**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

# 020592 / S-035, 039, 040, 041, 049,053, 055
# 021086 / S-21, 031, 032, 034
# 021253 / S-037, 039, 043

***Trade Name:*** Zyprexa

***Generic Name:*** olanzapine

***Sponsor:*** Eli Lilly and Company

***Approval Date:*** January 27, 2010

***Indications:*** For revisions to sections of product labeling

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**020592 / S-035, 039, 040, 041, 049,053, 055**

**021086 / S-21, 031, 032, 034**

**021253 / S-037, 039, 043**

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**020592 / S-035, 039, 040, 041, 049,053, 055**

**021086 / S-21, 031, 032, 034**

**021253 / S-037, 039, 043**

# APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020592 / S-053, S-055
NDA 021086 / S-032, S-034
NDA 021253 / S-039, S-043

**SUPPLEMENT APPROVAL**

Eli Lilly and Company
Attention: Christine Phillips, PhD, RAC
Director, Global Regulatory Affairs, US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Phillips:

Please refer to your Supplemental New Drug Applications (sNDAs) dated October 23, 2009 and received October 26, 2009 (S-053, S-032, and S-039) and dated and received April 1, 2010 (S-055, S-034, S-043), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zyprexa (olanzapine) Tablets (NDA 020592), 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg, Zyprexa Zydis (olanzapine) Orally Disintegrating Tablets (NDA 021086), 5 mg, 10 mg, 15 mg, and 20 mg, and Zyprexa (olanzapine) IM Injection (NDA 021253), 10 mg/vial.

These "Prior Approval" supplemental new drug applications contain revisions to the following sections of the product labeling:

**S-052, S-032, S-39:**

**ADVERSE REACTIONS, 6.2 Vital Signs and Laboratory Studies**

**S-055, S-034, S-043:**

**WARNINGS AND PRECAUTIONS, 5.6 Weight Gain**
**WARNINGS AND PRECAUTIONS, 5.8 Orthostatic Hypotension**

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

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE)

supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.
The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

**LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

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

**REPORTING REQUIREMENTS**

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

If you have any questions, email Keith Kiedrow, Pharm.D., Senior Regulatory Project Manager, at Keith.Kiedrow@FDA.HHS.GOV.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURES:
Content of Labeling, Medication Guide

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-21253 | SUPPL-43 | ELI LILLY AND CO | ZYPREXA IM (OLANZAPINE) 10MG VIALS INJ |
| NDA-21253 | SUPPL-39 | ELI LILLY AND CO | ZYPREXA IM (OLANZAPINE) 10MG VIALS INJ |
| NDA-21086 | SUPPL-34 | ELI LILLY AND CO | ZYPREXA ZYDIS(OLANZAPINE)5/10/15/20/ MGTS |
| NDA-21086 | SUPPL-32 | ELI LILLY AND CO | ZYPREXA ZYDIS(OLANZAPINE)5/10/15/20/ MGTS |
| NDA-20592 | SUPPL-55 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |
| NDA-20592 | SUPPL-53 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |

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/s/

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THOMAS P LAUGHREN
05/27/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

**Food and Drug Administration**
**Silver Spring MD 20993**

NDA 020592/S-052
NDA 021086/S-031
NDA 021253/S-037

**SUPPLEMENT APPROVAL**

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

Dear Dr. Brophy:

Please refer to your supplemental new drug applications dated and received on September 1, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zyprexa (olanzapine) Tablets, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg, Zyprexa Zydis (olanzapine) Orally Disintegrating Tablets 5 mg, 10 mg, 15 mg, and 20 mg, and Zyprexa (olanzapine) IM Injection, 10 mg/vial.

We acknowledge receipt of your submissions dated September 18, 2009, October 6, 2009, and December 16, 2009.

These "Prior Approval" supplemental new drug applications provide for revisions to Section 5.15(Hyperprolactinemia).

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.

## 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)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide). For administrative purposes, please designate this submission, **"SPL for approved supplement NDA 020592/S-052, 021086/S-031, & 021253/S-037021520/S-023."**

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

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

**LETTERS TO HEALTH CARE PROFESSIONALS**

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

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

**REPORTING REQUIREMENTS**

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

If you have any questions, call LCDR Keith Kiedrow, Regulatory Project Manager, at (301) 796-0240.

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

Enclosures: Package Insert
Medication Guide

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-21253 | SUPPL-37 | ELI LILLY AND CO | ZYPREXA IM (OLANZAPINE) 10MG VIALS INJ |
| NDA-21086 | SUPPL-31 | ELI LILLY AND CO | ZYPREXA ZYDIS(OLANZAPINE)5/10/15/20/ MGTS |
| NDA-20592 | SUPPL-52 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |

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/s/

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THOMAS P LAUGHREN
01/27/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020592/S-040/S-041

**SUPPLEMENT APPROVAL**

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

Dear Dr. Brophy:

Please refer to your supplemental new drug applications dated October 30, 2006, and received on October 31, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) Tablets, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg.

We acknowledge receipt of your submissions dated September 19, 2008, December 1, 2008, December 19, 2008, May 5, 2009, September 18, 2009 and October 13, 2009.

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

These supplemental new drug applications provide for the use of Zyprexa (olanzapine) for the treatment of manic or mixed episodes of bipolar I disorder and schizophrenia in adolescents, a proposed modification to the approved Risk Evaluation and Mitigation Strategy (REMS), and a REMS assessment.

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.

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

On October 13, 2009, you submitted a proposed modification and an assessment of your Risk Evaluation and Mitigation Strategy (REMS), originally approved on March 19, 2009. The proposed modified REMS contains a revised Medication Guide which includes new indications for the use of Zyprexa in treating manic or mixed episodes of bipolar I disorder and schizophrenia in adolescents ages 13 to 17, and a timetable for submission of assessments revised to specify the dates the assessments are due and that the assessments will be received by FDA on or before the due dates.

Your proposed modified REMS, appended to this letter, is approved. The REMS consists of the Medication Guide and a timetable for submission of assessments.

There are no changes to the REMS assessment plan.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessment provisions in 505-1(g) could result in enforcement action.

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

Prominently identify submissions containing the 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 20592 REMS ASSESSMENT**
**NEW SUPPLEMENT FOR NDA 20592**
**PROPOSED REMS MODIFICATION**
**REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)**
**FOR NDA 20592**
**REMS ASSESSMENT**
**PROPOSED REMS MODIFICATION (if included)**

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

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, **"SPL for approved NDA 20-592/S-040/S-041."**

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

## LETTERS TO HEALTH CARE PROFESSIONALS

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

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

## PROMOTIONAL MATERIALS

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

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

## REPORTING REQUIREMENTS

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

## MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

If you have any questions, please call Kimberly Updegraff, M.S., Senior Regulatory Project Manager, at (301) 796-2201.

Sincerely,

*{See appended electronic signature page}*

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

Enclosures
Content of Labeling
REMS

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-20592 | SUPPL-40 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |
| NDA-20592 | SUPPL-41 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |

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/s/

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THOMAS P LAUGHREN
12/04/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592 / S-051
NDA 21-086 / S-030
NDA 21-253 / S-036

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

Dear Dr. Brophy:

Please refer to your supplemental new drug applications dated and received on August 3, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ZYPREXA (olanzapine) Tablets, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg, ZYPREXA ZYDIS (olanzapine) Orally Disintegrating Tablets 5 mg, 10 mg, 15 mg, and 20 mg, and ZYPREXA (olanzapine) IM Injection, 10 mg/vial.

Reference is also made to our letter dated April 5, 2009, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for the entire class of antipsychotic drugs. This information pertains to the risk of leukopenia, neutropenia, and agranulocytosis. The decision to require safety labeling changes was based on new safety information about this risk identified since these products were approved. You were directed to submit a prior approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On May 5, 2009, FDA received your notification detailing the reasons why you believe a labeling change to address the risk of agranulocytosis is not warranted and your proposed labeling changes to address the risk of leukopenia and neutropenia. Our review of this and subsequent submissions found that your proposed labeling changes did not adequately address the new safety information regarding the risk of leukopenia, neutropenia, and agranulocytosis with the use of antipsychotic drugs, including Zyprexa (olanzapine). On July 19, 2009, we issued a letter ordering you, under the authority of Section 505(o)(4)(E) of the FDCA, to make specific changes in the HIGHLIGHTS OF PRESCRIBING INFORMATION and the WARNINGS AND PRECAUTIONS sections of labeling, pertaining to the risk of leukopenia, neutropenia, and agranulocytosis.

Your supplemental new drug applications provide for revisions to the HIGHLIGHTS OF PRESCRIBING INFORMATION and the WARNINGS AND PRECAUTIONS sections of labeling, to add information pertaining to the risks of leukopenia, neutropenia, and agranulocytosis, consistent with our July 19, 2009 Safety Label Change Order letter.

We have completed our review of these supplemental applications. These applications are approved, effective on the date of this letter, and the package insert has been revised accordingly (see enclosed package insert).

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, **"SPL for approved supplement NDA 20-592 / S-051, NDA 21-086 / S-030, and NDA 21-253 / S-036."**

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

Failure to make these changes within the specified period of time could make your products misbranded under 21 USC 321(n) and 352(a).

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

## LETTERS TO HEALTH CARE PROFESSIONALS

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

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

## REPORTING REQUIREMENTS

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

If you have any questions, please contact Doris J. Bates, Ph.D., Safety 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

Enclosure: Package Insert labeling

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/s/

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THOMAS P LAUGHREN
08/31/2009

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:

(b) (4)

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 dispending 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/

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

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**020592 / S-035, 039, 040, 041, 049,053, 055**

**021086 / S-21, 031, 032, 034**

**021253 / S-037, 039, 043**

## OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-592/S-(b) (4)/S-(b) (4)/S-(b) (4)/S-039/S-040/S-041/S-(b) (4)/S-(b) (4)
NDA 21-086/S-(b) (4)/S-(b) (4)/S-(b) (4)/S-021/S-(b) (4)/S-(b) (4)/S-(b) (4)
NDA 21-253/S-(b) (4)/S-(b) (4)/S-(b) (4)/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 applications dated September 28, 2006 (NDA 20-592/S-039 & NDA 21-086/S-021), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Zyprexa (olanzapine) tablets (NDA 20-592), Zyprexa Zydis (olanzapine) orally disintegrating tablets (NDA 21-086), and Zyprexa (olanzapine) injection (NDA 21-253).

