment. This was a small, pilot study ($n=28$) and therefore may not be readily generalizable, but it is noteworthy that treatment differences showed statistical separation despite the low power from a small sample size*
- *For Study HGIE, OFC showed statistically significantly greater reduction on the MADRS than both fluoxetine ($p=.010$) and olanzapine ($p=.006$) after 8 weeks of treatment, although the difference over fluoxetine was only numerically superior after 12 weeks of treatment. In the subgroup of patients in Study HGIE who had failed two antidepressants in their current episode (that is, those who most closely resemble patients in Study HDAO and Study HGFR), OFC showed statistically significantly greater reduction on the MADRS than did fluoxetine ($p=.021$) or olanzapine ($p=.003$) after 12 weeks of treatment.*

Regarding the sponsor’s supportive evidence listed above, this reviewer agreed with the sponsor’s numerical findings. However, this reviewer would like to emphasize that these analysis results were indeed based on **post-hoc analyses** and interpretations of these results are questionable. In particular, for Study HGFR, this reviewer has reservation to accept this study as a positive study. The reasons are as follows: (a) The sponsor failed to demonstrate the superiority of OFC with respect to the pre-specified primary endpoint based on HAMD-21 total score. (b) Although the sponsor pointed out that OFC was shown superior to each monotherapy with respect to the efficacy measure MADRS total score (primary efficacy measure for other pivotal studies), the result was hypothesis-generated. In addition, with any of several selected patients deleted from the analysis, the statistical significance disappeared at nominal significance level of 0.05. This suggests that even the strength of evidence based on the post-hoc analysis is not strong. (c) The ANOVA model used to analyze the MADRS total score did not consider the baseline differences. When the ANOVA model including the baseline as a covariate was used to analyze the change from baseline to endpoint visit for the MADRS total score, the statistically significant difference between the OFC and each monotherapy were inconclusive (p -values=0.0503 and 0.0848, respectively) at the 0.05 significance level.

For Study HGIE, the sponsor failed to demonstrate the superiority of OFC on the pre-specified patient population (patients who had failed at least one anti-depressant) at the pre-specified endpoint visit (Week 12) although the result at Visit 8 was statistically significant at nominal significance level $\alpha = 0.05$. Analysis of Visit 8 data can only be considered exploratory because the nominal significance level α was not adjusted for multiple analyses. Although OFC was shown to be superior to both individual components (at nominal significance level $\alpha = 0.05$) at the pre-specified endpoint visit

(Week 12) on the subset of patients who had failure of two antidepressants during the current episode, OFC failed to show superior to olanzapine at Week 8 on the same subset of patients. These inconsistencies suggest the weakness of data in support of efficacy.

This reviewer would like to further point out that the significant findings at Week 12 for that subset of patients was found to be driven by the highest olanzapine and fluoxetine combination group. Moreover, when the patients' onset dates of current episodes and dates of previous therapy use were utilized to identify the subset of patients, the quality of data appeared to be questionable.

To sum up, from the statistical perspective, OFC's efficacy in treating patients with TRD was only supported by one clearly positive study. Data from those seemingly positive studies do not provide clearly supportive efficacy evidence and certainly do not add up to one positive study.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Among the sponsor-submitted five efficacy studies, only one study (Study 2 of HDAO) clearly demonstrated the efficacy of olanzapine and fluoxetine combination (OFC) in treating patients with treatment resistant depression (TRD). Both HADO-1 and -2 studies had identical design and similar dropout rates. It was not clear what yielded inconsistent efficacy results between these two HDAO studies.

Although during an earlier meeting, FDA informed the sponsor that two positive studies would be required for an indication of treatment resistant depression, the sponsor argued in this NDA submission that based on the FDA Guidance (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products) one clearly positive study with multiple studies supporting the new use would be sufficient for the approval. So, they listed other significant findings from Studies HGFR, HGIE and HGHZ to support the efficacy of the OFC.

From the sponsor's listed supportive evidence from Studies HGFR, HGIE and HGHZ, this reviewer only thinks that at most the results from Study HGIE could possibly be considered if the medical division really agrees with the sponsor that the subset of patients who had failed two antidepressants in their current episode fairly represent the patients in Study HDAO and they are the most suitable patients for being determined as patients with treatment resistant depression. However, we should note that OFC was not statistically significantly different from the olanzapine at Week 8 for this subset of patients and the positive findings at Week 12 might only come from the highest olanzapine and fluoxetine combination (OFC 12/50). In addition, the quality of data for identifying this subset of patients appeared questionable.

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6. Appendices

Table 6.1 Sponsor's LOCF Analysis Results for MADRS Total Score for All Visits for Study 1 of Study HDAO

		Baseline	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16
OFC	n	102	101	101	101	101	101	101	101	101	101
Change from Baseline	Mean	29.598	-6.248	-10.129	-11.990	-11.554	-11.495	-11.455	-11.871	-11.970	-10.752
	SE	0.713	0.613	0.733	0.810	0.917	0.929	0.956	0.995	0.993	0.999
t-test*	p-val		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
FLX	n	104	102	102	102	102	102	102	102	102	102
Change from Baseline	Mean	29.673	-4.902	-6.353	-7.943	-8.029	-8.696	-8.667	-9.755	-9.824	-9.422
	SE	0.676	0.686	0.798	0.847	0.912	0.925	0.969	1.029	0.994	0.984
t-test*	p-val		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
OLZ	n	96	95	95	95	95	95	95	95	95	95
Change from Baseline	Mean	29.719	-7.000	-9.421	-10.916	-11.147	-10.932	-10.147	-10.137	-10.063	-10.137
	SE	0.717	0.669	0.886	0.902	0.890	0.985	0.961	0.970	0.998	0.984
t-test*	p-val		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Treatment Comparisons **											
THERAPY	p-val	0.940	0.078	<.001	<.001	0.007	0.064	0.073	0.191	0.160	0.563
POOLED INVESTIGATOR	p-val	<.001	0.028	0.061	0.084	0.193	0.133	0.051	0.169	0.135	0.023
OFC vs. FLX	p-val	0.866	0.133	<.001	<.001	0.003	0.023	0.022	0.093	0.086	0.287
OFC vs. OLZ	p-val	0.725	0.471	0.406	0.292	0.645	0.535	0.222	0.150	0.112	0.532
FLX vs. OLZ	p-val	0.852	0.027	0.004	0.008	0.014	0.104	0.298	0.828	0.918	0.669

OFC = olanzapine + fluoxetine, FLX = fluoxetine, OLZ = olanzapine

n = Patients having both baseline and post-baseline visits

* Within group t-test

** BASELINE - Type III sums of squares analysis of variance with THERAPY and POOLED INVESTIGATOR in the model

** POST-BASELINE - Type III sums of squares analysis of covariance with THERAPY, POOLED INVESTIGATOR, and BASELINE MADRS TOTAL SCORE in the model

Source: Sponsor's Table HDAO.11a.10.

Table 6.2 Sponsor's LOCF Analysis Results for MADRS Total Score for All Visits for Study 2 of Study HDAO

		Baseline	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16
OFC	n	98	97	97	97	97	97	97	97	97	97
Change from Baseline	Mean	30.520	-8.691	-12.299	-13.371	-13.794	-13.742	-13.938	-14.515	-14.722	-14.619
	SE	0.626	0.741	0.830	0.910	0.978	0.968	1.005	1.040	0.966	1.038
t-test*	p-val		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
FLX	n	102	101	101	101	101	101	101	101	101	101
Change from Baseline	Mean	30.137	-2.960	-4.682	-6.663	-7.455	-8.337	-9.030	-8.950	-9.584	-8.960
	SE	0.583	0.533	0.707	0.725	0.839	0.860	0.939	0.896	0.926	0.945
t-test*	p-val		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
OLZ	n	103	102	102	102	102	102	102	102	102	102
Change from Baseline	Mean	30.117	-6.902	-9.814	-11.471	-11.608	-10.480	-10.706	-9.314	-8.980	-7.706
	SE	0.622	0.586	0.723	0.813	0.890	0.908	0.918	0.841	0.880	0.812
t-test*	p-val		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Treatment Comparisons **											
THERAPY	p-val	0.869	<.001	<.001	<.001	<.001	<.001	0.001	<.001	<.001	<.001
POOLED INVESTIGATOR	p-val	<.001	<.001	0.229	0.655	0.442	0.287	0.388	0.311	0.053	0.045
OFC vs. FLX	p-val	0.721	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
OFC vs. OLZ	p-val	0.603	0.041	0.023	0.119	0.109	0.010	0.019	<.001	<.001	<.001
FLX vs. OLZ	p-val	0.870	<.001	<.001	<.001	<.001	0.073	0.161	0.746	0.679	0.348

OFC = olanzapine + fluoxetine, FLX = fluoxetine, OLZ = olanzapine

n = Patients having both baseline and post-baseline visits

* Within group t-test

** BASELINE - Type III sums of squares analysis of variance with THERAPY and POOLED INVESTIGATOR in the model

** POST-BASELINE - Type III sums of squares analysis of covariance with THERAPY, POOLED INVESTIGATOR, and BASELINE MADRS TOTAL SCORE in the model

Source: Sponsor's Table HDAO.11b.10.

Table 6.3 Sponsor's OC Analysis Results for MADRS Total Score for All Visits for Study 1 of Study HDAO

		Baseline	WEEK 0.5	WEEK 1.0	WEEK 2.0	WEEK 3.0	WEEK 4.0	WEEK 5.0	WEEK 6.0	WEEK 7.0	WEEK 8.0
OFC	n	101	101	95	93	90	84	78	76	73	74
Change from Baseline	Mean	29.47	-6.25	-10.19	-12.43	-12.12	-12.23	-12.94	-13.66	-14.12	-12.61
	Std	7.11	6.16	7.52	8.25	9.44	9.67	9.62	10.05	9.40	10.01
t-test*	p-val		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
FLX	n	102	102	100	100	99	92	88	87	85	83
Change from Baseline	Mean	29.66	-4.90	-6.37	-7.89	-8.02	-8.86	-8.76	-10.08	-10.29	-10.04
	Std	6.90	6.93	8.13	8.63	9.32	9.51	9.80	10.52	10.11	9.98
t-test*	p-val		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
OLZ	n	95	95	94	91	88	85	80	70	65	64
Change from Baseline	Mean	29.72	-7.00	-9.54	-11.19	-11.84	-11.49	-10.99	-12.14	-12.25	-12.55
	Std	7.06	6.52	8.60	8.75	8.40	9.61	9.40	9.32	9.78	9.52
t-test*	p-val		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Treatment Comparisons**											
Therapy	p-val		0.075	0.002	<.001	0.003	0.050	0.021	0.075	0.051	0.181
OFC vs. FLX	p-val		0.144	0.001	<.001	0.002	0.021	0.006	0.024	0.015	0.104
OFC vs. OLZ	p-val		0.422	0.583	0.325	0.836	0.620	0.204	0.362	0.262	0.971

OFC = olanzapine + fluoxetine combination, FLX = fluoxetine, OLZ = olanzapine.
n = number of patients with MADRS assessed at the visit.

*Within group p-values are from a paired t-test on mean change.

**p-values are from Type III Sums of Squares from an analysis of variance (ANOVA) model: change = therapy.

Source: Sponsor's Table B.1.

Table 6.4 Sponsor's OC Analysis Results for MADRS Total Score for All Visits for Study 2 of Study HDAO

		Baseline	WEEK 0.5	WEEK 1.0	WEEK 2.0	WEEK 3.0	WEEK 4.0	WEEK 5.0	WEEK 6.0	WEEK 7.0	WEEK 8.0
OFC	n	97	97	95	92	89	88	84	78	76	75
Change from Baseline	Mean	30.64	-8.69	-12.49	-13.70	-14.21	-14.19	-14.67	-15.36	-15.50	-15.55
	Std	6.12	7.29	8.14	9.03	9.85	9.79	9.95	10.36	9.52	10.37
t-test*	p-val		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
FLX	n	101	101	101	98	97	94	90	85	84	83
Change from Baseline	Mean	30.13	-2.96	-4.68	-6.56	-7.51	-8.34	-9.38	-9.29	-10.14	-9.34
	Std	5.91	5.36	7.10	7.26	8.40	8.67	9.38	8.98	9.30	9.61
t-test*	p-val		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
OLZ	n	102	102	97	94	88	84	76	71	67	65
Change from Baseline	Mean	30.08	-6.90	-10.10	-12.15	-13.05	-12.10	-13.03	-11.15	-10.76	-8.95
	Std	6.33	5.92	7.24	8.06	8.67	9.12	9.10	8.46	9.36	8.45
t-test*	p-val		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Treatment Comparisons**											
Therapy	p-val		<.001	<.001	<.001	<.001	<.001	0.001	<.001	<.001	<.001
OFC vs. FLX	p-val		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
OFC vs. OLZ	p-val		0.044	0.028	0.196	0.388	0.136	0.276	0.006	0.003	<.001

OFC = olanzapine + fluoxetine combination, FLX = fluoxetine, OLZ = olanzapine.
n = number of patients with MADRS assessed at the visit.