We acknowledge receipt of your following amendments submitted to supplemental applications 20-592/S-(b) (4)/S-039 and (b) (4)/S-(b) (4)/S-021:

(b) (4)

Your submission of February 4, 2008 constituted a complete response to our September 21, 2007 action letter.

These supplemental new drug applications provide for the addition of the following language to the Indications section of the Zyprexa labeling when fluoxetine and olanzapine are used concomitantly:

- (b) (4)
-

Please also refer to your supplemental new drug applications dated October 30, 2006 (NDA 20-592/S-040/S-041), submitted under section 505(b) of the Act for Zyprexa (olanzapine) tablets.

We acknowledge receipt of your submissions dated:

(b) (4)

Your submission of February 5, 2008 constituted a complete response to our April 30, 2007 action letter.

These supplemental new drug applications provide for the use of Zyprexa (olanzapine) tablets in the acute treatment of Bipolar Disorder (manic or mixed episodes) in adolescent patients (supplement 040) and the acute treatment of Schizophrenia in adolescent patients (supplement 041).

We also acknowledge receipt of the following supplements incorporated into the attached label:

**NDA 21-253/S-(b) (4), 20-592/S-(b) (4), & 21-086/S-(b) (4) dated (b) (4), and amended on (b) (4)**

- (b) (4)

We note that your additional supplemental applications (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:

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

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 holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

Since Zyprexa was approved in 1996, we have become aware of new safety information from analysis of data related to an increased risk of hyperglycemia, hyperlipidemia and weight gain in adolescents associated with olanzapine use. This information was not available when Zyprexa was granted marketing authorization. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk that is, weight gain, hyperglycemia, and hyperlipidemia in adolescents treated with Zyprexa.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this known serious risk.

Therefore, based on the new safety information described above, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct postmarketing clinical studies or trial(s) of Zyprexa tablets (NDA 20-592) to assess the known serious risks of weight gain, hyperglycemia, and hyperlipidemia. The specific details of the required postmarketing clinical studies or trial(s) will be described more fully in a future letter.

**RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS**

Title IX, Subtitle A, Section 901 of FDAAA amends the 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 Zyprexa was approved in 1996, we have become aware of new safety information from analysis of data related to increase risk of hyperglycemia, hyperlipidemia and weight gain associated with olanzapine use. This information was not available when Zyprexa was granted marketing authorization. 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 Zyprexa poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Zyprexa. FDA has determined that Zyprexa 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 Zyprexa. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Zyprexa.

Your proposed REMS must contain a Medication Guide including the metabolic risks of Zyprexa tablets and Zyprexa Zydis 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 Zyprexa
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 NDAs 20-592/21-086/21-253 PROPOSED REMS**

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

Enclosure

40 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

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/s/

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Thomas Laughren
8/1/2008 05:46:30 PM

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

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

Dear Dr. Melfi:

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

We acknowledge receipt of your submissions dated November 15, 2006, December 11, 2006, January 10, 2007, January 11, 2007, January 24, 2007, February 6, 2007, February 27, 2007, March 27, 2007, and April 12, 2007.

Please note that your submission dated March 27, 2007 was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

These supplemental new drug applications provide for the use of Zyprexa (olanzapine) tablets in the treatment of bipolar disorder (manic or mixed episodes) in adolescent patients (supplement 040) and the treatment of schizophrenia in adolescent patients (supplement 041).

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

**Updated Information on Risks of Weight Gain, Hyperglycemia, and Hyperlipidemia**
A primary concern with these applications is that we lack important safety information needed to adequately update the labeling with all relevant risk information. You must fully address these concerns before we will be able to take a final action on these applications.

Please refer to our January 12, 2007 letter regarding recent New York Times coverage of issues related to weight gain, hyperglycemia, and hyperlipidemia in patients taking olanzapine. Please also refer to our March 28, 2007 letter regarding your supplemental new drug application for Symbyax capsules [NDA 21-520, S-012].

Our overall goal is to improve labeling with regard to these findings, in both the adolescent and adult populations, 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 Zyprexa provides sufficient information on these risks, and we fully intend to insure that this label is enhanced with the best available information to characterize these risks.

**Additional Clinical Questions**

Please note that some of these questions address information in the overall combined database, and therefore may require information from both the bipolar disorder trial submitted in supplement S-040, and the schizophrenia trial submitted in supplement S-041 to this NDA.

1. For the acute phases of HGIU and HGIN, many patients had elevated prolactin at baseline, therefore the change from baseline to endpoint analyses can be difficult to interpret. Please provide additional analyses for the change from baseline to endpoint on the subset of patients with baseline prolactin within the normal range. Please also provide a separate analysis for gender and age.

2. Table APP.2.7.4.24 in summary-clin-safe-app provides prolactin data over time for the overall combined database. Please provide a similar table for only those patients who completed 19-32 weeks in the study (n = 83 bipolar, n = 93 schizophrenia) - e.g. provide baseline, 1-6 week, 7-18 week and 19-32 week data for only those patients completing 19-32 weeks.

3. Please provide narrative summaries for the following: 8 cases of gynecomastia, 2 cases with high prolactin concentrations ( HGIN 005-503, HGIN 900-9009) and the case with a CPK of 7289 U/L .

4. The summary-clin-safe-app document includes comparisons of adult and adolescent data for metabolic parameters and prolactin but not for hepatic laboratory analytes. Please provide these comparisons for hepatic laboratory analytes. Although it was stated in the submission that the hepatic laboratory analyte comparisons were not provided due to differences in reference ranges for adults and adolescents, these comparisons were provided for the prolactin data despite differences in reference ranges for these populations.

5. Please review the MedWatch reports for fatalities and submit updates where possible for incomplete data. It was noted that these MedWatch reports had "DRAFT" at the top of the page and the date of the report was 7/27/06. Have all of these reports been previously filed with the Agency?

6. For MedWatch fatality case US_010158510, the narrative states "This is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in (b) (6). The reporter stated he has also notified the FDA...". The only MedWatch report included in this submission is for US_010158510. Please provide the MedWatch reports for the additional 4 deaths indicated in this narrative.

7. Please provide an analysis of AIMs individual items and total score (change from baseline to endpoint) for the completers in the overall combined database.

8. One concern we have for study HGIN is a finding that the positive results for this trial appeared to come predominantly from the Russian sites. For this study, the total sample was roughly split between these 2 regions. Although olanzapine was favored over placebo numerically in both regions, the data from the Russian sites appeared to be driving the overall result. For the US patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -21 and -15, respectively (p=0.258). For the Russian patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -17 and -3, respectively (p=0.003). So the treatment effect in olanzapine patients was roughly the same in both regions, however, the placebo response was much larger in the US sites compared to the Russian sites. Please address this geographic discrepancy in the efficacy results.

**Pediatric Research and Equity Act (PREA)**
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, with regard to both bipolar disorder and schizophrenia, you have fulfilled the requirements for adolescents aged 13-17 years, but have not studied the drug for either safety or efficacy in children aged 10 - 13 years. We are waiving the requirement for assessment of the safety and effectiveness of the product in pediatric patients aged 10-13 years with regard to both indications; your current studies have met the terms of the initial Pediatric Written Request.

**Post Marketing Commitments**
Both bipolar disorder and schizophrenia are chronic illnesses, and patients will likely require medication for a prolonged period. The long-term cardiovascular risk of significant weight gain, hypertriglyceridemia and hypercholesterolemia is significant, and efforts to minimize these adverse events are important.

We note that you are planning to conduct a long-term safety study in adolescents with schizophrenia or bipolar disorder, to estimate the incidence and prevalence of identified and potential risks of olanzapine treatment in this population. We recommend that you consider examining the effect of interventions on weight gain in adolescents treated with Zyprexa as part of this study.

Please provide updated information on your planned study in your Complete Response to this letter. Since this will be considered a required Phase 4 commitment, please propose dates for submitting your protocol, and your final study report, to the Agency. Please note that this commitment applies to both indications and the same commitment will be applied to both supplements; your Complete Response should address this commitment in terms of both supplement S-040 and S-041.

**Labeling**
For both S-040 and S-041, you must submit draft/final printed labeling revised as indicated in the attached marked-up labeling. The marked-up version is based on your submitted proposed labeling; we have used track changes to indicate our additions and deletions, and have added bracketed comments to explain our actions or requests where needed. You may submit identical consolidated labeling in your Complete Response to both supplemental applications. We are willing to meet with you to discuss the proposed changes in the context of the additional safety information requested above and elsewhere in this letter.

In addition, all previous revisions, as reflected in the most recently approved package insert, must be included in the labeling proposed with your complete response to this letter. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes you have proposed.

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

**Request for Safety Update, World Literature Update, and Foreign Regulatory Update**
When you respond to the above deficiencies, for each supplement you should 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 Zyprexa. 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 Zyprexa. 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.

7. We require a review of the status of all Zyprexa 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. Provide English translations of current approved foreign labeling not previously submitted.

**Promotional Materials**

In addition, submit three copies of the introductory promotional materials that you propose to use for this product in both of the proposed indications. 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 applications, notify us of your intent to file an amendment to each, 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.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with either or both of these changes before approval of the relevant supplemental application.

If you have any questions, call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 796-2260, or contact her via secure email at doris.bates@fda.hhs.gov.

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

Enclosure: FDA revised labeling (package insert)

26 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

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/s/
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Thomas Laughren
4/30/2007 11:55:39 AM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**020592 / S-035, 039, 040, 041, 049,053, 055**

**021086 / S-21, 031, 032, 034**

**021253 / S-037, 039, 043**

# LABELING

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

**ZYPREXA (olanzapine) Tablet for Oral use**
**ZYPREXA ZYDIS (olanzapine) Tablet, Orally Disintegrating for Oral use**
**ZYPREXA IntraMuscular (olanzapine) Injection, Powder, For Solution for Intramuscular use**

**Initial U.S. Approval: 1996**

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

***See full prescribing information for complete boxed warning.***

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis. (5.1, 5.14, 17.2)**
  **When using ZYPREXA and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.**

**---------- RECENT MAJOR CHANGES ----------**

| | |
|---|---|
| Indications and Usage: | |
| Schizophrenia (1.1) | 12/2009 |
| Bipolar I Disorder (Manic or Mixed Episodes) (1.2) | 12/2009 |
| Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder (1.3) | 12/2009 |
| ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania (1.4) | 12/2009 |
| Dosage and Administration: | |
| Schizophrenia (2.1) | 12/2009 |
| Bipolar I Disorder (Manic or Mixed Episodes) (2.2) | 12/2009 |
| Warnings and Precautions: | |
| Orthostatic Hypotension (5.8) | 05/2010 |
| Leukopenia, Neutropenia, and Agranulocytosis (5.9) | 08/2009 |
| Hyperprolactinemia (5.15) | 01/2010 |

**---------- INDICATIONS AND USAGE ----------**

ZYPREXA® (olanzapine) is an atypical antipsychotic indicated:

*As oral formulation for the*

- Treatment of schizophrenia. (1.1)
  - Adults: Efficacy was established in three clinical trials in patients with schizophrenia: two 6-week trials and one maintenance trial. (14.1)
  - Adolescents (ages 13-17): Efficacy was established in one 6-week trial in patients with schizophrenia (14.1). The increased potential (in adolescents compared with adults) for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first in adolescents. (1.1)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. (1.2)
  - Adults: Efficacy was established in three clinical trials in patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one maintenance trial. (14.2)
  - Adolescents (ages 13-17): Efficacy was established in one 3-week trial in patients with manic or mixed episodes associated with bipolar I disorder (14.2). The increased potential (in adolescents compared with adults) for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first in adolescents. (1.2)
- Medication therapy for pediatric patients with schizophrenia or bipolar I disorder should be undertaken only after a thorough diagnostic evaluation and with careful consideration of the potential risks. (1.3)
- Adjunct to valproate or lithium in the treatment of manic or mixed episodes associated with bipolar I disorder. (1.2)
  - Efficacy was established in two 6-week clinical trials in adults (14.2). Maintenance efficacy has not been systematically evaluated.

*As ZYPREXA IntraMuscular for the*

- Treatment of acute agitation associated with schizophrenia and bipolar I mania. (1.4)
  - Efficacy was established in three 1-day trials in adults. (14.3)

*As ZYPREXA and Fluoxetine in Combination for the*

- Treatment of depressive episodes associated with bipolar I disorder. (1.5)
  - Efficacy was established with Symbyax (olanzapine and fluoxetine in combination) in adults; refer to the product label for Symbyax.
- Treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode). (1.6)
  - Efficacy was established with Symbyax (olanzapine and fluoxetine in combination) in adults; refer to the product label for Symbyax.

**---------- DOSAGE AND ADMINISTRATION ----------**

| | |
|---|---|
| Schizophrenia in adults (2.1) | Oral: Start at 5-10 mg once daily; Target: 10 mg/day within several days |
| Schizophrenia in adolescents (2.1) | Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day |
| Bipolar I Disorder (manic or mixed episodes) in adults (2.2) | Oral: Start at 10 or 15 mg once daily |
| Bipolar I Disorder (manic or mixed episodes) in adolescents (2.2) | Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day |
| Bipolar I Disorder (manic or mixed episodes) with lithium or valproate in adults (2.2) | Oral: Start at 10 mg once daily |
| Agitation associated with Schizophrenia and Bipolar I Mania in adults (2.4) | IM: 10 mg (5 mg or 7.5 mg when clinically warranted)<br>Assess for orthostatic hypotension prior to subsequent dosing (max. 3 doses 2-4 hrs apart) |
| Depressive Episodes associated with Bipolar I Disorder in adults (2.5) | Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily |
| Treatment Resistant Depression in adults (2.6) | Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily |

- Lower starting dose recommended in debilitated or pharmacodynamically sensitive patients or patients with predisposition to hypotensive reactions, or with potential for slowed metabolism. (2.1)
- Olanzapine may be given without regard to meals. (2.1)

*ZYPREXA and Fluoxetine in Combination*

- Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability. (2.5, 2.6)
- Olanzapine monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder or treatment resistant depression. (2.5, 2.6)
- Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated. (2.5, 2.6)

**---------- DOSAGE FORMS AND STRENGTHS ----------**

- Tablets (not scored): 2.5, 5, 7.5, 10, 15, 20 mg (3)
- Orally Disintegrating Tablets (not scored): 5, 10, 15, 20 mg (3)
- Intramuscular Injection: 10 mg vial (3)

**---------- CONTRAINDICATIONS ----------**

- None with ZYPREXA monotherapy.
- When using ZYPREXA and fluoxetine in combination, also refer to the Contraindications section of the package insert for Symbyax®. (4)
- When using ZYPREXA in combination with lithium or valproate, refer to the Contraindications section of the package inserts for those products. (4)

**---------- WARNINGS AND PRECAUTIONS ----------**

- *Elderly Patients with Dementia-Related Psychosis* Increased risk of death and increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack). (5.1)
- *Suicide* The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy; when using in combination with fluoxetine, also refer to the Boxed Warning and Warnings and Precautions sections of the package insert for Symbyax. (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 olanzapine 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)
- *Tardive Dyskinesia* Discontinue if clinically appropriate. (5.7)
- *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, cerebrovascular disease, and those conditions that could affect hemodynamic responses. (5.8)
- *Leukopenia, Neutropenia, and Agranulocytosis* Has been reported with antipsychotics, including ZYPREXA. Patients with a history of a clinically significant low white blood cell count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.9)
- *Seizures* Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.11)
- *Potential for Cognitive and Motor Impairment* Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery. (5.12)
- *Hyperprolactinemia* May elevate prolactin levels. (5.15)
- *Use in Combination with Fluoxetine, Lithium or Valproate* Also refer to the package inserts for Symbyax, lithium, or valproate. (5.16)
- *Laboratory Tests* Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment. (5.17)

**----------ADVERSE REACTIONS----------**

Most common adverse reactions (≥5% and at least twice that for placebo) associated with:

*Oral Olanzapine Monotherapy*
- Schizophrenia (Adults) – postural hypotension, constipation, weight gain, dizziness, personality disorder, akathisia (6.1)
- Schizophrenia (Adolescents) – sedation, weight increased, headache, increased appetite, dizziness, abdominal pain, pain in extremity, fatigue, dry mouth (6.1)
- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor (6.1)
- Manic or Mixed Episodes, Bipolar I Disorder (Adolescents) – sedation, weight increased, increased appetite, headache, fatigue, dizziness, dry mouth, abdominal pain, pain in extremity (6.1)

*Combination of ZYPREXA and Lithium or Valproate*
- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia (6.1)

*ZYPREXA and Fluoxetine in Combination* Also refer to the Adverse Reactions section of the package insert for Symbyax. (6)

*ZYPREXA IntraMuscular for Injection*
- Agitation with Schizophrenia and Bipolar I Mania (Adults) – somnolence (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----------**
- *Diazepam* May potentiate orthostatic hypotension. (7.1, 7.2)
- *Alcohol* May potentiate orthostatic hypotension. (7.1)
- *Carbamazepine* Increased clearance of olanzapine. (7.1)
- *Fluvoxamine* May increase olanzapine levels. (7.1)
- *ZYPREXA and Fluoxetine in Combination* Also refer to the Drug Interactions section of the package insert for Symbyax. (7.1)
- *CNS Acting Drugs* Caution should be used when taken in combination with other centrally acting drugs and alcohol. (7.2)
- *Antihypertensive Agents* Enhanced antihypertensive effect. (7.2)
- *Levodopa and Dopamine Agonists* May antagonize levodopa/dopamine agonists. (7.2)
- *Lorazepam (IM)* Increased somnolence with IM olanzapine. (7 2)
- *Other Concomitant Drug Therapy* When using olanzapine in combination with lithium or valproate, refer to the Drug Interactions sections of the package insert for those products. (7.2)

**----------USE IN SPECIFIC POPULATIONS----------**
- *Pregnancy* ZYPREXA 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 ZYPREXA in children <13 years of age have not been established. (8.4)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide**

**Revised: MM/YYYY**

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## FULL PRESCRIBING INFORMATION

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1, 5.14) and Patient Counseling Information (17.2)]*.**

**When using ZYPREXA and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.**

## 1 INDICATIONS AND USAGE

### 1.1 Schizophrenia

Oral ZYPREXA is indicated for the treatment of schizophrenia. Efficacy was established in three clinical trials in adult patients with schizophrenia: two 6-week trials and one maintenance trial. In adolescent patients with schizophrenia (ages 13-17), efficacy was established in one 6-week trial *[see Clinical Studies (14.1)]*.

When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Warnings and Precautions (5.5, 5.6)]*.

### 1.2 Bipolar I Disorder (Manic or Mixed Episodes)

Monotherapy — Oral ZYPREXA is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. Efficacy was established in three clinical trials in adult patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one monotherapy maintenance trial. In adolescent patients with manic or mixed episodes associated with bipolar I disorder (ages 13-17), efficacy was established in one 3-week trial *[see Clinical Studies (14.2)]*.

When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Warnings and Precautions (5.5, 5.6)]*.

Adjunctive Therapy to Lithium or Valproate — Oral ZYPREXA is indicated for the treatment of manic or mixed episodes associated with bipolar I disorder as an adjunct to lithium or valproate. Efficacy was established in two 6-week clinical trials in adults. The effectiveness of adjunctive therapy for longer-term use has not been systematically evaluated in controlled trials *[see Clinical Studies (14.2)]*.

### 1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder

Pediatric schizophrenia and bipolar I disorder are serious mental disorders; however, diagnosis can be challenging. For pediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, pediatric patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for pediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment for both pediatric schizophrenia and bipolar I disorder should be part of a total treatment program that often includes psychological, educational and social interventions.

### 1.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania

ZYPREXA IntraMuscular is indicated for the treatment of acute agitation associated with schizophrenia and bipolar I mania.

Efficacy was demonstrated in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients with: schizophrenia or bipolar I disorder (manic or mixed episodes) *[see Clinical Studies (14.3)]*.

"Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

### 1.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder

Oral ZYPREXA and fluoxetine in combination is indicated for the treatment of depressive episodes associated with bipolar I disorder, based on clinical studies in adult patients. When using ZYPREXA and fluoxetine in combination, refer to the Clinical Studies section of the package insert for Symbyax.

ZYPREXA monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

### 1.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

Oral ZYPREXA and fluoxetine in combination is indicated for the treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode), based on clinical studies in adult patients. When using ZYPREXA and fluoxetine in combination, refer to the Clinical Studies section of the package insert for Symbyax.