*Within group p-values are from a paired t-test on mean change.

**p-values are from Type III Sums of Squares from an analysis of variance (ANOVA) model: change = therapy.

Source: Sponsor's Table B.2.

Table 6.5 Sponsor's LOCF Analysis Results for HAM-A Total Score for All Visits for Study 1 of Study HDAO

		Baseline	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16

OFC	n	102	101	101	101	101	101	101	101	101	101
Change from Baseline	Mean	19.18	-3.58	-5.36	-6.06	-6.22	-6.02	-6.00	-6.33	-6.71	-5.97
	SE	0.71	0.52	0.57	0.64	0.71	0.71	0.73	0.71	0.71	0.66
t-test	p-val		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
FLX	n	104	102	102	102	102	102	102	102	102	102
Change from Baseline	Mean	19.26	-3.06	-3.83	-4.30	-4.94	-5.40	-5.96	-6.21	-6.31	-6.27
	SE	0.70	0.49	0.51	0.59	0.55	0.53	0.57	0.61	0.62	0.62
t-test	p-val		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
OLZ	n	96	95	95	95	95	95	95	95	95	95
Change from Baseline	Mean	17.96	-3.65	-4.18	-4.98	-5.54	-5.15	-4.64	-5.11	-5.13	-5.13
	SE	0.56	0.53	0.57	0.63	0.58	0.69	0.69	0.71	0.72	0.74
t-test	p-val		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Treatment Comparison (ANOVA)											
THERAPY	p-val	0.305	0.706	0.097	0.112	0.332	0.626	0.250	0.338	0.221	0.427
Pooled Investigator	p-val	<0.001	0.174	0.006	<0.001	0.016	<0.001	<0.001	<0.001	0.004	0.001
OFC vs. FLX	p-val	0.887	0.471	0.039	0.038	0.139	0.534	0.985	0.915	0.686	0.656
OFC vs. OLZ	p-val	0.207	0.996	0.114	0.203	0.418	0.341	0.151	0.184	0.096	0.399
FLX vs. OLZ	p-val	0.159	0.473	0.648	0.439	0.514	0.732	0.144	0.219	0.202	0.198

OFC = olanzapine + fluoxetine, FLX = fluoxetine, OLZ = olanzapine

n = Patients having both baseline and post-baseline measures

*1 - Within group p-Values are from t-test on mean change

**Means are analyzed using a Type III sums of squares analysis of variance (ANOVA); CHANGE = POOLINV THERAPY

Source: Sponsor's Table HDAO.11a.12.

Table 6.6 Sponsor's LOCF Analysis Results for HAM-A Total Score for All Visits for Study 2 of Study HDAO

		Baseline	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16

OFC	n	98	97	97	97	97	97	97	97	97	97
Change from Baseline	Mean	19.73	-4.60	-6.65	-6.71	-7.35	-7.14	-7.69	-7.71	-8.24	-7.96
	SE	0.54	0.51	0.55	0.56	0.67	0.67	0.66	0.65	0.65	0.69
t-test	p-val		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
FLX	n	102	101	101	101	101	101	101	101	101	101
Change from Baseline	Mean	18.76	-2.08	-2.69	-3.60	-4.42	-4.84	-5.32	-5.08	-5.33	-5.09
	SE	0.51	0.42	0.44	0.50	0.59	0.59	0.64	0.61	0.64	0.67
t-test	p-val		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
OLZ	n	103	102	102	102	102	102	102	102	102	102
Change from Baseline	Mean	19.40	-2.85	-4.31	-5.06	-5.62	-4.93	-5.41	-5.36	-5.07	-4.72
	SE	0.52	0.43	0.52	0.54	0.55	0.57	0.57	0.57	0.60	0.57
t-test	p-val		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Treatment Comparison (ANOVA)											
THERAPY	p-val	0.392	<0.001	<0.001	<0.001	0.003	0.007	0.007	0.003	<0.001	<0.001
Pooled Investigator	p-val	<0.001	0.019	0.132	0.317	0.318	0.125	0.308	0.130	0.087	0.116
OFC vs. FLX	p-val	0.177	<0.001	<0.001	<0.001	<0.001	0.005	0.005	0.002	<0.001	0.001
OFC vs. OLZ	p-val	0.615	0.009	0.002	0.030	0.041	0.007	0.008	0.006	<0.001	<0.001
FLX vs. OLZ	p-val	0.389	0.187	0.017	0.033	0.149	0.895	0.846	0.729	0.889	0.728

OFC = olanzapine + fluoxetine, FLX = fluoxetine, OLZ = olanzapine

n = Patients having both baseline and post-baseline measures

*1 - Within group p-Values are from t-test on mean change

**Means are analyzed using a Type III sums of squares analysis of variance (ANOVA); CHANGE = POOLINV THERAPY

Source: Sponsor's Table HDAO.11b.12.

Table 6.7 Sponsor's LOCF Analysis Results for CGI-Severity Score for All Visits for Study 1 of Study HDAO

		Baseline	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16
OFC	n	102	100	101	101	101	101	101	101	101	101
Change from Baseline	Mean	4.539	-0.410	-0.792	-1.010	-1.040	-1.119	-1.099	-1.168	-1.208	-1.089
t-test	SE	0.069	0.075	0.096	0.101	0.118	0.123	0.125	0.129	0.125	0.133
	p-val		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
FLX	n	104	102	102	102	102	102	102	102	102	102
Change from Baseline	Mean	4.702	-0.451	-0.618	-0.676	-0.725	-0.873	-0.912	-1.118	-1.059	-0.951
t-test	SE	0.073	0.075	0.099	0.092	0.100	0.109	0.117	0.120	0.121	0.114
	p-val		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
OLZ	n	96	95	95	95	95	95	95	95	95	95
Change from Baseline	Mean	4.583	-0.579	-0.705	-0.884	-0.989	-0.947	-0.926	-1.042	-1.011	-1.053
t-test	SE	0.075	0.079	0.096	0.104	0.109	0.114	0.105	0.117	0.113	0.111
	p-val		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Treatment Comparison (ANOVA)											
THERAPY	p-val	0.164	0.307	0.334	0.039	0.067	0.211	0.368	0.670	0.371	0.681
POOLED INVESTIGATOR	p-val	<0.001	0.243	0.054	0.023	0.103	0.313	0.328	0.143	0.081	0.009
OFC vs. FLX	p-val	0.065	0.759	0.139	0.011	0.027	0.088	0.214	0.673	0.301	0.384
OFC vs. OLZ	p-val	0.605	0.145	0.439	0.328	0.650	0.217	0.230	0.371	0.179	0.722
FLX vs. OLZ	p-val	0.193	0.244	0.492	0.127	0.084	0.653	0.982	0.630	0.744	0.614

OFC = olanzapine + fluoxetine, FLX = fluoxetine, OLZ = olanzapine

n = Patients having both baseline and post-baseline measures

*1 - Within group p-Value are from t-test on mean change

**Mean are analyzed using a Type III sums of squares analysis of variance (ANOVA); CHANGE = POOLINV THERAPY

Source: Sponsor's Table HDAO.11a.14.

Table 6.8 Sponsor's LOCF Analysis Results for CGI-Severity Score for All Visits for Study 2 of Study HDAO

		Baseline	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16
OFC	n	98	96	97	97	97	97	97	97	97	97
Change from Baseline	Mean	4.684	-0.708	-1.144	-1.361	-1.371	-1.433	-1.443	-1.557	-1.588	-1.526
t-test	SE	0.073	0.098	0.093	0.106	0.115	0.120	0.125	0.133	0.138	0.135
	p-val		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
FLX	n	102	101	101	101	101	101	101	101	101	101
Change from Baseline	Mean	4.735	-0.287	-0.475	-0.683	-0.782	-0.881	-0.990	-1.000	-1.040	-1.050
t-test	SE	0.074	0.071	0.091	0.099	0.099	0.102	0.114	0.116	0.124	0.116
	p-val		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
OLZ	n	103	102	102	102	102	102	102	102	102	102
Change from Baseline	Mean	4.728	-0.686	-0.951	-1.216	-1.225	-1.088	-1.157	-0.931	-0.961	-0.814
t-test	SE	0.072	0.096	0.108	0.112	0.127	0.124	0.129	0.115	0.120	0.108
	p-val		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Treatment Comparison (ANOVA)											
THERAPY	p-val	0.766	<0.001	<0.001	<0.001	0.001	0.004	0.033	<0.001	<0.001	<0.001
POOLED INVESTIGATOR	p-val	<0.001	0.005	<0.001	0.059	0.370	0.448	0.394	0.276	0.223	0.095
OFC vs. FLX	p-val	0.584	<0.001	<0.001	<0.001	<0.001	0.001	0.009	0.001	0.002	0.004
OFC vs. OLZ	p-val	0.487	0.944	0.203	0.358	0.399	0.040	0.112	<0.001	<0.001	<0.001
FLX vs. OLZ	p-val	0.882	<0.001	<0.001	<0.001	0.007	0.200	0.300	0.716	0.722	0.189

OFC = olanzapine + fluoxetine, FLX = fluoxetine, OLZ = olanzapine

n = Patients having both baseline and post-baseline measures

*1 - Within group p-Value are from t-test on mean change

**Mean are analyzed using a Type III sums of squares analysis of variance (ANOVA); CHANGE = POOLINV THERAPY

Source: Sponsor's Table HDAO.11b.14.

Table 6.9 Sponsor's Analysis Results for BPRS Total and Positive Scores
for Study HDAO Study 1

Therapy	Baseline**	Change*	p-value	
			overall	OFC v.s.
BPRS Total Score				
OFC* (N=98)	17.122 (7.701)	-5.378 (7.484)	0.646	
Fluoxetine (N=97)	17.619 (7.724)	-4.825 (7.722)		0.562
Olanzapine (N=89)	16.112 (6.513)	-4.337 (7.402)		0.357
BPRS Positive Score				
OFC* (N=98)	0.163 (0.512)	-0.082 (0.586)	0.485	
Fluoxetine (N=97)	0.165 (0.425)	0.021 (0.878)		0.284
Olanzapine (N=89)	0.191 (0.520)	-0.079 (0.588)		0.960

* OFC = olanzapine + fluoxetine

** Reported Values are raw mean and standard deviation.

Source: Sponsor's Table HDAO.11a.15.

Table 6.10 Sponsor's Analysis Results for BPRS Total and Positive Scores
for Study HDAO Study 2

Therapy	Baseline**	Change*	p-value	
			overall	OFC v.s.
BPRS Total Score				
OFC* (N=91)	15.165 (5.659)	-5.879 (6.841)	0.001	
Fluoxetine (N=96)	15.344 (5.629)	-4.281 (6.140)		0.058
Olanzapine (N=100)	14.790 (5.469)	-2.370 (6.180)		0.000
BPRS Positive Score				
OFC* (N=91)	0.132 (0.371)	0.000 (0.715)	0.659	
Fluoxetine (N=96)	0.115 (0.380)	0.094 (0.504)		0.401
Olanzapine (N=100)	0.150 (0.411)	0.050 (0.575)		0.899

* OFC = olanzapine + fluoxetine

** Reported values are raw mean and standard deviation.

Source: Sponsor's Table HDAO.11b.15.