ZYPREXA monotherapy is not indicated for the treatment of treatment resistant depression.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Schizophrenia

**Adults**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical assessment. Olanzapine is not indicated for use in doses above 20 mg/day.

Dosing in Special Populations — The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*. When indicated, dose escalation should be performed with caution in these patients.

Maintenance Treatment — The effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for relapse has been demonstrated in a placebo-controlled trial *[see Clinical Studies (14.1)]*. The physician who elects to use ZYPREXA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

**Adolescents**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents with schizophrenia was

demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 12.5 mg/day (mean dose of 11.1 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended.

The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials *[see Clinical Studies (14.1)]*.

Maintenance Treatment — The efficacy of ZYPREXA for the maintenance treatment of schizophrenia in the adolescent population has not been systematically evaluated; however, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 2.2 Bipolar I Disorder (Manic or Mixed Episodes)

**Adults**

Dose Selection for Monotherapy — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials *[see Clinical Studies (14.2)]*.

Maintenance Monotherapy — The benefit of maintaining bipolar I patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of 2 weeks, was demonstrated in a controlled trial *[see Clinical Studies (14.2)]*. The physician who elects to use ZYPREXA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Dose Selection for Adjunctive Treatment — When administered as adjunctive treatment to lithium or valproate, oral olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals.

Antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials *[see Clinical Studies (14.2)]*. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

**Adolescents**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents with bipolar I disorder (manic or mixed episodes) was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 10.7 mg/day (mean dose of 8.9 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended.

The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials *[see Clinical Studies (14.2)]*.

Maintenance Treatment — The efficacy of ZYPREXA for the maintenance treatment of bipolar I disorder in the adolescent population has not been evaluated; however, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 2.3 Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)

After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

### 2.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania

Dose Selection for Agitated Adult Patients with Schizophrenia and Bipolar I Mania — The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant *[see Clinical Studies (14.3)]*. If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., 3 doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension *[see Warnings and Precautions (5.8)]*. Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended.

If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate *[see Dosage and Administration (2.1, 2.2)]*.

Intramuscular Dosing in Special Populations — A dose of 5 mg/injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg/injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

Administration of ZYPREXA IntraMuscular — ZYPREXA IntraMuscular is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for Preparation of ZYPREXA IntraMuscular with Sterile Water for Injection — Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. ZYPREXA IntraMuscular reconstituted with Sterile Water for Injection should be used immediately (within 1 hour) after reconstitution. *Discard any unused portion.*

The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

| Dose, mg Olanzapine | Volume of Injection, mL |
|---|---|
| 10 | Withdraw total contents of vial |
| 7.5 | 1.5 |
| 5 | 1 |
| 2.5 | 0.5 |

Physical Incompatibility Information — ZYPREXA IntraMuscular should be reconstituted only with Sterile Water for Injection. ZYPREXA IntraMuscular should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed. Lorazepam injection should not be used to reconstitute ZYPREXA IntraMuscular as this combination results in a delayed reconstitution time. ZYPREXA IntraMuscular should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

### 2.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 12.5 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was demonstrated with ZYPREXA and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg.

Safety and efficacy of ZYPREXA and fluoxetine in combination was determined in clinical trials supporting approval of Symbyax (fixed dose combination of ZYPREXA and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. The following table demonstrates the appropriate individual component doses of ZYPREXA and fluoxetine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

**Table 1: Approximate Dose Correspondence Between Symbyax[a] and the Combination of ZYPREXA and Fluoxetine**

| For Symbyax (mg/day) | Use in Combination | |
|---|---|---|
| | ZYPREXA (mg/day) | Fluoxetine (mg/day) |
| 3 mg olanzapine/25 mg fluoxetine | 2.5 | 20 |
| 6 mg olanzapine/25 mg fluoxetine | 5 | 20 |
| 12 mg olanzapine/25 mg fluoxetine | 10+2.5 | 20 |
| 6 mg olanzapine/50 mg fluoxetine | 5 | 40+10 |
| 12 mg olanzapine/50 mg fluoxetine | 10+2.5 | 40+10 |

[a] Symbyax (olanzapine/fluoxetine HCl) is a fixed-dose combination of ZYPREXA and fluoxetine.

While there is no body of evidence to answer the question of how long a patient treated with ZYPREXA and fluoxetine in combination 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.

Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

ZYPREXA monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

### 2.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 20 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was

demonstrated with olanzapine and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 18 mg and fluoxetine 25 to 50 mg.

Safety and efficacy of olanzapine in combination with fluoxetine was determined in clinical trials supporting approval of Symbyax (fixed dose combination of olanzapine and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. Table 1 above demonstrates the appropriate individual component doses of ZYPREXA and fluoxetine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

While there is no body of evidence to answer the question of how long a patient treated with ZYPREXA and fluoxetine in combination 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.

Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

ZYPREXA monotherapy is not indicated for treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode).

### 2.7 ZYPREXA and Fluoxetine in Combination: 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. 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. ZYPREXA 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 (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

## 3 DOSAGE FORMS AND STRENGTHS

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. Tablets are not scored. The tablets are available as follows:

| | TABLET STRENGTH | | | | | |
|---|---|---|---|---|---|---|
| | 2.5 mg | 5 mg | 7.5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4112 | 4115 | 4116 | 4117 | 4415 | 4420 |
| Identification | LILLY<br>4112 | LILLY<br>4115 | LILLY<br>4116 | LILLY<br>4117 | LILLY<br>4415 | LILLY<br>4420 |

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. Tablets are not scored. The tablets are available as follows:

| | TABLET STRENGTH | | | |
|---|---|---|---|---|
| ZYPREXA ZYDIS Tablets | 5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4453 | 4454 | 4455 | 4456 |
| Debossed | 5 | 10 | 15 | 20 |

ZYPREXA IntraMuscular is available in 10 mg vial (1s).

## 4 CONTRAINDICATIONS

- None with ZYPREXA monotherapy.
- When using ZYPREXA and fluoxetine in combination, also refer to the Contraindications section of the package insert for Symbyax.
- For specific information about the contraindications of lithium or valproate, refer to the Contraindications section of the package inserts for these other products.

## 5 WARNINGS AND PRECAUTIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Warnings and Precautions section of the package insert for Symbyax.

### 5.1 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. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.14), and Patient Counseling Information (17.2)]*.**

In 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 is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Patient Counseling Information (17.2)]*.

### 5.2 Suicide

The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

### 5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (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 a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported *[see Patient Counseling Information (17.3)]*.

### 5.4 Hyperglycemia

Physicians should consider the risks and benefits when prescribing olanzapine 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 olanzapine should be monitored regularly for worsening of glucose control. Patients starting treatment with olanzapine 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 (17.4)]*.

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. 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.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with a median treatment duration of approximately 3 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). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (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, and/or a baseline fasting glucose level ≥126 mg/dL). Olanzapine-treated patients had a greater mean HbA1c increase from baseline of 0.04% (median exposure 21 days), compared to a mean HbA1c decrease of 0.06% in placebo-treated subjects (median exposure 17 days).

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). Table 2 shows short-term and long-term changes in fasting glucose levels from adult olanzapine monotherapy studies.

**Table 2: Changes in Fasting Glucose Levels from Adult Olanzapine Monotherapy Studies**

| | Up to 12 weeks | At least 48 weeks |
|---|---|---|

| | | | exposure | | exposure | |
|---|---|---|---|---|---|---|
| **Laboratory Analyte** | **Category Change (at least once) from Baseline** | **Treatment Arm** | **N** | **Patients** | **N** | **Patients** |
| Fasting Glucose | Normal to High (<100 mg/dL to ≥126 mg/dL) | Olanzapine | 543 | 2.2% | 345 | 12.8% |
| | | Placebo | 293 | 3.4% | NA[a] | NA[a] |
| | Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL) | Olanzapine | 178 | 17.4% | 127 | 26.0% |
| | | Placebo | 96 | 11.5% | NA[a] | NA[a] |

[a] Not Applicable.

The mean change in fasting glucose for 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 have not been established in patients under the age of 13 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 versus -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 exposure | | At least 24 weeks exposure | |
|---|---|---|---|---|---|---|
| **Laboratory Analyte** | **Category Change (at least once) from Baseline** | **Treatment Arm** | **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 olanzapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using olanzapine, is recommended *[see Patient Counseling Information (17.5)]*.

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

Olanzapine Monotherapy in Adults — 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, or patients with high baseline lipid levels.

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. 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 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 4 shows categorical changes in fasting lipids values.

**Table 4: Changes in Fasting Lipids Values from Adult Olanzapine Monotherapy 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** |
| Fasting | Increase by ≥50 mg/dL | Olanzapine | 745 | 39.6% | 487 | 61.4% |
| | | Placebo | 402 | 26.1% | NA[a] | NA[a] |
| | Normal to High | Olanzapine | 457 | 9.2% | 293 | 32.4% |

| | | | | | | |
|---|---|---|---|---|---|---|
| Triglycerides | (<150 mg/dL to ≥200 mg/dL) | Placebo | 251 | 4.4% | NA[a] | NA[a] |
| | Borderline to High | Olanzapine | 135 | 39.3% | 75 | 70.7% |
| | (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL) | Placebo | 65 | 20.0% | NA[a] | NA[a] |
| | | | | | | |
| Fasting Total Cholesterol | Increase by ≥40 mg/dL | Olanzapine | 745 | 21.6% | 489 | 32.9% |
| | | Placebo | 402 | 9.5% | NA[a] | NA[a] |
| | Normal to High | Olanzapine | 392 | 2.8% | 283 | 14.8% |
| | (<200 mg/dL to ≥240 mg/dL) | Placebo | 207 | 2.4% | NA[a] | NA[a] |
| | Borderline to High | Olanzapine | 222 | 23.0% | 125 | 55.2% |
| | (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL) | Placebo | 112 | 12.5% | NA[a] | NA[a] |
| | | | | | | |
| Fasting LDL Cholesterol | Increase by ≥30 mg/dL | Olanzapine | 536 | 23.7% | 483 | 39.8% |
| | | Placebo | 304 | 14.1% | NA[a] | NA[a] |
| | Normal to High | Olanzapine | 154 | 0% | 123 | 7.3% |
| | (<100 mg/dL to ≥160 mg/dL) | Placebo | 82 | 1.2% | NA[a] | NA[a] |
| | Borderline to High | Olanzapine | 302 | 10.6% | 284 | 31.0% |
| | (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL) | 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 mean increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 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 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 5 shows categorical changes in fasting lipids values in adolescents.