Table 6.11 Sponsor's Analysis Results for Response and Remission Endpoints Based on
MADRS Total Score for HDAO Study 1

Therapy	Rate (Response or Remission)	Median Days to Incidence	p-value (OFC v.s.)	
			Based on Rate**	Based on time***
Partial Response (anytime)				
OFC* (N=101)	83.2%	6.5		
Fluoxetine (N=102)	79.4%	9.0	0.425	0.004
Olanzapine (N=95)	86.3%	7.4	0.518	0.090
Response				
OFC* (N=101)	36.6%	13.5		
Fluoxetine (N=102)	29.4%	15.5	0.298	0.049
Olanzapine (N=95)	35.8%	15	1	1.00

Therapy	Rate (Response or Remission)	25 Percentiles of Days to Incidence	p-value (OFC v.s.)	
			Based on Rate**	Based on time***
Remission				
OFC* (N=101)	23.8%	58		
Fluoxetine (N=102)	17.7%	71	0.303	0.168
Olanzapine (N=95)	19.0%	60	0.487	0.298
Sustained Remission				
OFC* (N=101)	20.8%	58		
Fluoxetine (N=102)	13.7%	NA	0.198	0.100
Olanzapine (N=95)	14.7%	NA	0.351	0.306

*OFC = olanzapine + fluoxetine

** by Fisher's exact test

***by Log-rank test

Source: Tables HDAO.11.a.17., 11.a.18, 11.a.21 and 11.a.22.

Table 6.12 Sponsor's Analysis Results for Response and Remission Endpoints Based on MADRS Total Score for Study 2

Therapy	Rate (Response or Remission)	Median Days to Incidence	p-value (OFC v.s.)	
			Based on Rate*	Based on time***
Partial Response (anytime)				
OFC* (N=97)	93.8%	6.3		
Fluoxetine (N=101)	77.2%	10.2	0.003	<.001
Olanzapine (N=102)	85.3%	6.3	0.209	0.989
Response				
OFC* (N=97)	44.3%	10		
Fluoxetine (N=101)	29.7%	26	0.039	0.012
Olanzapine (N=102)	16.7%	15	<0.001	<0.001

Therapy	Rate (Response or Remission)	25 Percentiles of Days to Incidence	p-value (OFC v.s.)	
			Based on Rate**	Based on time***
Remission				
OFC* (N=97)	30.9%	47		
Fluoxetine (N=101)	15.8%	NA	0.018	0.006
Olanzapine (N=102)	10.8%	NA	<0.001	0.001
Sustained Remission				
OFC* (N=97)	25.8%	55		
Fluoxetine (N=101)	11.9%	NA	0.017	0.005
Olanzapine (N=102)	8.8%	NA	0.002	0.008

*OFC = olanzapine + fluoxetine

** by Fisher's exact test

*** by Log-rank test

Source: Sponsor's Tables HDAO.11b.17, 11.b.18, 11.b.21 and 11.b.22

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/s/

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-520/S-012

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA: 20-592, 21-520
Drug: Olanzapine (ZYPREXA and SYMBYAX (olanzapine/fluoxetine))
Route: Oral
Indication: Schizophrenia, bipolar disorder (ZYPREXA); depressive episodes associated with bipolar disorder, treatment resistant depression (SYMBYAX)
Sponsor: Eli Lilly
Review Date: 7/17/08
Reviewer: Sally Usdin Yasuda, Safety Team Leader
Neurology Drug Products, HFD-120

1. Background

In an approvable letter, received by Lilly on March 28, 2007, for a supplemental New Drug Application (sNDA) for Symbyax® [olanzapine/fluoxetine combination (OFC)] for the treatment of treatment-resistant depression (TRD), FDA requested analyses related to weight gain, hyperlipidemia, and hyperglycemia. FDA included similar requests in the approvable letter for two sNDAs for Zyprexa for the treatment of schizophrenia and bipolar disorder (acute manic or mixed episodes) in adolescent patients, received by Lilly on April 30, 2007. FDA and Lilly established a plan for specific analyses to be submitted; this plan was discussed in a meeting between FDA and Lilly on May 24, 2007. Lilly provided the requested data in a series of 4 rolling submissions, the last of which was received May 12, 2008.

Subject groups evaluated included all adult subjects, pediatric and adolescent subjects, and antipsychotic-naïve subjects. For each group the data were to be from placebo controlled trials, comparator controlled trials, and all data controlled and uncontrolled. The OFC databases were from studies in depression that included an OFC treatment group and at least an olanzapine treatment group or a fluoxetine treatment group. Excluded were studies without a source drug monotherapy arm, studies with duration under 7 days, studies with a relapse-prevention study design in which subjects had source drug exposure prior to randomization, and studies evaluating the source drug using routes of drug delivery other than oral drug delivery.

This memorandum summarizes the safety team review of these submissions. The primary review was conducted by Dr. Evelyn Mentari. In addition to the specific analyses that were agreed upon, the sponsor's proposed labeling includes data on metabolic changes from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies that Dr. Mentari has reviewed. In addition to summarizing the findings from Dr. Mentari's review, I will summarize in more detail the Sponsor's Risk Management Plan.

2. Summary of Findings from the Safety Review

2.1 Weight Gain

In adult placebo controlled trials (3-8 weeks, median exposure approximately 7 weeks) olanzapine-treated patients had a mean weight gain of 2.64 kg compared to a mean weight loss of 0.26 kg in placebo-treated subjects ($P < 0.001$). Mean differences in weight change between olanzapine-treated subjects and placebo treated subjects were similar across baseline BMI groups. Mean weight gain in olanzapine-treated subjects increased and mean weight loss in placebo-treated subjects was also successively greater at successive endpoints from 2-48 weeks. In addition, the proportion of olanzapine-treated subjects with clinically significant weight gain generally increased at successive time points from 6 weeks to 36 months. The incidence of treatment-emergent weight gain of at least 7% was 22.2% for olanzapine and 3.0% for placebo (median exposure time of about 8 weeks in both treatment groups).

In comparator-controlled trials, weight gain (mean change in weight, % of patients with potentially clinically significant weight gain, and proportion with upward shift in BMI category) was similar for olanzapine and clozapine-treated patients. Results were also similar for olanzapine compared to quetiapine-treated patients, although Dr. Mentari notes that the majority of patients in that database were overweight or obese at baseline, resulting in limited utility in generalizing beyond that population. Greater weight gain was observed for olanzapine compared to risperidone, olanzapine compared to ziprasidone, and for olanzapine compared to haloperidol.

In the OFC Adult controlled database, mean weight gain in OFC treated subjects was 4.29 kg at 8 weeks compared with a mean weight loss of 0.54 kg in placebo treated subjects ($p < 0.001$). There was no significant difference in weight gain between OFC-treated subjects and olanzapine treated subjects.

Adolescents treated with olanzapine also experienced clinically significant and statistically significant ($p < 0.001$) mean weight gain of 4.6 kg in 3 weeks median exposure time for olanzapine-treated adolescents compared to 0.34 kg in placebo treated patients. As compared to the data above for adults, the rate of increase was greater than that observed in approximately 7 weeks median exposure in adults. In long term studies (at least 24 weeks), the mean weight gain was 11.2 kg. With short-term exposure, 40.6% of adolescents gained (median exposure 3.5 weeks) at least 7% of baseline body weight vs 9.8% of placebo-treated adolescents (median exposure 14 weeks), and with long-term exposure the percentages who gained at least 7%, 15% or 25% of baseline body weight were 89%, 55%, and 29%, respectively. Since OFC has not been systematically studied in adolescents, data from the olanzapine monotherapy studies has been added to the SYMBYAX label to provide information on adolescents.

Dr. Mentari shows that the mean increases in weight were generally greater for the olanzapine-treated antipsychotic naïve population than for the olanzapine-treated adult

population (naïve and non-naïve) when patients were normal, overweight or obese at baseline.

2.2 Hyperlipidemia

In adult placebo-controlled trials, the Last Observation Carried Forward (LOCF) analyses of mean change from baseline to endpoint showed statistically significantly greater mean increases for olanzapine compared to placebo for fasting and non-fasting total cholesterol, fasting LDL cholesterol and fasting triglycerides (median olanzapine exposure times of 6-8 weeks). Mean increases in fasting lipid measurements were greater in patients without evidence of lipid dysregulation at baseline. Data are also shown to suggest that the mean nonfasting total cholesterol in patients who completed 12 months of therapy did not increase further after approximately 4-6 months. Proportions of patients with clinically significant changes in total cholesterol, LDL cholesterol, or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low were greater in long-term studies compared with short term studies.

The following data were extracted from Dr. Mentari's review.

	Mean Change to Endpoint in Adult Placebo-Controlled (Olanzapine had median exposure times of 6-8 weeks)		Mean Change to Endpoint in Patients with at least 48 weeks of exposure
	OLZ	PLA	OLZ
Fasting total cholesterol (mg/dL)	5.27	-6.07	5.57
Non-Fasting Total cholesterol (mg/dL)	6.75	-4.51	
Fasting LDL (mg/dL)	3.03	-4.26	2.5
Fasting HDL (mg/dL)	-0.4	-0.21	
Fasting Triglycerides (mg/dL)	20.77	-10.74	18.71

Statistically significantly higher proportions of olanzapine-treated patients than placebo-treated patients met criteria for treatment-emergent significant increases for nonfasting total cholesterol, fasting total cholesterol, fasting triglycerides, and fasting LDL cholesterol based on the criteria of the National Cholesterol Education Program (NCEP).

In comparator-controlled trials, patients treated with olanzapine had greater mean increases in total cholesterol than did patients treated with risperidone. Patients treated with clozapine and olanzapine had comparable changes with respect to total cholesterol. In the quetiapine database there were no statistically significant changes in fasting or nonfasting lipid parameters. Dr. Mentari points out that the median exposure time on olanzapine-treated subjects was significantly greater than the median exposure time for quetiapine-treated subjects, and that the study population in one of the studies had overweight or obese as an entry criteria. For the ziprasidone-controlled database, olanzapine-treated patients had significantly different decreased HDL cholesterol, statistically significantly smaller decrease of mean fasting LDL, and a statistically

significant difference in mean fasting triglycerides that increased in olanzapine-treated patients and decreased in ziprasidone-treated patients. Information was also provided from the CATIE study to suggest that patients who received olanzapine had an exposure-adjusted mean increase in total cholesterol and in triglycerides compared to ziprasidone, risperidone, quetiapine, and perphenazine. In that study the mean exposure-adjusted increase in triglycerides was 40.5 mg/dL and in total cholesterol was 9.4 mg/dL in patients who received olanzapine.

In the OFC database, information was available for only total cholesterol and triglycerides. Dr. Mentari reports that OFC-treated subjects had an increase from baseline in mean random total cholesterol of 12.1 mg/dL that was statistically significant compared to an increase of 4.8 mg/dL for olanzapine-treated subjects and a decrease of 5.5 mg/dL for placebo-treated subjects. From controlled clinical studies up of to 12 weeks, there were statistically significantly more patients with increases in nonfasting total cholesterol of ≥ 40 mg/dL in 35% of OFC patients compared to either olanzapine (22.7%) or placebo (9%) and statistically significantly more patients changing from borderline to high or normal to high in OFC vs either olanzapine or placebo. In long-term studies (at least 48 weeks) changes in nonfasting total cholesterol from normal to high occurred at least once in 12% of patients and changes from borderline to high occurred in 56% of patients. Dr. Mentari points out that the incidence of statistically significant changes in lipid parameters in patients treated with OFC and olanzapine in the OFC database was greater than the incidence in patients treated with olanzapine in the olanzapine databases, and hypothesizes that this is due to the different populations in the 2 databases, making them difficult to compare.

Placebo-controlled studies in adolescents had a short median duration of exposure at the time of lipid measurement of 2-3 weeks. In the analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescents, olanzapine-treated adolescents had statistically significant increases from baseline in mean fasting total cholesterol, LDL, and triglycerides of 12.9 mg/dL, 6.5 mg/dL, and 28.4 mg/dL, respectively, compared to increases from baseline in 1.3 mg/dL, 1.0 mg/dL for fasting total cholesterol and LDL, respectively and a decrease in triglycerides of 1.1 mg/dL for placebo treated adolescents. In long-term studies (at least 24 weeks), there were increases in mean fasting total cholesterol, LDL, and triglycerides of 5.5 mg/dL, 5.4 mg/dL, and 20.5 mg/dL, respectively and a mean decrease in fasting HDL of 4.5 mg/dL. In a median exposure of 3 weeks, 14.5% of olanzapine-treated adolescents had an increase in fasting total cholesterol of ≥ 40 mg/dL compared to 4.5% of placebo controlled subjects ($p=0.036$); 37% of olanzapine treated subjects had a of ≥ 50 mg/dL increase in fasting triglycerides compared with 15.2% of placebo-treated subjects ($p=0.02$). 17.5% of olanzapine subjects had a mean increase in fasting LDL of ≥ 30 mg/dL compared with 11.1% of placebo ($p=0.297$).

Antipsychotic naïve adults treated with olanzapine had mean increases in fasting and nonfasting cholesterol, fasting LDL, and fasting and non-fasting triglycerides all of which were statistically significantly different from decreases observed in placebo-treated antipsychotic naïve adults. There were no statistically significant differences between

olanzapine and placebo on HDL analyses. Changes in non-fasting triglycerides were larger in the antipsychotic naïve subset of patients compared to olanzapine-treated patients overall.

2.3 Hyperglycemia

In olanzapine placebo-controlled monotherapy studies with median duration of up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL vs 0.17 mg/dL). Mean increases in nonfasting glucose and HbA1c were statistically significantly greater for olanzapine-treated subjects than for placebo treated subjects. Differences between olanzapine-treated subjects and placebo-treated subjects in glucose-related laboratory analytes were greater in subjects with baseline potential glucose dysregulation, for example for nonfasting glucose in patients without potential for glucose dysregulation at baseline, the mean change was 11.76 mg/dL for olanzapine vs 4.62 mg/dL for placebo; in patients with potential for dysregulation at baseline, the mean change for olanzapine was 27.03 mg/dL vs. -8.73 mg/dL for placebo. Differences in mean change in fasting or nonfasting glucose occurred in the earliest measurements and Dr. Mentari reports that no clear time-related pattern of mean change in fasting or nonfasting glucose was noted in subsequent measurements in these studies. In an analysis of 8 placebo-controlled studies (median treatment exposure 4-5 weeks), 6.1% of olanzapine-treated subjects (N=855) had treatment-emergent glycosuria compared to 2.8% of placebo-treated subjects (N=599) (P=0.004). Dr. Mentari has summarized data from the CATIE study in which the median time to discontinuation for olanzapine was 9.2 months. In that database, the mean change in blood glucose without adjustment for exposure in olanzapine-treated patients was 15.0 mg/dL. In patients with at least 48 weeks of exposure, the mean change in fasting glucose was 4.2 mg/dL. (b) (4)

However, Dr. Mentari provides data from the Sponsor's submission that do not strongly support this statement; she has suggested removing this statement from the labeling and I agree.

In comparator-controlled trials, a range of differences was observed between olanzapine and other antipsychotics. In general changes in nonfasting glucose measures were higher for clozapine than for olanzapine. In the quetiapine-controlled database, in which approximately 80% of patients were overweight or obese, there were no statistically significant differences between quetiapine and olanzapine in glucose measures. In the risperidone controlled database, the only statistically significant difference was a higher proportion of olanzapine treated patients going from normal/borderline nonfasting glucose at baseline to high glucose post-baseline. Data in the ziprasidone-controlled database, collected under fasting conditions, suggests that patients treated with olanzapine experience greater adverse changes in glucose-related parameters than patients treated with ziprasidone. Similarly, in the haloperidol-controlled database, collected under nonfasting conditions, patients treated with olanzapine had greater adverse changes in glucose than patients treated with haloperidol. The sponsor states in the proposed labeling the increase in glucose levels with atypical antipsychotics fall on a

continuum and olanzapine appears to have a greater association than some other atypical antipsychotics. This statement is acceptable.

In the OFC database, with treatment duration of up to 12 weeks, OFC was associated with a statistically significantly greater mean change in random glucose compared to placebo (8.65 mg/dL vs -3.86 mg/dL). In an analysis of mean change by baseline values, patients with high fasting glucose at baseline had a mean increase in fasting glucose that was higher than the mean increase in patients with normal glucose at baseline. In an analysis of 6 controlled clinical studies (median exposure 6-8 weeks), 4.4% of SYMBYAX-treated subjects (N=477) had treatment-emergent glycosuria compared to 1.4% of placebo-treated subjects (N=284) (P=0.003).

In adolescent subjects in placebo controlled trials (trial duration 3-6 weeks), the mean change in fasting glucose was statistically significantly different for olanzapine (increase of 2.68 mg/dL) and placebo (decrease of 2.59 mg/dL). In patients with at least 24 weeks exposure, mean change in fasting glucose was 3.13 mg/dL. In patients taking olanzapine for up to 12 weeks or for at least 24 weeks, the percentage of patients shifting from borderline to high fasting glucose while taking olanzapine was generally greater than the percentage switching from normal glucose at baseline to high glucose, although the numbers of adolescent patients in these groups were very small, particularly those with baseline borderline glucose (n<15).

Olanzapine-treated antipsychotic naïve adults had mean increases in both fasting and nonfasting glucose, which were greater than increases observed in placebo-treated antipsychotic-naïve adults, but not statistically significant. In the placebo controlled databases, compared to olanzapine-treated adults as a whole, mean changes in fasting and nonfasting glucose were greater for olanzapine-treated antipsychotic-naïve adults, but proportions with categorical changes were generally lower.

2.4 Labeling

Dr. Mentari has suggested changes to the Sponsor's proposed labeling for the weight gain and hyperglycemia sections of WARNINGS and PRECAUTIONS based on her review of the Sponsor's submitted data. She does not recommend changes to the hyperlipidemia section. She has also recommended additions to the Highlights section of the prescribing information and to the laboratory tests section. I agree with Dr. Mentari's recommendations. Please refer to her review for her recommendations.

In addition to the changes proposed by Dr. Mentari for the WARNINGS and PRECAUTIONS section, the Sponsor has included a listing of several metabolic changes in Section 6.1 under "Other Events Observed...." . (b) (4)

According to the definition in the label, infrequent adverse events are those occurring in 1/100 to 1/1000 patients and frequent events are those occurring in at least 1/100 patients. In this case, hyperglycemia would be considered frequent. However, I do not believe that

inclusion of these events in section 6.1 contributes substantially to the information that is in the WARNINGS and PRECAUTIONS section regarding hyperglycemia.

2.5 Postmarketing Risk Management Plan

The Sponsor has submitted a Risk Management Plan that I will discuss only with respect to the metabolic changes that are the subject of Dr. Mentari's review.

- The Sponsor describes in the Risk Management Plan a retrospective cohort study to characterize the risks of diabetes and dyslipidemia among adolescents with schizophrenia or bipolar disorder and in the adolescent general population. This was a retrospective claims database analysis using eligibility and medical claims from a U.S health insurance plan. Outcomes were defined by 1) the presence of specific ICD-9 diagnosis codes in at least 2 physician visits or 2) at least one dispensing of specific medications. The Study has been completed and was submitted with the 2/5/08 submission. The Sponsor concludes that adolescents with bipolar disorder or schizophrenia had an increased risk of developing diabetes and dyslipidemia compared to adolescents without these disorders in the general population and that patients treated with antipsychotics were at higher risk of developing diabetes and dyslipidemia than those not treated with antipsychotics. The study investigated antipsychotics as a class rather than individual drugs. This study report has not been reviewed by the safety team.
- The sponsor states in the Action Plan (Section 2.4.2) that a long-term (52-week) open label safety study of oral olanzapine in the treatment of adolescents with bipolar disorder or schizophrenia will be conducted with measurements to include assessment of body weight, fasting glucose, and fasting lipids. Only a protocol outline for study F1D-MC-HGMX has been provided. The Sponsor should submit a full protocol for review.
- The sponsor states that the risk minimization plan (Section 4 of the Risk Management Plan 1.1) includes labeling and the product website that is accessible to the general public and provides advice on weight management and nutrition.
- The Risk Minimization Plan in NDA 20-592 refers to the Lilly Wellness Program that has been in place for 5 years that the Sponsor states is a successful program of healthcare professional and patient education. (b) (4)

- [REDACTED]
- Outcomes of this program in terms of random blood glucose or dyslipidemia are not provided.
- I believe that the Sponsor's currently proposed approach to risk mitigation is not adequate. Dr. Mentari recommends that olanzapine and OFC will require Medication Guides regarding the metabolic issues. I agree. The Sponsor should be requested to develop Medication Guides and to outline in more detail appropriate educational plans for healthcare professionals that would highlight to a larger extent these risks to healthcare professionals.

3. Conclusions

Dr. Mentari's review supports labeling that she has proposed for weight gain, hyperlipidemia, and hyperglycemia. In addition to the labeling changes, we recommend

Safety Team Leader Memo
NDA 20-592, 21-520

that a proposal for risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide, be requested from the Sponsor. Future studies that include evaluation of metabolic changes might benefit from dose-response consideration.

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/s/

Sally Yasuda
7/17/2008 03:19:57 PM
BIOPHARMACEUTICS

DRUGS: ZYPREXA, PROZAC**PRIMARY REVIEWER:** Andre Jackson**ZYPREXA**

(b) (4)
(b) (4)

(b) (4)
(b) (4)

NDA 20-592/SE8-039
NDA 21-086/SE8-021

Submission date : 2-4-08
Submission date : 2-4-08

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

Submission date : 2-5-08
Submission date : 2-5-08

(b) (4)
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(b) (4)

SYMBYAX (Zyprexa/Prozac)

NDA 21-520/SE1-012
(b) (4)

Submission date : 2-1-08

(b) (4)

PROZAC

NDA 18-936/SE8-077
NDA 18-936/SLR-075

Submission date : 2-4-08
Submission date : 3-21-07

Applicant : Eli Lilly

FORMULATIONS: Zyprexa (Tablet, Intramuscular, ODT), Fluoxetine (Capsules),
Zyprexa/Prozac) Capsules

Review of a CBE Labeling Supplement**Background:**

The firm has submitted a detailed list of outstanding Label revisions for Zyprexa NDA 20-592, Zyprexa Zydis NDA 21086 and Zyprexa Intramuscular NDA 21-253 and Prozac NDA 18-936, Symbyax NDA 21520.

Only those supplement items with relevant concerns for OCP will be listed.

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A. Supplements for Zyprexa tablets NDA 20-592

- o (b) (4)
- o S-039 (PAS for use of Zyprexa and Prozac in combination to treat treatment-resistant depression)
- o S-040 (PAS: adolescent use in bipolar disorder [acute manic or mixed episodes])
- o S-041 (PAS: adolescent use in schizophrenia)

FIRM'S PROPOSED LABEL FOR ZYPREXA

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FDA LABEL CHANGES FOR ZYPREXA

2.3 Bipolar Disorder (Depressive Episodes)

Dosing in Special Populations — The starting dose of oral olanzapine 2.5-5 mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine. (b) (4) Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. (b) (4) When indicated, dose escalation should be performed with caution in these patients. (b) (4) and fluoxetine in combination have not been systematically studied in patients over 65 years of age or in patients <18 years of age [see *Warnings and Precautions* (b) (4), *Drug Interactions* (7), and *Clinical Pharmacology* (12.3)].

(b) (4) Treatment Resistant Depression

Dosing in Special Populations — The starting dose of oral olanzapine 2.5-5 mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine. (b) (4) Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. (b) (4) When indicated, dose escalation should be performed with caution in these patients. (b) (4) and fluoxetine in combination have not been systematically studied in patients over 65 years of age or in patients <18 years of age [see *Warnings and Precautions* (b) (4), *Drug Interactions* (7), and *Clinical Pharmacology* (12.3)].

B. Supplements for Zyprexa Zydis NDA 21-086

- o S- (b) (4)
- o S-021 (PAS for use of Zyprexa and Prozac in combination to treat treatment-resistant depression)
- o S- (b) (4)

Wording only: No issues for OCP

C. Supplements for Zyprexa IntraMuscular (21-253)

o S- (b) (4)

FDA RESPONSE FOR ZYPREXA INTRAMUSCULAR

Wording only: No issues for OCP

D. Supplements For NDA 18-936 S075 PROZAC

NDA 18-936/S075, S077, and (b) (4)

- 26 June 2006: Provided revised label language consistent with that provided in Symbyax NDA 21-520/S010 (submitted 22 June 2006 to add a lower starting dose); revised language in the DESCRIPTION, DOSAGE AND ADMINISTRATION, Special Populations and HOW SUPPLIED sections.

FIRM'S PROPOSED LABEL FOR PROZAC

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FDA LABEL CHANGES FOR PROZAC

2.3 Bipolar Disorder (Depressive Episodes)

Dosing in Special Populations — The starting dose of oral olanzapine (b) (4) mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine (b) (4). Dosing (b) (4) may be necessary in patients who exhibit a combination of factors that may slow metabolism (b) (4). When indicated, dose escalation should be performed with caution in these patients. Olanzapine and fluoxetine in combination have not been systematically studied in patients over 65 years of age or in patients (b) (4) of age [see Warnings and Precautions (5.10), Drug Interactions (b) (4)].