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

| | | | Up to 6 weeks exposure | | At least 24 weeks exposure | |
|---|---|---|---|---|---|---|
| **Laboratory Analyte** | **Category Change (at least once) from Baseline** | **Treatment Arm** | **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 | Olanzapine | 67 | 26.9% | 66 | 36.4% |
| | (<90 mg/dL to >130 mg/dL) | Placebo | 28 | 10.7% | NA[a] | NA[a] |
| | Borderline to High | Olanzapine | 37 | 59.5% | 31 | 64.5% |
| | (≥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 | Olanzapine | 87 | 6.9% | 78 | 7.7% |
| | (<170 mg/dL to ≥200 mg/dL) | Placebo | 43 | 2.3% | NA[a] | NA[a] |
| | Borderline to High | Olanzapine | 36 | 38.9% | 33 | 57.6% |
| | (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL) | 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 | Olanzapine | 98 | 5.1% | 92 | 10.9% |
| | (<110 mg/dL to ≥130 mg/dL) | Placebo | 44 | 4.5% | NA[a] | NA[a] |
| | Borderline to High | Olanzapine | 29 | 48.3% | 21 | 47.6% |
| | (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL) | 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 olanzapine. Patients receiving olanzapine should receive regular monitoring of weight *[see Patient Counseling Information (17.6)]*.

Olanzapine Monotherapy in Adults — In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg (5.7 lb) compared to an average 0.3 kg (0.6 lb) weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, compared to 3% of placebo-treated patients, with a median exposure to event of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 0.3% of placebo-treated patients, with a median exposure to event of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in 0% of placebo-treated patients.

In long-term 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 6 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 6: 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 have not been established in patients under the age of 13 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 7: 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 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 8 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 8: 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 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.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

For specific information about the warnings of lithium or valproate, refer to the Warnings section of the package inserts for these other products.

### 5.8 Orthostatic Hypotension

Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its $\alpha_1$-adrenergic antagonistic properties *[see Patient Counseling Information (17.7)]*.

For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD *[see Dosage and Administration (2)]*. A more gradual titration to the target dose should be considered if hypotension occurs.

Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in nonagitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥30 mmHg) *[see Dosage and Administration (2.4)]*. Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the reactions occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. For intramuscular olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation.

Olanzapine 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, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression *[see Drug Interactions (7)]*. Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine is not recommended due to the potential for excessive sedation and cardiorespiratory depression.

### 5.9 Leukopenia, Neutropenia, and Agranulocytosis

Class Effect — In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including ZYPREXA. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/$mm^3$) should discontinue ZYPREXA and have their WBC followed until recovery.

### 5.10 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. Olanzapine is not approved for the treatment of patients with Alzheimer's disease.

### 5.11 Seizures

During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine 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. Olanzapine 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 or older.

### 5.12 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse reaction associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse reaction was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine 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 olanzapine therapy does not affect them adversely *[see Patient Counseling Information (17.8)]*.

### 5.13 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine 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 (17.9)]*.

### 5.14 Use in Patients with Concomitant Illness

Clinical experience with olanzapine in patients with certain concomitant systemic illnesses is limited *[see Clinical Pharmacology (12.3)]*.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with olanzapine, olanzapine 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 discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or 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 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 (5.1), and Patient Counseling Information (17.2)]*.

Olanzapine 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 premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients *[see Warnings and Precautions (5.8)]*.

### 5.15 Hyperprolactinemia

As with other drugs that antagonize dopamine $D_2$ receptors, olanzapine elevates prolactin levels, and the elevation persists during chronic 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 which 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 placebo-controlled olanzapine clinical studies (up to 12 weeks), changes from normal to high in prolactin concentrations were observed in 30% of adults treated with olanzapine as compared to 10.5% of adults treated with placebo. In a pooled analysis from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestations included menstrual-related events[1] (2% [49/3240] of females), sexual function-related events[2] (2% [150/8136] of females and males), and breast-related events[3] (0.7% [23/3240] of females, 0.2% [9/4896] of males).

In placebo-controlled olanzapine monotherapy studies in adolescent patients (up to 6 weeks) with schizophrenia or bipolar I disorder (manic or mixed episodes), changes from normal to high in prolactin concentrations were observed in 47% of olanzapine-treated patients compared to 7% of placebo-treated patients. In a pooled analysis from clinical trials including 454 adolescents treated with olanzapine, potentially associated clinical manifestations included menstrual-related events[1] (1% [2/168] of females), sexual function-related events[2] (0.7% [3/454] of females and males), and breast-related events[3] (2% [3/168] of females, 2% [7/286] of males) *[see Use in Specific Populations (8.4)]*.

[1] Based on a search of the following terms: amenorrhea, hypomenorrhea, menstruation delayed, and oligomenorrhea.

[2] Based on a search of the following terms: anorgasmia, delayed ejaculation, erectile dysfunction, decreased libido, loss of libido, abnormal orgasm, and sexual dysfunction.

[3] Based on a search of the following terms: breast discharge, enlargement or swelling, galactorrhea, gynecomastia, and lactation disorder.

### 5.16 Use in Combination with Fluoxetine, Lithium, or Valproate

When using ZYPREXA and fluoxetine in combination, the prescriber should also refer to the Warnings and Precautions section of the package insert for Symbyax. When using ZYPREXA in combination with lithium or valproate, the prescriber should refer to the Warnings and Precautions sections of the package inserts for lithium or valproate *[see Drug Interactions (7)]*.

### 5.17 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 (17.4, 17.5)]*.

## 6 ADVERSE REACTIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Adverse Reactions section of the package insert for Symbyax.

### 6.1 Clinical Trials Experience

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.

**Clinical Trials in Adults**

The information below for olanzapine is derived from a clinical trial database for olanzapine consisting of 8661 adult patients with approximately 4165 patient-years of exposure to oral olanzapine and 722 patients with exposure to intramuscular olanzapine for injection. This database includes: (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine premarketing bipolar I disorder (manic or mixed episodes) trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5788 patients from 88 additional oral olanzapine clinical trials as of December 31, 2001; and (5) 722 patients who participated in intramuscular olanzapine for injection premarketing trials in agitated patients with schizophrenia, bipolar I disorder (manic or mixed episodes), or dementia. In addition, information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar I disorder (manic or mixed episodes) trials with approximately 22 patient-years of exposure, is included below.

The conditions and duration of treatment with olanzapine 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 longer-term exposure. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse reactions, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar I disorder (manic or mixed episodes) or agitation. However, this information is also generally applicable to bipolar I disorder (manic or mixed episodes) and agitation.

Adverse reactions during exposure were obtained by spontaneous report and recorded by clinical investigators using 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 smaller number of standardized reaction categories. In the tables and tabulations that follow, MedDRA and COSTART Dictionary terminology has been used to classify reported adverse reactions.

The stated frequencies of adverse reactions 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. The reported reactions do not include those reaction terms that were so general as to be uninformative. Reactions listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the reactions occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

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 trials. 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 physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reactions incidence in the population studied.

Incidence of Adverse Reactions in Short-Term, Placebo-Controlled and Combination Trials

The following findings are based on premarketing trials of (1) oral olanzapine for schizophrenia, bipolar I disorder (manic or mixed episodes), a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease, and premarketing combination trials, and (2) intramuscular olanzapine for injection in agitated patients with schizophrenia or bipolar I mania.

*Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials*

Schizophrenia — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (5% for oral olanzapine vs 6% for placebo). However, discontinuations due to increases in ALT were considered to be drug related (2% for oral olanzapine vs 0% for placebo).

Bipolar I Disorder (Manic or Mixed Episodes) Monotherapy — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (2% for oral olanzapine vs 2% for placebo).

Agitation — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (0.4% for intramuscular olanzapine for injection vs 0% for placebo).

*Adverse Reactions Associated with Discontinuation of Treatment in Short-Term Combination Trials*

Bipolar I Disorder (Manic or Mixed Episodes), Olanzapine as Adjunct to Lithium or Valproate — In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 11% for the combination of oral olanzapine with lithium or valproate compared to 2% for patients who remained on lithium or valproate monotherapy. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and peripheral edema (1%).

*Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials*

The most commonly observed adverse reactions associated with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

**Table 9: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Trials — SCHIZOPHRENIA**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine (N=248)** | **Placebo (N=118)** |
| Postural hypotension | 5 | 2 |
| Constipation | 9 | 3 |
| Weight gain | 6 | 1 |
| Dizziness | 11 | 4 |
| Personality disorder[a] | 8 | 4 |
| Akathisia | 5 | 1 |

[a] Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.

**Table 10: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 3-Week and 4-Week Trials — Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine (N=125)** | **Placebo (N=129)** |
| Asthenia | 15 | 6 |
| Dry mouth | 22 | 7 |
| Constipation | 11 | 5 |
| Dyspepsia | 11 | 5 |
| Increased appetite | 6 | 3 |

| | | |
|---|---|---|
| Somnolence | 35 | 13 |
| Dizziness | 18 | 6 |
| Tremor | 6 | 3 |

Olanzapine Intramuscular — There was 1 adverse reaction (somnolence) observed at an incidence of 5% or greater among intramuscular olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar I mania was 6% for intramuscular olanzapine for injection and 3% for placebo.