(b) (4)

Treatment Resistant Depression

Dosing in Special Populations — The starting dose of oral olanzapine (b) (4) mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine (b) (4). Dosing (b) (4) may be necessary in patients who exhibit a combination of factors that may slow metabolism (b) (4). When indicated, dose escalation should be performed with caution in these patients. (b) (4) in combination have not been systematically studied in patients over 65 years of age or in patients (b) (4) of age [see Warnings and Precautions (5.10), Drug Interactions (b) (4)].

7. DRUG INTERACTIONS

(b) (4)

7.12 Tryptophan

Five patients receiving PROZAC in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress. [The concomitant use with tryptophan is not recommended.-This statement was added by the sponsor and should be noted by the Medical Officer since it was not in the original label]

7.13 Monoamine oxidase inhibitors

[There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, PROZAC should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks [perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses [see Clinical Pharmacology (12.3)] should be allowed after stopping PROZAC before starting an MAOI.-This statement has been moved from Contraindications and placed in this position by the sponsor and should be noted by the Medical Officer]

(b) (4)

(b) (4)

FIRM'S PROPOSED LABEL FOR SYMBYAX

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(b) (4) elderly nonsmoking females. SYMBYAX dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of the olanzapine component [see *Dosage and Administration* (2.3)].

FDA LABEL CHANGES FOR SYMBYAX

2.3 (b) (4) Populations

The starting dose of SYMBYAX 3 mg/25 (b) (4) 6 mg/25 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of SYMBYAX (female gender, geriatric age, nonsmoking status) or those patients who may be pharmacodynamically sensitive to olanzapine. Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. (b) (4) When indicated, dose escalation should be performed with caution in these patients. SYMBYAX has not been systematically studied in patients (b) (4) 65 years of age or in patients <18 years of age [see *Warnings and Precautions* (b) (4), *Use in Specific Populations* (b) (4) and *Clinical Pharmacology* (b) (4)].

5.23 Long Half-Life of Fluoxetine

Because of the long elimination half-lives of fluoxetine and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (b) (4)

(b) (4) This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine. (b) (4)

7 DRUG INTERACTIONS

(b) (4)

7.13 Monoamine oxidase inhibitors

[SYMBYAX should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. There have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with an MAOI, and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks, perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses (b) (4) should be allowed after stopping SYMBYAX before starting an MAOI. [See *Contraindications* (4) (b) (4)]

7.18 Thioridazine

[Thioridazine should not be administered with SYMBYAX or administered within a minimum of 5 weeks after discontinuation of SYMBYAX.

In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs that inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine [see *Contraindications* (4)].

Thioridazine administration produces a dose-related prolongation of the QT_c interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism [see *Contraindications* (4)] (b) (4)

12.3 Pharmacokinetics

Absorption and Bioavailability

Distribution

SIGNATURES

Andre Jackson _____
Reviewer, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialized by Raman Baweja , Ph.D. _____
Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

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/s/

Andre Jackson
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BIOPHARMACEUTICS

Raman Baweja
7/15/2008 03:25:37 PM
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-520/S-012

OTHER REVIEW(S)

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

DATE: 19 March 2009

FROM: Mitchell V. Mathis, M.D.
Deputy Director
Division of Psychiatry Products, HFD-130

TO: NDA 21-520/S-012 Symbyax (fluoxetine/olanzapine) Capsules, NDA20-592/S-039 Zyprexa (olanzapine) tablets, NDA 21-086/S-021 Zyprexa (olanzapine) Zydys, 18-936/S-077 Prozac (fluoxetine) tablets

SUBJECT: Medication Guides for Symbyax, Zyprexa, and Prozac

The Division is in the process of evaluating Symbyax (olanzapine and fluoxetine in combination) for the treatment of Treatment Resistant Depression (TRD). Symbyax is a marketed product approved for the acute treatment of depressive episodes of Bipolar I Disorder. At the same time, Zyprexa (olanzapine) and Prozac (fluoxetine) are being evaluated to be used in combination to treat TRD and the acute treatment of depressive episodes of Bipolar I Disorder. The Division determined that modifications to the existing Medication Guide would be necessary for Symbyax secondary to the metabolic changes seen with olanzapine (hyperglycemia, hyperlipidemia, and weight gain) so that patients will be able, in light of these metabolic changes, to make an informed decision about the risks and benefits of the drug.

Having made a decision to include this information in a Medication Guide, and given that Zyprexa and Prozac also have supplements pending to be used together to treat TRD and the acute episodes of Bipolar I Disorder, it became clear that the Division would have to include the information from the updated Symbyax Medication Guide in the Medication Guides for both Zyprexa and Prozac.

For Zyprexa, the Medication Guide is new and was derived from those portions of the Symbyax Medication Guide pertinent to olanzapine. For Prozac, the already existing class Medication Guide for suicidality had to be modified to include the other particular serious and significant concerns for fluoxetine.

In sum, the Division decided to make changes to the Zyprexa and Prozac Medications Guides to ensure that when a patient is treated with both drugs for TRD or depressive episodes of Bipolar I Disorder, they receive the same information from the combination of the two individual product Medication Guides that is presented in the single combination product Medication Guide for Symbyax.

We requested draft Medication Guides for all three products from the sponsor in our August 1, 2008 complete response letter. The sponsor submitted a response to the Agency letter on September 19, 2008 and the review division consulted the Division of Risk Management (DRISK) in the Office of

Surveillance and Epidemiology (OSE) to assist us with editing these prior to negotiation with the sponsor. Although DRISK was consulted early in the process (September 25, 2008), they were unable to provide draft edits to our Medication Guides until much later (February 20, 2009). We had two meetings (February 19, 2009 and March 10, 2009) with DRISK to understand their draft edits to the Medication Guides.

The advice we received from DRISK was useful in helping us to formulate our final documents, and we incorporated many of their suggested changes. However, we did not agree with some of their proposed changes because we felt they significantly detracted from the overall message we intended to send to the patients receiving these products. Specifically, the recommendations from DRISK included adding information from every bullet within the Warnings and Precautions section of labeling in an effort to provide a comprehensive picture of the risk of these drugs. While this seemed reasonable on face, it practically meant that the Medication Guides would be nearly eight pages long, which in our opinion made it a much less likely document to be distributed by pharmacists and read by the patients. In addition, 21CFR 208.20 states that Medication Guides should be written to convey, “the particular serious and significant public health concern that has created the need for a Medication Guide...” and we did not believe that including every warning and precaution, particularly if there was no direct way to communicate risk to the patient, would be consistent with our interpretation of this regulation.

Therefore, we included only the particular serious and significant public health concerns in our versions of the Medication Guides sent to the sponsor for negotiation, and we will include these Medication Guides in any future approval letters for these products.

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/s/

Mitchell Mathis
3/19/2009 12:20:43 PM
MEDICAL OFFICER

SEALD LABELING REVIEW

APPLICATION NUMBER	21-520
APPLICANT	Eli Lilly and Company
DRUG NAME	SYMBYAX
SUBMISSION DATE	09/19/08
SEALD REVIEW DATE	03/06/09
SEALD REVIEWER(S)	Cicely Vaughn
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

31 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

Cicely Vaughn

3/9/2009 01:05:47 PM

CSO

SEALD comments sent to review division on 3-06-09

Laurie Burke

3/11/2009 12:35:19 PM

INTERDISCIPLINARY

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: January 18, 2007

TO: Renmeet Grewal, Regulatory Project Manager
Jing Zhang, M. D., Medical Officer
Division of Psychiatry Products, HFD-130

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-520/SE1-012

APPLICANT: Eli Lilly and Company

DRUG: Symbyax (olanzapine and fluoxetine in combination) Capsules

THERAPEUTIC CLASSIFICATION: Priority Review (6 months)

INDICATION: Treatment-Resistant Depression.

CONSULTATION REQUEST DATE: November 14, 2006

DIVISION ACTION GOAL DATE: February 1, 2007

PDUFA DATE: March 29, 2007

I. BACKGROUND:

The review division requested inspection of protocol H6P-MC-HDAO-2: "The Study of Olanzapine plus Fluoxetine in Combination for Treatment-Resistant Depression without Psychotic Features" and protocol F1D-MC-HGIE: "Olanzapine Plus Fluoxetine Combination Therapy in Treatment-Resistant Depression: A Dose Ranging Study". The sponsor submitted results from these two protocols in support of NDA 21-520/SE1-012. The inspections targeted two clinical investigators who enrolled a relatively large number of subjects.

The following two clinical investigators were selected for data audit in support of this application:

Site# 610 (Richard Bergeron, M.D.- Quebec, Canada)

Site# 004 (Louise Beckett, M.D. – Oklahoma City, OK)

II. RESULTS (by protocol/site):

Name of CI and site #, if known	Country	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Richard Bergeron, M.D. Site #610	Canada	Hull, Quebec	HDAO-2	1/15/07	pending	NAI*
Louise Beckett, M.D Site# 004	USA	Oklahoma City, OK	HGIE	1/9/07	pending	VAI*

* based on e-mail summary information or telephone call from the field investigators.

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.

Protocol H6P-MC-HDAO

1. Richard Bergeron, M.D.

Observations noted below are based on a telephone message from the FDA field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR.

At this site a total of 956 subjects were screened, 770 subjects were reported as screen failures, 186 subjects signed informed consent, 14 subjects were discontinued/withdrawn, 82 subjects were randomized to the study, 63 subjects continued on the extension phase of the study, with 49 subjects completing the extension phase of the study. All 186 subjects were verified to have signed informed consent prior to entry into the study. The medical records for 10 subjects were reviewed in depth and compared to case report forms and data listings for primary efficacy end points and adverse events.

The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and no significant problems were found that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

Protocol F1D-MC-HGIE

2. Louise Beckett, M.D.

Observations noted below are based on an e-mail summary statement from the FDA field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR.

At this site a total of 40 subjects were screened, 20 subjects were screened failures, 20 subjects were randomized and completed the study. The medical records for eight (8) subjects were reviewed. Informed consent for 40 subjects was verified and minor regulatory violations were

found. These include failure to re-consent 6 subjects with the revised IRB approved informed consent, and at least two subjects (1176 & 1184) did not date, and one subject (1190) did not sign the consent form. One subject (1167) received two prohibited medications (Valium & Restoril) while on the study. There was inadequate and inaccurate record keeping in that missing doses were not recorded, and no documentation to show that the dose of venlafaxine was increased per Doctor's orders in at least 5 out of 8 subjects records reviewed. Drug accountability and dispensing records for at least 6 subjects were incomplete and therefore, the FDA investigator could not verify the amount of drug dispensed versus the amount returned by subjects for certain visits. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of Dr. Beckett revealed problems with the informed consent procedures, a protocol deviation, inadequate records, and inadequate drug accountability record keeping. However, in general these deviations do not adversely impact data acceptability. The data submitted are acceptable in support of the pending application.

The inspection of Dr. Bergeron revealed no significant problems that would adversely impact data acceptability. Therefore, the data from this site are acceptable in support of the pending application.

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

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

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

/s/

Antoine El-Hage
1/29/2007 08:30:54 AM
PHARMACOLOGIST

Constance Lewin
1/29/2007 10:28:28 AM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA #	18-936	Supplement #	077	Efficacy Supplement Type	SE-	1
	21-086		021			
	21-520		012			
	20-592		039			

Proprietary Name: Symbyax, Zyprexa, Zyprexa Zydis, Prozac
Established Name:
Strengths:

Applicant: Eli Lilly
Agent for Applicant (if applicable):

Date of Application: 9-28-06
Date of Receipt: 9-29-06
Date clock started after UN: 9-29-06
Date of Filing Meeting: 11-7-06
Filing Date: 11-28-06
Action Goal Date (optional):

User Fee Goal Date: 3-29-07

Indication(s) requested: Treatment Resistant Depression

Type of Original NDA:	(b)(1)	<input type="checkbox"/>	(b)(2)	<input type="checkbox"/>
AND (if applicable)				
Type of Supplement:	(b)(1)	X	(b)(2)	<input type="checkbox"/>

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 or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification:	S	<input type="checkbox"/>	P	X
Resubmission after withdrawal?		<input type="checkbox"/>	Resubmission after refuse to file?	<input type="checkbox"/>
Chemical Classification: (1,2,3 etc.)	1			
Other (orphan, OTC, etc.)				