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term, Placebo-Controlled Trials*

Table 11 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with oral olanzapine (doses ≥2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

**Table 11: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials with Oral Olanzapine**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Body System/Adverse Reaction** | **Olanzapine (N=532)** | **Placebo (N=294)** |
| **Body as a Whole** | | |
| Accidental injury | 12 | 8 |
| Asthenia | 10 | 9 |
| Fever | 6 | 2 |
| Back pain | 5 | 2 |
| Chest pain | 3 | 1 |
| **Cardiovascular System** | | |
| Postural hypotension | 3 | 1 |
| Tachycardia | 3 | 1 |
| Hypertension | 2 | 1 |
| **Digestive System** | | |
| Dry mouth | 9 | 5 |
| Constipation | 9 | 4 |
| Dyspepsia | 7 | 5 |
| Vomiting | 4 | 3 |
| Increased appetite | 3 | 2 |
| **Hemic and Lymphatic System** | | |
| Ecchymosis | 5 | 3 |
| **Metabolic and Nutritional Disorders** | | |
| Weight gain | 5 | 3 |
| Peripheral edema | 3 | 1 |
| **Musculoskeletal System** | | |
| Extremity pain (other than joint) | 5 | 3 |
| Joint pain | 5 | 3 |
| **Nervous System** | | |
| Somnolence | 29 | 13 |
| Insomnia | 12 | 11 |
| Dizziness | 11 | 4 |
| Abnormal gait | 6 | 1 |
| Tremor | 4 | 3 |
| Akathisia | 3 | 2 |
| Hypertonia | 3 | 2 |
| Articulation impairment | 2 | 1 |
| **Respiratory System** | | |
| Rhinitis | 7 | 6 |
| Cough increased | 6 | 3 |
| Pharyngitis | 4 | 3 |
| **Special Senses** | | |
| Amblyopia | 3 | 2 |
| **Urogenital System** | | |

| | | |
|---|---|---|
| Urinary incontinence | 2 | 1 |
| Urinary tract infection | 2 | 1 |

*Commonly Observed Adverse Reactions in Short-Term Trials of Oral Olanzapine as Adjunct to Lithium or Valproate*

In the bipolar I disorder (manic or mixed episodes) adjunct placebo-controlled trials, the most commonly observed adverse reactions associated with the combination of olanzapine and lithium or valproate (incidence of ≥5% and at least twice placebo) were:

**Table 12: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Adjunct to Lithium or Valproate Trials — Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine with lithium or valproate (N=229)** | **Placebo with lithium or valproate (N=115)** |
| Dry mouth | 32 | 9 |
| Weight gain | 26 | 7 |
| Increased appetite | 24 | 8 |
| Dizziness | 14 | 7 |
| Back pain | 8 | 4 |
| Constipation | 8 | 4 |
| Speech disorder | 7 | 1 |
| Increased salivation | 6 | 2 |
| Amnesia | 5 | 2 |
| Paresthesia | 5 | 2 |

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term Trials of Olanzapine as Adjunct to Lithium or Valproate*

Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

**Table 13: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials of Oral Olanzapine as Adjunct to Lithium or Valproate**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Body System/Adverse Reaction** | **Olanzapine with lithium or valproate (N=229)** | **Placebo with lithium or valproate (N=115)** |
| **Body as a Whole** | | |
| Asthenia | 18 | 13 |
| Back pain | 8 | 4 |
| Accidental injury | 4 | 2 |
| Chest pain | 3 | 2 |
| **Cardiovascular System** | | |
| Hypertension | 2 | 1 |
| **Digestive System** | | |
| Dry mouth | 32 | 9 |
| Increased appetite | 24 | 8 |
| Thirst | 10 | 6 |
| Constipation | 8 | 4 |
| Increased salivation | 6 | 2 |
| **Metabolic and Nutritional Disorders** | | |
| Weight gain | 26 | 7 |
| Peripheral edema | 6 | 4 |
| Edema | 2 | 1 |
| **Nervous System** | | |
| Somnolence | 52 | 27 |
| Tremor | 23 | 13 |
| Depression | 18 | 17 |
| Dizziness | 14 | 7 |
| Speech disorder | 7 | 1 |
| Amnesia | 5 | 2 |
| Paresthesia | 5 | 2 |

| | | |
|---|---|---|
| Apathy | 4 | 3 |
| Confusion | 4 | 1 |
| Euphoria | 3 | 2 |
| Incoordination | 2 | 0 |
| **Respiratory System** | | |
| Pharyngitis | 4 | 1 |
| Dyspnea | 3 | 1 |
| **Skin and Appendages** | | |
| Sweating | 3 | 1 |
| Acne | 2 | 0 |
| Dry skin | 2 | 0 |
| **Special Senses** | | |
| Amblyopia | 9 | 5 |
| Abnormal vision | 2 | 0 |
| **Urogenital System** | | |
| Dysmenorrhea[a] | 2 | 0 |
| Vaginitis[a] | 2 | 0 |

[a] Denominator used was for females only (olanzapine, N=128; placebo, N=51).

For specific information about the adverse reactions observed with lithium or valproate, refer to the Adverse Reactions section of the package inserts for these other products.

*Adverse Reactions Occurring at an Incidence of 1% or More among Intramuscular Olanzapine for Injection-Treated Patients in Short-Term, Placebo-Controlled Trials*

Table 14 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 1% or more of patients treated with intramuscular olanzapine for injection (dose range of 2.5-10 mg/injection) and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar I mania.

**Table 14: Treatment-Emergent Adverse Reactions: Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trials with Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia or Bipolar I Mania**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Body System/Adverse Reaction** | **Olanzapine (N=415)** | **Placebo (N=150)** |
| **Body as a Whole** | | |
| Asthenia | 2 | 1 |
| **Cardiovascular System** | | |
| Hypotension | 2 | 0 |
| Postural hypotension | 1 | 0 |
| **Nervous System** | | |
| Somnolence | 6 | 3 |
| Dizziness | 4 | 2 |
| Tremor | 1 | 0 |

**Additional Findings Observed in Clinical Trials**

Dose Dependency of Adverse Reactions in Short-Term, Placebo-Controlled Trials

*Extrapyramidal Symptoms:* The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

**Table 15: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | **Placebo** | **Olanzapine 5 ± 2.5 mg/day** | **Olanzapine 10 ± 2.5 mg/day** | **Olanzapine 15 ± 2.5 mg/day** |
| Parkinsonism[a] | 15 | 14 | 12 | 14 |
| Akathisia[b] | 23 | 16 | 19 | 27 |

[a] Percentage of patients with a Simpson-Angus Scale total score >3.

[b] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

**Table 16: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | **Placebo (N=68)** | **Olanzapine 5 ± 2.5 mg/day (N=65)** | **Olanzapine 10 ± 2.5 mg/day (N=64)** | **Olanzapine 15 ± 2.5 mg/day (N=69)** |
| Dystonic events[a] | 1 | 3 | 2 | 3 |
| Parkinsonism events[b] | 10 | 8 | 14 | 20 |
| Akathisia events[c] | 1 | 5 | 11 | 10 |
| Dyskinetic events[d] | 4 | 0 | 2 | 1 |
| Residual events[e] | 1 | 2 | 5 | 1 |
| Any extrapyramidal event | 16 | 15 | 25 | 32 |

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[c] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[e] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

The following table enumerates the percentage of adolescent patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy (dose range: 2.5 to 20 mg/day).

**Table 17: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in Placebo-Controlled Clinical Trials of Oral Olanzapine in Schizophrenia and Bipolar I Disorder — Adolescents**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Categories[a]** | **Placebo (N=89)** | **Olanzapine (N=179)** |
| Dystonic events | 0 | 1 |
| Parkinsonism events | 2 | 1 |
| Akathisia events | 4 | 6 |
| Dyskinetic events | 0 | 1 |
| Nonspecific events | 0 | 4 |
| Any extrapyramidal event | 6 | 10 |

[a] Categories are based on Standard MedDRA Queries (SMQ) for extrapyramidal symptoms as defined in MedDRA version 12.0.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with placebo in agitation. Patients in each dose group could receive up to 3 injections during the trials *[see Clinical Studies (14.3)]*. Patient assessments were conducted during the 24 hours following the initial dose of intramuscular olanzapine for injection.

**Table 18: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia**

| | Percentage of Patients Reporting Event | | | | |
|---|---|---|---|---|---|
| | **Placebo** | **Olanzapine IM 2.5 mg** | **Olanzapine IM 5 mg** | **Olanzapine IM 7.5 mg** | **Olanzapine IM 10 mg** |
| Parkinsonism[a] | 0 | 0 | 0 | 0 | 3 |
| Akathisia[b] | 0 | 0 | 5 | 0 | 0 |

[a] Percentage of patients with a Simpson-Angus Scale total score >3.

[b] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions in the same controlled clinical trial comparing fixed doses of intramuscular olanzapine for injection with placebo in agitated patients with schizophrenia.

**Table 19: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia**

| | Percentage of Patients Reporting Event | | | | |
|---|---|---|---|---|---|
| | Placebo (N=45) | Olanzapine IM 2.5 mg (N=48) | Olanzapine IM 5 mg (N=45) | Olanzapine IM 7.5 mg (N=46) | Olanzapine IM 10 mg (N=46) |
| Dystonic events[a] | 0 | 0 | 0 | 0 | 0 |
| Parkinsonism events[b] | 0 | 4 | 2 | 0 | 0 |
| Akathisia events[c] | 0 | 2 | 0 | 0 | 0 |
| Dyskinetic events[d] | 0 | 0 | 0 | 0 | 0 |
| Residual events[e] | 0 | 0 | 0 | 0 | 0 |
| Any extrapyramidal events | 0 | 4 | 2 | 0 | 0 |

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[c] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[e] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

*Dystonia, Class Effect:* 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 olanzapine use.

*Other Adverse Reactions:* The following table addresses dose relatedness for other adverse reactions using data from a schizophrenia trial involving fixed dosage ranges of oral olanzapine. It enumerates the percentage of patients with treatment-emergent adverse reactions for the 3 fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse reactions for which there was a trend.

**Table 20: Percentage of Patients from a Schizophrenia Trial with Treatment-Emergent Adverse Reactions for the 3 Dose Range Groups and Placebo**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| Adverse Reaction | Placebo (N=68) | Olanzapine 5 ± 2.5 mg/day (N=65) | Olanzapine 10 ± 2.5 mg/day (N=64) | Olanzapine 15 ± 2.5 mg/day (N=69) |
| Asthenia | 15 | 8 | 9 | 20 |
| Dry mouth | 4 | 3 | 5 | 13 |
| Nausea | 9 | 0 | 2 | 9 |
| Somnolence | 16 | 20 | 30 | 39 |
| Tremor | 3 | 0 | 5 | 7 |

Differences among Fixed-Dose Groups 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 oral olanzapine in patients with schizophrenia or schizoaffective disorder, 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/mL (female) or >18.77 ng/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 During the Clinical Trial Evaluation of Oral Olanzapine

Following is a list of treatment-emergent adverse reactions reported by patients treated with oral olanzapine (at multiple doses ≥1 mg/day) 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; rare reactions are those occurring in fewer than 1/1000 patients.

**Body as a Whole** — *Infrequent:* chills, face edema, photosensitivity reaction, suicide attempt[1]; *Rare:* chills and fever, hangover effect, sudden death[1].

**Cardiovascular System** — *Infrequent:* cerebrovascular accident, vasodilatation.

**Digestive System** — *Infrequent:* nausea and vomiting, tongue edema; *Rare:* ileus, intestinal obstruction, liver fatty deposit.

**Hemic and Lymphatic System** — *Infrequent:* leukopenia, thrombocytopenia.

**Metabolic and Nutritional Disorders** — *Infrequent:* alkaline phosphatase increased, bilirubinemia, hypoproteinemia.

**Musculoskeletal System** — *Rare:* osteoporosis.

**Nervous System** — *Infrequent:* ataxia, dysarthria, libido decreased, stupor; *Rare:* coma.

**Respiratory System** — *Infrequent:* epistaxis; *Rare:* lung edema.

**Skin and Appendages** — *Infrequent:* alopecia.

**Special Senses** — *Infrequent:* abnormality of accommodation, dry eyes; *Rare:* mydriasis.

**Urogenital System** — *Infrequent:* amenorrhea[2], breast pain, decreased menstruation, impotence[2], increased menstruation[2], menorrhagia[2], metrorrhagia[2], polyuria[2], urinary frequency, urinary retention, urinary urgency, urination impaired.

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

[2] Adjusted for gender.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Intramuscular Olanzapine for Injection

Following is a list of treatment-emergent adverse reactions reported by patients treated with intramuscular olanzapine for injection (at 1 or more doses ≥2.5 mg/injection) 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) for 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.

**Body as a Whole** — *Frequent:* injection site pain.

**Cardiovascular System** — *Infrequent:* syncope.

**Digestive System** — *Infrequent:* nausea.

**Metabolic and Nutritional Disorders** — *Infrequent:* creatine phosphokinase increased.

Clinical Trials in Adolescent Patients (age 13 to 17 years)

*Commonly Observed Adverse Reactions in Oral Olanzapine Short-Term, Placebo-Controlled Trials*

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 5% or more and reported at least twice as frequently as placebo-treated patients are listed in Table 21.

**Table 21: Treatment-Emergent Adverse Reactions of ≥5% Incidence among Adolescents (13-17 Years Old) with Schizophrenia or Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | 6 Week Trial % Schizophrenia Patients | | 3 Week Trial % Bipolar Patients | |
| Adverse Reactions | Olanzapine (N=72) | Placebo (N=35) | Olanzapine (N=107) | Placebo (N=54) |
| Sedation[a] | 39 | 9 | 48 | 9 |
| Weight increased | 31 | 9 | 29 | 4 |
| Headache | 17 | 6 | 17 | 17 |
| Increased appetite | 17 | 9 | 29 | 4 |
| Dizziness | 8 | 3 | 7 | 2 |
| Abdominal pain[b] | 6 | 3 | 6 | 7 |
| Pain in extremity | 6 | 3 | 5 | 0 |
| Fatigue | 3 | 3 | 14 | 6 |
| Dry mouth | 4 | 0 | 7 | 0 |

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.

[b] Patients with the following MedDRA terms were counted in this category: abdominal pain, abdominal pain lower, abdominal pain upper.

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term (3-6 weeks), Placebo-Controlled Trials*

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 2% or more and greater than placebo are listed in Table 22.

**Table 22: Treatment-Emergent Adverse Reactions of ≥2% Incidence among Adolescents (13-17 Years Old) (Combined Incidence from Short-Term, Placebo-Controlled Clinical Trials of Schizophrenia or Bipolar I Disorder [Manic or Mixed Episodes])**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine (N=179)** | **Placebo (N=89)** |
| Sedation[a] | 44 | 9 |
| Weight increased | 30 | 6 |
| Increased appetite | 24 | 6 |
| Headache | 17 | 12 |
| Fatigue | 9 | 4 |
| Dizziness | 7 | 2 |
| Dry mouth | 6 | 0 |
| Pain in extremity | 5 | 1 |
| Constipation | 4 | 0 |
| Nasopharyngitis | 4 | 2 |
| Diarrhea | 3 | 0 |
| Restlessness | 3 | 2 |
| Liver enzymes increased[b] | 8 | 1 |
| Dyspepsia | 3 | 1 |
| Epistaxis | 3 | 0 |
| Respiratory tract infection[c] | 3 | 2 |
| Sinusitis | 3 | 0 |
| Arthralgia | 2 | 0 |
| Musculoskeletal stiffness | 2 | 0 |

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.

[b] The terms alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hepatic enzyme were combined under liver enzymes.

[c] Patients with the following MedDRA terms were counted in this category: lower respiratory tract infection, respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection.

### 6.2 Vital Signs and Laboratory Studies

Vital Sign Changes — Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials *[see Warnings and Precautions (5)]*.

Laboratory Changes

*Olanzapine Monotherapy in Adults:* An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in ALT, AST, and GGT. Within the original premarketing database of about 2400 adult patients with baseline ALT ≤90 IU/L, the incidence of ALT elevations to >200 IU/L was 2% (50/2381). 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.

In placebo-controlled olanzapine monotherapy studies in adults, clinically significant ALT elevations (change from <3 times the upper limit of normal [ULN] at baseline to ≥3 times ULN) were observed in 5% (77/1426) of patients exposed to olanzapine compared to 1% (10/1187) of patients exposed to placebo. ALT elevations ≥5 times ULN were observed in 2% (29/1438) of olanzapine-treated patients, compared to 0.3% (4/1196) of placebo-treated patients. ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine or discontinued olanzapine. No patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule.

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.

Olanzapine administration was also associated with increases in serum prolactin *[see Warnings and Precautions (5.15)]*, with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

*Olanzapine Monotherapy in Adolescents:* In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar I disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT (≥3X ULN in patients with ALT at baseline <3X ULN), (12% vs 2%); elevated AST (28% vs 4%); low total bilirubin (22% vs 7%); elevated GGT (10% vs 1%); and elevated prolactin (47% vs 7%).

In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from <3 times ULN at baseline to ≥3 times ULN) were observed in 12% (22/192) of patients exposed to olanzapine compared to 2% (2/109) of patients exposed to placebo. ALT elevations ≥5 times ULN were observed in 4% (8/192) of olanzapine-treated patients, compared to 1% (1/109) of placebo-treated patients. ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine or discontinued olanzapine. No adolescent patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule.

ECG Changes — In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc (Fridericia corrected), and PR intervals. Olanzapine use was associated with a mean increase in heart rate compared to placebo (adults: +2.4 beats per minute vs no change with placebo; adolescents: +6.3 beats per minute vs -5.1 beats per minute with placebo). This increase in heart rate may be related to olanzapine's potential for inducing orthostatic changes *[see Warnings and Precautions (5.8)]*.

### 6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZYPREXA. 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 ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, diabetic ketoacidosis, discontinuation reaction (diaphoresis, nausea or vomiting), jaundice, neutropenia, pancreatitis, priapism, rash, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

## 7 DRUG INTERACTIONS

The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies.

### 7.1 Potential for Other Drugs to Affect Olanzapine

Diazepam — The co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Cimetidine and Antacids — Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Inducers of CYP1A2 — Carbamazepine therapy (200 mg bid) causes an approximately 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.

Alcohol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The co-administration of alcohol (i.e., ethanol) with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Inhibitors of CYP1A2

*Fluvoxamine:* Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine Cmax following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

Inhibitors of CYP2D6

*Fluoxetine:* Fluoxetine (60 mg single dose or 60 mg daily dose for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended. When using ZYPREXA and fluoxetine in combination, also refer to the Drug Interactions section of the package insert for Symbyax.

Warfarin — Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics *[see Drug Interactions (7.2)]*.

Inducers of CYP1A2 or Glucuronyl Transferase — Omeprazole and rifampin may cause an increase in olanzapine clearance.

Charcoal — The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

### 7.2 Potential for Olanzapine to Affect Other Drugs

CNS Acting Drugs — Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Antihypertensive Agents — Olanzapine, because of its potential for inducing hypotension, may enhance the effects of certain antihypertensive agents.

Levodopa and Dopamine Agonists — Olanzapine may antagonize the effects of levodopa and dopamine agonists.

Lorazepam (IM) — Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone *[see Warnings and Precautions (5.8)]*.

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium *[see Warnings and Precautions (5.16)]*.

Valproate — Olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate *[see Warnings and Precautions (5.16)]*.

Effect of Olanzapine on Drug Metabolizing Enzymes — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Imipramine — Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

Warfarin — Single doses of olanzapine did not affect the pharmacokinetics of warfarin *[see Drug Interactions (7.1)]*.

Diazepam — Olanzapine did not influence the pharmacokinetics of diazepam or its active metabolite N-desmethyldiazepam. However, diazepam co-administered with olanzapine increased the orthostatic hypotension observed with either drug given alone *[see Drug Interactions (7.1)]*.

Alcohol — Multiple doses of olanzapine did not influence the kinetics of ethanol *[see Drug Interactions (7.1)]*.

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

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

## 8 USE IN SPECIFIC POPULATIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Use in Specific Populations section of the package insert for Symbyax.

### 8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C — 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 maximum recommended human daily oral dose on a $mg/m^2$ basis, respectively) no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a $mg/m^2$ basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a $mg/m^2$ basis). In an oral 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 maximum recommended human daily oral dose on a $mg/m^2$ 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 trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion.

### 8.2 Labor and Delivery

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

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

The safety and effectiveness of oral ZYPREXA in the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder were established in short-term studies in adolescents (ages 13 to 17 years). Use of ZYPREXA in adolescents is supported by evidence from adequate and well-controlled studies of ZYPREXA in which 268 adolescents received ZYPREXA in a range of 2.5 to 20 mg/day *[see Clinical Studies (14.1, 14.2)]*. Recommended starting dose for adolescents is lower than that for adults *[see Dosage and Administration (2.1, 2.2)]*. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic transaminase levels *[see Warnings and Precautions (5.5, 5.6, 5.15, 5.17) and Adverse Reactions (6.2)]*. When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Indications and Usage (1.1, 1.2)]*.

Safety and effectiveness of olanzapine in children <13 years of age have not been established *[see Patient Counseling Information (17.13)]*.

Safety and effectiveness of ZYPREXA and fluoxetine in combination in children and adolescents <18 years of age have not been established.

### 8.5 Geriatric Use

Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to 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 events (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. 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 *[see Boxed Warning, Dosage and Administration (2.1), and Warnings and Precautions (5.1)]*.