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

User Fee Status: Paid X 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 by contacting the User Fee staff in the Office of Regulatory Policy. 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 any approved (b)(1) or (b)(2) application? YES ☒ X NO ☐
If yes, explain: It is with Eli Lilly

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
If no, explain:

- 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:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐

This application is: All electronic ☒ Combined paper + eNDA ☐

This application is in: NDA format ☒ CTD format ☐

Combined NDA and CTD formats ☐

Does the eNDA, follow the guidance?

(<http://www.fda.gov/cder/guidance/2353fnl.pdf>)

YES ☒ NO ☐

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES ☐

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO ☐
- Exclusivity requested? YES, _____ Years NO X
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X 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 . . .”

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES ☐ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO ☐
(Forms 3454 and/or 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) YES ☐ NO X
- PDUFA and Action Goal dates correct in tracking system? YES X NO ☐
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.
- List referenced IND numbers: 20-592, 21-086, (b) (4)
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO ☐
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☐
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) January 11, 2006 NO ☐
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO ☒
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES ☒ NO ☐

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: a waiver was submitted for the highlights page
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO ☒
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO ☒
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A ☒ YES ☐ NO ☐
- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐

- | | | | | |
|---|-----|--------------------------|----|--------------------------|
| If EA submitted, consulted to EA officer, OPS? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |
| • Establishment Evaluation Request (EER) submitted to DMPQ? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |
| • If a parenteral product, consulted to Microbiology Team? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/7/06

NDA #: 21-520/012, 20-592/039, 18-936/077,21-086/021

DRUG NAMES: Symbyax, Zyprexa, Zyprexa Zydis, Prozac

APPLICANT: Eli Lilly

BACKGROUND: It is already approved for a different indication
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Tom Laughren, Mitch Mathis, Ni Khin, Jing Zhang, Barry Rosloff, Linda Fossom, Peiling Yang, George Kordzakhia

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Medical:
Secondary Medical:
Statistical:
Pharmacology:
Statistical Pharmacology:
Chemistry:
Environmental Assessment (if needed):
Biopharmaceutical:
Microbiology, sterility:
Microbiology, clinical (for antimicrobial products only):
DSI:
OPS:
Regulatory Project Management:
Other Consults:

Reviewer

Jing Zhang
Greg Dubitsky
Peiling Yang, George Kordzakhia
Barry Rosloff, Linda Fossom

Janice Brown, Teshara Bouie

Connie Lewin, Tony El Hage

Renmeet Grewal, Bill Bender

Per reviewers, are all parts in English or English translation?	YES	X	NO	<input type="checkbox"/>
If no, explain:				

CLINICAL

FILE	REFUSE TO FILE	<input type="checkbox"/>
We will only file 21-520/012		

- | | | | | |
|--------------------------------------|--------------------|-------|----|--------------------------|
| • Clinical site audit(s) needed? | YES | X | NO | <input type="checkbox"/> |
| If no, explain: | | | | |
| • Advisory Committee Meeting needed? | YES, date if known | _____ | NO | x |

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☐ X ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☐ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed?
YES ☐ NO ☐

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☐ NO ☐
- If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

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

X The application is unsuitable for filing. Explain why: we will only file NDA 21-520/012

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

☐ No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
- ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
- ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Renmeet Grewal, Pharm.D.
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

If “No,” skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an “old” antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☐

If “Yes,” skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☐

If “Yes “contact your ODE’s Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES ☐ NO ☐

(Pharmaceutical equivalents are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If “No,” to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES ☐ NO ☐

If “Yes,” (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If “No,” to (c) list the pharmaceutical equivalent and contact your ODE’s Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

If “Yes,” to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))?
If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)?
(This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐
13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- ☐ Not applicable (e.g., solely based on published literature. See question # 7)
- ☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- ☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- ☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- ☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.
- ☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☐

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

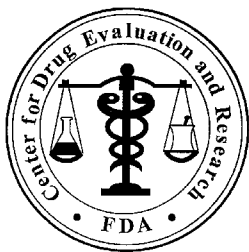
/s/

Renmeet Grewal
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CSO

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-520/S-012

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 12, 2009

To: Thomas Laughren, M.D., Division Director
Division of Psychiatry Products (DPP)

Through: Claudia Karwoski, PharmD, Director (Acting)
Division of Risk Management
Jodi Duckhorn, M.A., Team Leader
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

Subject: DRISK Review Proposed Risk Evaluation and Mitigation
Strategy (REMS), Review #2

Drug Name(s): Symbyax

Application Type/Number: NDA 21-520

Submission Number: S-012

Applicant/sponsor: Eli Lilly & Company

OSE RCM #: 2008-1547

1 INTRODUCTION

This review is written in response to a request from the Division of Psychiatry Products (DPP) for the Division of Risk Management to review the sponsor's proposed Amended Risk Evaluation and Mitigation Strategy (REMS), which includes the draft Medication Guide (MG) and Timetable for Submission of Assessments of the effectiveness of the REMS.

FDA has determined that Symbyax (olanzapine and fluoxetine hydrochloride) 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 Symbyax (olanzapine and fluoxetine hydrochloride). FDA has determined that Symbyax (olanzapine and fluoxetine hydrochloride) meets two of the three criteria for a Medication Guide as set forth in 21 CFR 208.1: Symbyax (olanzapine and fluoxetine hydrochloride) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use or continue to use; Symbyax (olanzapine and fluoxetine hydrochloride) is a product for which patient labeling could help prevent serious adverse events.

2 MATERIAL REVIEWED

- Proposed Symbyax (olanzapine and fluoxetine hydrochloride) Risk Evaluation and Mitigation Strategy (REMS), submitted on December 1, 2008, and the Amendment to the Proposed REMS, submitted on February 27, 2009.

3 BACKGROUND

DRISK previously reviewed the sponsor's proposed Medication Guide and Risk Evaluation and Mitigation Strategy (REMS) for Symbyax (olanzapine and fluoxetine hydrochloride) on February 28, 2009. Prior to completion of the consult, DRISK provided preliminary email comments to DPP in advance in order to facilitate negotiations with the sponsor. These comments were also conveyed in the memo for the review of the MG and REMS.

The sponsor submitted an original proposed REMS as part of a Complete Response to the August 1, 2008 Approvable Letter for multiple outstanding supplements for Symbyax (olanzapine and fluoxetine hydrochloride) on September 19, 2008. Based on feedback from OSE regarding the Proposed REMS, and questions from the sponsor about the REMS and MG, the sponsor submitted a REMS Amendment, on February 27, 2009 using the provided REMS template.

The review division has not requested for further review of the MG at this time; therefore, this review addresses only the sponsor's amended REMS proposal.

4 DISCUSSION

4.1 PROPOSED REMS

- a. Goal

The sponsor has proposed the following revised REMS goal, as requested:

The goal of the REMS is to inform patients of the serious risks associated with the use of Zyprexa (olanzapine), including the risks of suicidality, hyperglycemia, hyperlipidemia, and weight gain.

b. REMS elements

- Medication Guide: The proposed REMS states that the Medication Guide will be made available for distribution.
- The Timetable for Submission of Assessments is as follows:
 - 1st assessment: September 2010, 18 months after approval
 - 2nd assessment: March 2012, 3 years after approval
 - 3rd assessment: March 2016, 7 years from approval unless it is determined that serious risks have been adequately identified and assessed and are being adequately managed.

5 CONCLUSIONS AND RECOMMENDATIONS

DRISK believes that the sponsor's amended proposed REMS for Symbyax (olanzapine and fluoxetine hydrochloride) generally meets the statutory requirements outlined in 21 CFR 208 and in accordance with 505-1. The sponsor revised the REMS goal as requested, but also included the risk of suicidality, which is associated with Symbyax (olanzapine and fluoxetine hydrochloride). Given that Symbyax currently carries the Antidepressant Drug Product class approved MG for the issue of suicidality, the sponsor's proposed revised goal, is acceptable. Below we have additional recommendations on the proposed REMS. If the revisions are acceptable to DPP, DRISK does not need to review this material again prior to approval.

Recommendations to be conveyed to Sponsor

1. See the appended Symbyax (olanzapine and fluoxetine hydrochloride) REMS proposal (Appendix A) for minor additional track changes corresponding to comments in this review.
2. We remind the sponsor of their requirement to comply with 21 CFR 208.24
 - A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
 - “Dispense the enclosed Medication Guide to each patient.” or
 - “Dispense the accompanying Medication Guide to each patient.”
 - Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose. For example:

- A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
 - A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.
3. The timetable for submission of assessments will be at minimum at 18 months, 3 years and within the 7th year following the approval of the REMS.
- The REMS assessments should include information needed to assess the effectiveness of the REMS including:
 - Patients' understanding of the serious risks of Symbyax (olanzapine and fluoxetine hydrochloride)
 - 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
 - If the sponsor feels the REMS assessment at 7 years of the patient's understanding of the Medication Guide is not needed because they have determined that serious risks have been adequately identified and assessed, the sponsor should submit a modification to the REMS following the REMS 3 year assessment. The agency will then determine if additional assessments of the patient's understanding of the Medication Guide are necessary.
4. We recommend the Sponsor submit a complete description of methodology and the instruments used to measure patient's understanding of the risks and safe use of Symbyax to FDA 60 days prior to conducting the survey. The submission should include:
- All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of Symbyax (olanzapine and fluoxetine hydrochloride). 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.

Recommendation for DPP

5. We recommend including in the approval letter a reminder of the sponsor's responsibility to provide the information needed (methodology) to assess the effectiveness of the REMS as stated above, including an evaluation of:
 - Patients' understanding of the serious risks of Symbyax (olanzapine and fluoxetine hydrochloride)
 - 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

Please let us know if you have any questions.

2 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

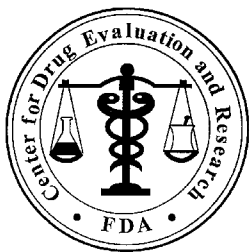
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sharon Mills
3/12/2009 02:46:50 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
3/12/2009 02:48:08 PM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
3/12/2009 03:32:49 PM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 27, 2009

To: Thomas Laughren, M.D., Division Director
Division of Psychiatry Products (DPP)

Through: Jodi Duckhorn, M.A., Team Leader
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

Subject: DRISK Review of Patient Labeling (Medication Guide) and
Proposed Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): Symbyax (olanzapine and fluoxetine hydrochloride) Capsule

Application Type/Number: NDA 21-520

Submission Number: S-012

Applicant/sponsor: Eli Lilly & Company

OSE RCM #: 2008-1521

1 INTRODUCTION

This review is written in response to a request from the Division of Psychiatry Products (DPP) for the Division of Risk Management's Patient Labeling and Education Team to review the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS), which includes the draft Medication Guide (MG) and Timetable for Submission of Assessments of the effectiveness of the REMS.

FDA has determined that Symbyax (olanzapine and fluoxetine hydrochloride) capsules pose 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 Symbyax (olanzapine and fluoxetine hydrochloride) capsules. FDA has determined that Symbyax (olanzapine and fluoxetine hydrochloride) capsules meets two of the three criteria for a Medication Guide as set forth in 21 CFR 208.1: Symbyax (olanzapine and fluoxetine hydrochloride) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use or continue to use; Symbyax (olanzapine and fluoxetine hydrochloride) is a product for which patient labeling could help prevent serious adverse events.

2 MATERIAL REVIEWED

- Draft Symbyax (olanzapine and fluoxetine hydrochloride) capsule Prescribing Information (PI) submitted September 19, 2008 and revised by the Review Division on February 18, 2009.
- Draft Symbyax (olanzapine and fluoxetine hydrochloride) Medication Guide (MG) submitted on September 19, 2008.
- Proposed Symbyax (olanzapine and fluoxetine hydrochloride) Risk Evaluation and Mitigation Strategy (REMS), submitted on September 19, 2008.

3 BACKGROUND

Eli Lilly & Company submitted New Drug Applications, NDA 21-520 for Symbyax (olanzapine and fluoxetine hydrochloride) capsules November 4, 2002. Symbyax is indicated as follows:

Depressive Episodes Associated with Bipolar I Disorder:

Symbyax is indicated for the acute treatment of depressive episodes associated with Bipolar I Disorder in adults.

Treatment Resistant Depression:

Symbyax is indicated for the acute treatment of treatment resistant depression (Major Depressive Disorder in adults who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode.)

Since Symbyax was approved in 2003, DPP has become aware of new safety information from analysis of data related to an increased risk of hyperglycemia, hyperlipidemia, and weight gain associated with olanzapine treatment. This information was not available when Symbyax was granted approval.

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 provide FDA with new authorities to require sponsors of approved drugs to develop and comply with REMS section 505-1 of the FDCA if FDA finds that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. These provisions took effect on March 25, 2008.

DPP informed the sponsor in an Approvable Letter for multiple outstanding supplements, dated August 1, 2008, that a REMS is necessary for Symbyax (olanzapine and fluoxetine). The only elements of the REMS will be a Medication Guide and a timetable of submission of assessments of the REMS.

The sponsor submitted a proposed REMS as part of a Complete Response to the August 1, 2008 Approvable Letter for multiple outstanding supplements for Symbyax (olanzapine and fluoxetine) on September 19, 2008.

4 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the sponsor has a Flesch Kinkaid grade level of 9.3, and a Flesch Reading Ease score of 52.1%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level.) Our revised MG has a Flesch Kinkaid grade level of 8.2 and a Flesch Reading Ease score of 60.3%.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- rearranged information as necessary to be consistent with the MG format as specified in 21 CFR 208.20
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are **bolded, underlined and italicized**.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

5 CONCLUSIONS AND RECOMMENDATIONS

We have the following comments on the proposed REMS:

1. 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 sponsor's proposed REMS does not follow the recommended format.
2. We recommend that the review division provide the sponsor with the attached REMS template (Appendix A) and request that the sponsor revise and submit their proposed REMS according to the REMS template.
3. We recommend the REMS goal be revised as follows:

 (b) (4)

4. To date, the sponsor has not submitted revised carton and containers. The sponsor must comply with 21 CFR 208.24(d), which requires a statement alerting pharmacists to dispense the MG with the product is on the carton and container on all strengths and formulations. DMEPA will review the carton and containers under separate cover, once they are submitted.
5. 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 *Symbyax (olanzapine and fluoxetine hydrochloride)* 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 *Symbyax (olanzapine and fluoxetine hydrochloride)*. 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.

6. We recommend including in the approval letter a reminder of the sponsor's responsibility to provide the information needed (methodology) to assess the effectiveness of the REMS as stated above, including an evaluation of:
 - Patients' understanding of the serious risks of
 - A report *Symbyax (olanzapine and fluoxetine hydrochloride)* 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

We have the following comments on the sponsor's Questions Regarding REMS:

The following comments were sent to DPP on February 20, 2009 to share with the sponsor prior to completion of a full review of the MG and REMS for Symbyax:

7. The sponsor included within their Complete Response Document a *Discussion of Approvable Letters Received 1 August 2008* for Zyprexa, (olanzapine), Symbyax (olanzapine/fluoxetine combination), and Prozac (fluoxetine hydrochloride), beginning on page 19. Section 3 poses questions regarding the REMS on pages 22 and 23 of the Complete Response Document.

3.1 Clarify the Scope of the Medication Guides for Zyprexa and Symbyax

Question 1: Does the Division agree with the scope of the draft Medication Guides provided for Zyprexa and Symbyax?

DRISK Response: The MG for Symbyax is under review. We will provide subsequent comments about the scope of the MG in the future. The Zyprexa MG review is being addressed by DRISK under separate cover.

Question 2: Does the Division agree that the Medication Guide for Zyprexa only applies to the tablet and Zydis formulations?

DRISK Response: We defer to the review division to respond to this question.

3.2 Clarify the Wording of the Suicidality Medication Guides for Symbyax and Prozac

Question 3: Does the Division agree that we should use the 2007 template for the suicidality Medication Guide for Symbyax and Prozac?

DRISK Response: We defer to the review division to address this with the sponsor.

3.3 Clarify Expectations for Assessments and Timetable for Evaluation of the REMS for Zyprexa and Symbyax.

Question 4: Does the Division agree with the REMS proposal for Zyprexa and Symbyax?

DRISK Response is as follows:

- We are aware that the Lilly was not provided with a REMS template prior to submission of the REMS as part of your Complete Response. As a result, the proposed REMS does not follow the recommended format.
- We recommend that the Lilly revise and resubmit the proposed REMS to follow the template that the review division provides.
- We recommend the REMS goal be revised as follows:

(b) (4)

- 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)* 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)*. 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.

We have the following comments on the proposed Medication Guide:

8. We have placed the antidepressant class information about suicidal thoughts and actions first in the MG, followed by the other important information. This MG includes comprehensive information about both active ingredients in Symbyax. In an effort to set off the suicidality text from the other serious side effects, we put this information in a box.
9. We recommend that the review division re-visit the placement of Neuroleptic Malignant Syndrome (NMS) in both the Symbyax and Zyprexa PI before the metabolic issues. This prominent placement gives the appearance that the concern about NMS is more

important than the metabolic issues. Given that the metabolic issues have not been elevated to the level of a Boxed or Bolded Warning, but have been determined to require distribution of a MG, healthcare providers may be confused by the fact that this is more prominently placed.

10. In the section “What is the most important information I should know about Symbyax?”

- We moved “Increase in weight” so that it follows “high cholesterol and triglyceride levels in the blood” to be consistent with the ordering of metabolic events in PI section 5 *Warnings and Precautions*.
- Under “High blood sugar (hyperglycemia), we added the following language:
If you have diabetes, follow your doctor’s instructions about how often to check your blood sugar while taking Symbyax.
- In the bullet “High cholesterol and triglyceride levels (fat in the blood)” we revised the language that we recommended in our review of the Zyprexa MG, to point out that levels may be increased, especially triglyceride levels to address the possibility of very high levels. DPP should consider revising the language in this bullet in the Zyprexa MG as well.

11. In the section “What is Symbyax?”

- Information about the onset of feeling better and instruction to call your doctor if you do not think you are getting better does not belong in the section (b) (4)
(b) (4) This section should reflect the labeled indications for the product. We deleted the first two sentences entirely and moved the last statement to the section “(b) (4)”
- We revised the statement (b) (4)
(b) (4) to be consistent with PI sections 5.4 and 8.4, as follows:

It is not known if olanzapine is safe and works in children under 18 years of age.

It is not known if olanzapine and fluoxetine hydrochloride taken together, or as SYMBYAX, is safe and works in children under 18 years of age.

12. In the section “What should I tell my doctor before taking Symbyax?”

- In the first paragraph, we deleted (b) (4) The patient’s medical conditions are relevant, (b) (4)
- A bullet was added for “bowel obstruction” to convey the “paralytic ileus.”
- The list of drug interactions is extensive for Symbyax; therefore, we did not use a bullet list here. Instead patients are instructed to “tell your doctor about all the medicines you take...”, with the exception of those medicines that also contain the same active ingredients. We have placed these in a box to call attention to the potential for overdose. For consistency, the review division should consider also deleting the bullet list from the Zyprexa MG. Zyprexa shares a number of the same interactions with Symbyax due to the common active ingredient. The Zyprexa MG also includes the patient instruction to “tell your doctor about all the medicines you take...”

13. In the section “How should I take Zyprexa?”

- We deleted the second bullet in this section. (b) (4)
- [REDACTED]
- Add an instruction to section 17 if the PI telling patients to contact their doctor if they do not think that they are getting better or have any concerns about their condition while taking Symbyax. The language in the MG must be consistent with the language in the PI. We made the language in the last bullet consistent with the language that we recommended in the DRISK review of the Zyprexa MG.
14. In the section “What should I avoid while taking Symbyax?” the review division should clarify if using the term “react quickly” accurately addresses the issue of (b) (4) as proposed by the sponsor.” We made the language in these bullets consistent with the language recommended in the DRISK review of the Zyprexa MG.
15. In the section “What are the possible side effects of Symbyax?”
- All serious side effects should be listed first and should be consistent with the Warnings and Precautions section of the PI, followed by a list of the common side effects of Symbyax. We added, revised, and moved information as appropriate.
 - We added the bullet “Decreased blood pressure when you change positions” to address the issue of orthostatic hypotension. Add the reportable signs and symptoms of orthostatic hypotension to section 17 of the PI and an instruction for patients to change positions carefully to help prevent this from happening.
 - We added bullets to address dysphagia, somnolence, and body temperature regulation.
 - The review division should review and revise the list of common side effects below in the MG and make it consistent with the PI section 6 Adverse Reactions. For consistency, give further consideration as to whether there are distinctions between teens and adults as we recommended in the DRISK review of the Zyprexa MG. If so, include a separate list. If there is no distinction, combine into one list. Use a consistent percentage cutoff for the common side effects.
 - We have revised the side effect statement at the end of the section, “What are the possible side effects of Zyprexa?” to state:

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This verbatim statement is required for all Medication Guides.¹
16. We added the MG section “How should I store Symbyax?”

Please let us know if you have any questions.

¹ 21 CFR 208.20 (b)(7)(iii)

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:

- 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.

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

25 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

Sharon Mills
2/27/2009 01:07:34 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
2/28/2009 08:38:24 PM
DRUG SAFETY OFFICE REVIEWER

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
8/1/2008 05:03:50 PM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-520/S-012

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Monday, March 16, 2009 3:30 PM
To: 'Christine Ann Phillips'
Cc: Grewal, Renmeet
Subject: REMS proposal templates for Zyprexa, Symbyax & Prozac
Attachments: Appendix A.pdf

Hi Christine,

Regarding the REMS template we have the following comments from our DRISK team. Please respond by COB, Tuesday, March 17th with an updated template for Symbyax, Zyprexa and Prozac. We have also provided you (in appendix A) the appended Symbyax REMS proposal with track changes and comments below to help you understand the minor track changes.

1. We remind you of your requirement to comply with 21 CFR 208.24

- A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

“Dispense the enclosed Medication Guide to each patient.” or “Dispense the accompanying Medication Guide to each patient.”

- Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose. For example:

- A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.

- A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

3. The timetable for submission of assessments will be at minimum at 18 months, 3 years and within the 7th year following the approval of the REMS.

- The REMS assessments should include information needed to assess the effectiveness of the REMS including:
- Patients’ understanding of the serious risks of Symbyax (olanzapine and fluoxetine hydrochloride)
- 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
- If you feel the REMS assessment at 7 years of the patient’s understanding of the Medication Guide is not needed because you have determined that serious risks have been adequately identified and assessed, submit a modification to the REMS following the REMS 3 year assessment. The agency will then determine if additional assessments of the patient’s understanding of the Medication Guide are necessary.

4. We recommend submitting a complete description of methodology and the instruments used to measure patient’s understanding of the risks and safe use of Symbyax to FDA 60 days prior to conducting the survey. The submission should include:

- All methodology and instruments that will be used to evaluate the patients’ understanding about the safe use of Symbyax (olanzapine and fluoxetine hydrochloride). 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.

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:

(b) (4)

- 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 [REDACTED] (b) (4)
 [REDACTED] 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



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.

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 - 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

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 it 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
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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,

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Sincerely,
Rimmy

*Renmeet Grewal, Pharm.D., LCDR USPHS
Senior Regulatory Project Manager
Division of Psychiatry Products
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Office of Drug Evaluation I
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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				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input checked="" type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> 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) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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/s/

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


Grewal, Renmeet

From: Grewal, Renmeet
Sent: Tuesday, May 27, 2008 7:46 AM
To: 'Matt Kuntz'
Cc: 'Christine Ann Phillips'; Grewal, Renmeet
Subject: Symbyax information request





Hi Matt,

We are writing to request revised versions of tables assessing weight gain outliers in each subject group, stratifying by treatment exposure time. (See Table 1 below for the table format.)



Revised tables will use the same methods as previously submitted tables, except that revised tables will assess weight gain at 6 weeks, 6 months, 12 months, 24 months, and 36 months  (b) (4)

Use the following time windows to correspond to each column in the table:

- 6 weeks = the subject's last visit from Day 35 to Day 48
- 6 months = the subject's last visit in a window of 6 months  (b) (4)
- 12 months = the subject's last visit in a window of 12 months  (b) (4)
- 24 months = the subject's last visit in a window of 24 months  (b) (4)
- 36 months = the subject's last visit in a window of 36 months  (b) (4)

Please provide revised tables for Integrated Controlled and Uncontrolled data for:

- Adult Subjects
- Pediatric and Adolescent Subjects
- Antipsychotic-Naïve Subjects

We request that these tables be submitted by June 4, 2008.

Best Regards,
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
5/27/2008 07:54:37 AM
CSO



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) Zydys, 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

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Friday, September 28, 2007 3:56 PM
To: 'Robin Pitts Wojcieszek'
Cc: Gregory T Brophy; 'Catherine Melfi'; Bates, Doris J
Subject: Dear Health Care Provider Letter

Dear Robin,

The division met regarding the Dear Health Care Provider letter you submitted September 25, 2007. As you are aware, we will of course have to review the supporting data before we can make a final determination about the acceptability of the proposed labeling changes. Nevertheless, we don't have any objections to what has been proposed, either for the letter or labeling. However, we do think the labeling would be improved by the addition of language regarding hyperglycemia and potential weight gain in the Information for Patients section of the labeling.

Thank you,
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
9/28/2007 04:11:14 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592 / S-040

NDA 20-592 / S-041

NDA 21-520 / S-012

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

Dear Dr. Melfi and Ms. Wojcieszek:

We acknowledge receipt on August 31, 2007 of your August 30, 2007 resubmissions to your supplemental new drug applications for Zyprexa (olanzapine) Tablets and Symbyax (olanzapine /fluoxetine combination) Capsules.

We do not consider these submissions to be complete responses to our March 28, 2007 and April 30, 2007 action letters. Therefore, we will not start the review clocks until we receive a complete response. The following deficiencies from our action letters still need to be addressed:

As we noted in our action letters, a primary concern with these applications is that we lack important safety information related to hyperglycemia, hyperlipidemia, and weight gain, in order to adequately update the labeling with all relevant risk information. As we stated in the letters, we need you to address these concerns, including the provision of pertinent data and analyses, before we will be able to take a final action on these applications. We referenced then, and again refer to, our letter dated January 12, 2007 regarding New York Times coverage of these issues.

We note that your resubmissions include only the requested information that relates to placebo controlled fasting/nonfasting adult and adolescent analyses. You have indicated that other information related to these issues remains outstanding and is slated for submission in September/October 2007 [Comparator-controlled fasting/nonfasting adult and adolescent analyses], December 2007 [long-term integrated database information for adult and adolescent use of olanzapine], and February 2008 [first episode/antipsychotic naive patient analyses, analyses for patients suffering from Alzheimer's and Parkinson's Disease, and single study analyses for the published longitudinal data studies HGJU and HGGF].

As was discussed in our meeting of May 24, 2007 related to NDA 21-520 S-012, a rolling timetable of submissions is acceptable, and we will consider after each such submission whether or not it can be considered to represent a complete response. However, upon receipt of the first portion of data, we

have determined that review of certain of the analyses targeted for later completion will in fact be necessary before adequate labeling pertaining to metabolic effects can be drafted. In particular, we will need to receive the data slated for submission in December, 2007, i.e., the long-term integrated database information for adult and adolescent use of olanzapine. It is not possible for us to adequately assess the safety of olanzapine with respect to the three metabolic issues noted above, until we have received this additional information requested in our March 28, 2007 and April 30, 2007 action letters. Although the first portion of data in the current submission does contain some long-term data, most of the metabolic data related to long-term exposure to olanzapine will be available in the long-term integrated database. Data pertaining to the metabolic effects of olanzapine over the longer term are necessary to fully and adequately characterize its metabolic effects. Therefore, your submissions will not be considered complete until we have received this outstanding information.

You must make separate submissions to NDA 21-520 / S-012 and NDA 20-592 / S-040 and S-041 when responding to this letter.

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 these supplemental applications for Zyprexa tablets are pediatric submissions in fulfillment of the requirement. Please refer to our April 30, 2007 action letter for further details.

If you have any questions, call Doris Bates, Regulatory Project Manager, at (301) 796-1040, or contact her via secure electronic mail at doris.bates@fda.hhs.gov, with respect to NDA 20-592 S-040 and S-041; for any questions relevant to NDA 21-520 S-012, contact LCDR Renmeet Grewal, Regulatory Project Manager, at (301) 796-1080, or contact her via secure electronic mail at renmeet.grewal@fda.hhs.gov.

Sincerely,

{See Appended Electronic Signature Page}

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

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/s/

Thomas Laughren
9/13/2007 04:06:18 PM

From: [Grewal, Renmeet](#)
To: ["Robin Pitts Wojcieszek";](#)
CC:
Subject: Questions NDA 21-520/SE1-012
Date: Monday, February 05, 2007 3:22:38 PM
Attachments:

Hi Robin,

Please clarify the following regarding your submission NDA 21-520/S-012, Symbyax for treatment-resistant depression:

- 1) Please explain the regression methodology utilized to correct the QT interval in the OFC studies.
- 2) In your proposed labeling, section (b) (4), we are unable to verify the data described in the last sentence of the first paragraph pertaining to the incidence of ALT elevations in the premarketing Symbyax-controlled database. Please provide the location of this information in your submission so that this may be confirmed.
- 3) Please clarify the total number of patients exposed to OFC in the ten-study placebo-controlled study database. We note that in some instances that this figure is stated to be 771, (b) (4). Proposed labeling indicates an N of 771. Please verify the correct figure.

Thank you,
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
2/5/2007 03:25:19 PM
CSO

From: [Grewal, Renmeet](#)
To: ["Robin Pitts Wojcieszek";](#)
CC: [Grewal, Renmeet;](#)
Subject: NDA 21-520/ S012
Date: Monday, January 29, 2007 12:58:23 PM
Attachments:

Hi Robin,
The statistics team has the following request:

Please refer to your sNDA 21-520 (Symbyax) submitted in September 2006. For Study HGIE, please provide AS SOON AS POSSIBLE an indicator variable that indicates patients with historical failure to SSRI in current episode. If this variable was already included in your sNDA submission, please specify its location.

Thank you,
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
1/29/2007 01:02:16 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-520/S-012

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, received September 29, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbyax (fluoxetine/olanzapine) Capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 28, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

As you are aware, the Physician Labeling Rule (PLR) requires that the Highlights section be limited to no more than 1/2 a page. Your submitted PLR exceeds this limitation. As such, you must formally request a waiver of this requirement

We are providing the above comments to give you preliminary notice of the potential review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Renmeet Grewal, 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
12/11/2006 10:58:53 AM

From: [Grewal, Renmeet](#)
To: ["Robin Pitts Wojcieszek";](#)
CC: [Bender, William; Grewal, Renmeet;](#)
Subject: sNDA 21-520/S012
Date: Tuesday, December 05, 2006 4:05:02 PM
Attachments:

Hi Robin,

The medical officer needs the following information:

1. Separated table of all concomitant meds during acute phase for Study HDAO-1 and 2, not pooled data.
2. Visit-wise OC analysis for MADRS (which is not the primary for Study HGFR) for Study HDAO, HGFR and HGIE.

Thank you,
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
12/5/2006 04:07:34 PM
CSO

From: [Grewal, Renmeet](#)
To: [Lewin, Constance; El Hage, Antoine N;](#)
CC:
Subject: FW: NDA 21-520/SE1-012 DSI consult
Date: Tuesday, November 14, 2006 11:06:51 AM
Attachments:

Hi Connie & Tony,

We think site 610 in Quebec from Study HDAO-2 and site 004 in Oklahoma from HGEI are more critical if we only can chose two sites.

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
11/14/2006 11:18:33 AM
CSO

DSI CONSULT: Request for Clinical Inspections

DATE: November 8, 2006

TO: Constance Lewin, M.D.
Division of Scientific Investigations, HFD-48

THROUGH: Thomas Laughren, M.D.
Division Director, Division of Psychiatry, HFD-130

FROM: Renmeet Gujral, Pharm.D., Regulatory Project Manager, HFD-130

SUBJECT: Request for Clinical Inspections
NDA 21-520/S-012
Symbyax (olanzapine and fluoxetine in combination) Capsules
O/F mg, 6/25mg, 12/25mg, 6/50mg, 12/50mg

Study/Site Identification:

We have received a supplemental NDA from Eli Lilly for Symbyax capsules to treat Treatment Resistant Depression in adults. We have granted Priority review for this application so the PDUFA date is March 29, 2007. Our 45-day filing meeting was on November 7, 2006, and the filing date for this application is November 28, 2006.

Clinical Sites Identification:

Study	Site	Investigator	Address	# of pts
HDAO-2	610	Bergeron, Richard	Hospitalier Pierre-Fanet 20 Rue Pharand Hull, Quebec J9A 1K7 Canada	82
	53	Downs, John	Clinical Trials of Memphis, Inc. 707 West Brookhaven Circle Memphis, TN 38117	15
	60	Beckett, Loise	IPS Research Company, Inc 1211 N Shartel-Suite 407 Oklahoma City, OK 73130	8
HGIE	004	Beckett, Loise	IPS Research Company, Inc 1211 N Shartel-Suite 407 Oklahoma City, OK 73130	20
HGFR	001	Shelton, Richard	Vanderbilt Univ. Medical Ctr. Dept. of Psychiatry and Psychopharmacology Clinic 1500 21 st Ave. S, Suite 2200 Nashville, TN 37212	31

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by February 1, 2007. We intend to issue an action letter on this application by March 29, 2007.

Should you require any additional information, please contact Renmeet Grewal, Pharm.D., at 301-796-1080 or renmeet.grewal@fda.hhs.gov .

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/s/

Thomas Laughren
11/14/2006 08:19:58 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

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.

NDA 21-520/S-012
NDA 20-592/S-039
NDA 21-086/S-021
NDA 18-936/S-077
Page 2

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

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/s/

Thomas Laughren
10/16/2006 01:29:43 PM

October 17, 2006

This document has been replaced by Acknowledgment Letter dated 10/16/2006.

This document incorrectly states "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."

However this is a supplement and is not approved under subpart H.



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

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

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/s/

Thomas Laughren
10/11/2006 02:06:25 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): HFD- 710/Stat Attention: Peiling Yang			FROM: HFD-130/ Division of Psychiatry Products	
DATE 10-10-06	IND NO.	NDA NO. 21-520/S-12,20-592/S-39,21-086/S-21,18-936/S-77	TYPE OF DOCUMENT New Efficacy Supplements	DATE OF DOCUMENT 9-28-06
NAME OF DRUG Symbyax, Zyprexa Zyprexa Zydis, Prozac		PRIORITY CONSIDERATION Priority Review	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE Filing meeting: 11-7-06 PDUFA date: 3/29/07
NAME OF FIRM: (b) (4)				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS:				
Lilly has submitted 4 efficacy supplements for TRD for Symbyax (21-520/S-12), Zyprexa (20-592/S-39), Zyprexa Zydis (21-086/S-21), and Prozac (18-936/S-77). I have included the links of each efficacy supplement in the edr: \\CDSESUB1\N21520\S_012\2006-09-28 \\Cdsesub1\p20592\S_039\2006-09-28 \\CDSESUB1\N18936\S_077\2006-09-28 If you have any questions you can call me at 301-796-1080 or email at renmeet.grewal@fda.hhs.gov .				
SIGNATURE OF REQUESTER Renmeet Grewal, Pharm.D. Regulatory Project Manager 301-796-1080 Renmeet.grewal@fda.hhs.gov			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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/s/

Renmeet Gujral
10/10/2006 02:44:54 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): HFD- 860/Biopharm Attention: Raman Baweja			FROM: HFD-130/ Division of Psychiatry Products	
DATE 10-06-06	IND NO.	NDA NO. 21-520/S-12,20-592/S-39,21-086/S-21,18-936/S-77	TYPE OF DOCUMENT New Efficacy Supplements	DATE OF DOCUMENT 9-28-06
NAME OF DRUG Symbyax, Zyprexa Zyprexa Zydis, Prozac		PRIORITY CONSIDERATION Priority Review	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE Filing meeting: 11-7-06 PDUFA date: 3/29/07
NAME OF FIRM: (b) (4)				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS:				
Lilly has submitted 4 efficacy supplements for TRD for Symbyax (21-520/S-12), Zyprexa (20-592/S-39), Zyprexa Zydis (21-086/S-21), and Prozac (18-936/S-77). I have included the links of each efficacy supplement in the edr: \\CDSESUB1\N21520\S_012\2006-09-28 \\Cdsesub1\n20592\S_039\2006-09-28 \\CDSESUB1\N18936\S_077\2006-09-28 If you have any questions you can call me at 301-796-1080 or email at renmeet.grewal@fda.hhs.gov .				
SIGNATURE OF REQUESTER Renmeet Grewal, Pharm.D. Regulatory Project Manager 301-796-1080 Renmeet.grewal@fda.hhs.gov			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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

/s/

Renmeet Gujral
10/10/2006 02:42:34 PM