Clinical studies of ZYPREXA and fluoxetine in combination did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients.

## 9 DRUG ABUSE AND DEPENDENCE

### 9.3 Dependence

In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily oral dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily oral dose on a $mg/m^2$ basis.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials 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, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

## 10 OVERDOSAGE

### 10.1 Human Experience

In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

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 and 1 patient experiencing 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.

### 10.2 Management of Overdose

The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

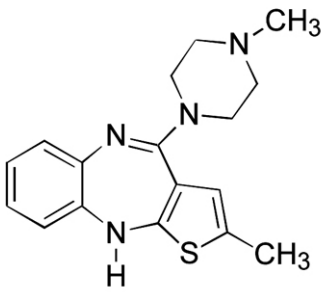
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. 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 beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

For specific information about overdosage with lithium or valproate, refer to the Overdosage section of the package inserts for these products. For specific information about overdosage with olanzapine and fluoxetine in combination, refer to the Overdosage section of the Symbyax package insert.

## 11 DESCRIPTION

ZYPREXA (olanzapine) is an atypical antipsychotic that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-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. The chemical structure is:




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

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 µmol), 5 mg (16 µmol), 7.5 mg (24 µmol), 10 mg (32 µmol), 15 mg (48 µmol), or 20 mg (64 µmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 µmol), 10 mg (32 µmol), 15 mg (48 µmol) or 20 mg (64 µmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

ZYPREXA IntraMuscular (olanzapine for injection) is intended for intramuscular use only.

Each vial provides for the administration of 10 mg (32 µmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT2) antagonism. The mechanism of action of olanzapine in the treatment of acute manic or mixed episodes associated with bipolar I disorder is unknown.

### 12.2 Pharmacodynamics

Olanzapine binds with high affinity to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$ ($K_i$=4, 11, and 5 nM, respectively), dopamine $D_{1\text{-}4}$ ($K_i$=11-31 nM), histamine $H_1$ ($K_i$=7 nM), and adrenergic $\alpha_1$ receptors ($K_i$=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ ($K_i$=57 nM) and muscarinic $M_{1\text{-}5}$ ($K_i$=73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds weakly to $GABA_A$, BZD, and β-adrenergic receptors ($K_i$>10 µM).

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 $M_{1\text{-}5}$ receptors may explain its anticholinergic-like effects. Olanzapine's antagonism of histamine $H_1$ receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic $\alpha_1$ receptors may explain the orthostatic hypotension observed with this drug.

### 12.3 Pharmacokinetics

Oral Administration, Monotherapy — Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics 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.

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/mL, binding primarily to albumin and $\alpha_1$-acid glycoprotein.

Metabolism and Elimination — 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 cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, 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.

Intramuscular Administration — ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is similar to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

*Specific Populations*

Renal Impairment — 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 metabolite elimination has not been studied.

Hepatic Impairment — 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 (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Geriatric — In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (≥65 years) than in nonelderly subjects (<65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity *[see Dosage and Administration (2)]*.

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 recommended.

Race — In vivo studies have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine *[see Dosage and Administration (2)]*.

Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents were nonsmokers and this population had a lower average body weight, which resulted in higher average olanzapine exposure compared to adults.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily oral dose on a $mg/m^2$ basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a $mg/m^2$ basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily oral dose on a $mg/m^2$ basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in 1 mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a $mg/m^2$ basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily oral dose on a $mg/m^2$ 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 maximum recommended human daily oral dose on a $mg/m^2$ 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 (5.15)]*.

Mutagenesis — 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.

Impairment of Fertility — 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 maximum recommended human daily oral dose on a $mg/m^2$ 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 maximum recommended human daily oral dose on a $mg/m^2$ basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a $mg/m^2$ basis); therefore olanzapine may produce a delay in ovulation.

### 13.2 Animal Toxicology and/or Pharmacology

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily oral dose on a $mg/m^2$ basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a $mg/m^2$ basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily oral dose on a $mg/m^2$ basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a $mg/m^2$ basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

## 14 CLINICAL STUDIES

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

### 14.1 Schizophrenia

**Adults**

The efficacy of oral olanzapine in the treatment of schizophrenia was established in 2 short-term (6-week) controlled trials of adult inpatients who met DSM III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in 1 of the 2 trials, but this trial did not compare these 2 drugs on the full range of clinically relevant doses for both.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, 2 more recently developed scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which are embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving 2 fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5 ± 2.5 mg/day, 10 ± 2.5 mg/day, and 15 ± 2.5 mg/day) on a once daily schedule, the 2 highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high-dose group over the medium-dose group.

(3) In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open-label treatment for at least 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however, criteria were met for stopping the trial early due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months.

Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

**Adolescents**

The efficacy of oral olanzapine in the acute treatment of schizophrenia in adolescents (ages 13 to 17 years) was established in a 6-week double-blind, placebo-controlled, randomized trial of inpatients and outpatients with schizophrenia (n=107) who met diagnostic criteria according to DSM-IV-TR and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL).

The primary rating instrument used for assessing psychiatric signs and symptoms in this trial was the Anchored Version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score.

In this flexible-dose trial, olanzapine 2.5 to 20 mg/day (mean modal dose 12.5 mg/day, mean dose of 11.1 mg/day) was more effective than placebo in the treatment of adolescents diagnosed with schizophrenia, as supported by the statistically significantly greater mean reduction in BPRS-C total score for patients in the olanzapine treatment group than in the placebo group.

While there is no body of evidence available to answer the question of how long the adolescent patient treated with ZYPREXA should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 14.2 Bipolar I Disorder (Manic or Mixed Episodes)

**Adults**

Monotherapy — The efficacy of oral olanzapine in the treatment of manic or mixed episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in adult patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar I disorder who had responded during an initial open-label treatment phase for about 2 weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to ≤12 and HAM-D 21 to ≤8. Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to ≥15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Adjunct to Lithium or Valproate — The efficacy of oral olanzapine with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in 2 controlled trials in patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course. The results of the trials follow:

(1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

**Adolescents**

Acute Monotherapy — The efficacy of oral olanzapine in the treatment of acute manic or mixed episodes in adolescents (ages 13 to 17 years) was established in a 3-week, double-blind, placebo-controlled, randomized trial of adolescent inpatients and outpatients who met the diagnostic criteria for manic or mixed episodes associated with bipolar I disorder (with or without psychotic features) according to the DSM-IV-TR (n=161). Diagnosis was confirmed by the K-SADS-PL.

The primary rating instrument used for assessing manic symptoms in this trial was the Adolescent Structured Young-Mania Rating Scale (Y-MRS) total score.

In this flexible-dose trial, olanzapine 2.5 to 20 mg/day (mean modal dose 10.7 mg/day, mean dose of 8.9 mg/day) was more effective than placebo in the treatment of adolescents with manic or mixed episodes associated with bipolar I disorder, as supported by the statistically significantly greater mean reduction in Y-MRS total score for patients in the olanzapine treatment group than in the placebo group.

While there is no body of evidence available to answer the question of how long the adolescent patient treated with ZYPREXA should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 14.3 Agitation Associated with Schizophrenia and Bipolar I Mania

The efficacy of intramuscular olanzapine for injection for the treatment of agitation was established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients from 2 diagnostic groups: schizophrenia and bipolar I disorder (manic or mixed episodes). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar I mania study). Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥14 on the 5 items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least 1 individual item score ≥4 using a 1-7 scoring system (1=absent, 4=moderate, 7=extreme). In the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to 3 injections during the 24 hour IM treatment periods; however, patients could not receive the second injection until after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

(1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270), 4 fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the 3 highest doses. There were no significant pairwise differences for the 7.5 and 10 mg doses over the 5 mg dose.

(2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=311), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

(3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for bipolar I disorder (and currently displaying an acute manic or mixed episode with or without psychotic features) (n=201), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. The tablets are available as follows:

| | TABLET STRENGTH | | | | | |
|---|---|---|---|---|---|---|
| | 2.5 mg | 5 mg | 7.5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4112 | 4115 | 4116 | 4117 | 4415 | 4420 |
| Identification | LILLY 4112 | LILLY 4115 | LILLY 4116 | LILLY 4117 | LILLY 4415 | LILLY 4420 |
| NDC Codes: | | | | | | |
| Bottles 30 | NDC 0002-4112-30 | NDC 0002-4115-30 | NDC 0002-4116-30 | NDC 0002-4117-30 | NDC 0002-4415-30 | NDC 0002-4420-30 |
| Blisters – ID[a] 100 | NDC 0002-4112-33 | NDC 0002-4115-33 | NDC 0002-4116-33 | NDC 0002-4117-33 | NDC 0002-4415-33 | NDC 0002-4420-33 |
| Bottles 1000 | NDC 0002-4112-04 | NDC 0002-4115-04 | NDC 0002-4116-04 | NDC 0002-4117-04 | NDC 0002-4415-04 | NDC 0002-4420-04 |

[a] Identi-Dose® (unit dose medication, Lilly).

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:

| ZYPREXA ZYDIS Tablets[a] | TABLET STRENGTH 5 mg | 10 mg | 15 mg | 20 mg |
|---|---|---|---|---|
| Tablet No. | 4453 | 4454 | 4455 | 4456 |
| Debossed | 5 | 10 | 15 | 20 |
| NDC Codes: | | | | |
| Dose Pack 30 (Child Resistant) | NDC 0002-4453-85 | NDC 0002-4454-85 | NDC 0002-4455-85 | NDC 0002-4456-85 |

ZYPREXA is a registered trademark of Eli Lilly and Company.

ZYDIS is a registered trademark of Catalent Pharma Solutions.

[a] ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Catalent Pharma Solutions, United Kingdom, SN5 8RU.

ZYPREXA IntraMuscular is available in:

NDC 0002-7597-01 (No. VL7597) – 10 mg vial (1s)

### 16.2 Storage and Handling

Store ZYPREXA tablets, ZYPREXA ZYDIS, and ZYPREXA IntraMuscular vials (before reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP] for up to 1 hour if necessary. *Discard any unused portion of reconstituted ZYPREXA IntraMuscular.* The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect ZYPREXA tablets and ZYPREXA ZYDIS from light and moisture. Protect ZYPREXA IntraMuscular from light, do not freeze.

## 17 PATIENT COUNSELING INFORMATION

*See FDA-approved Medication Guide for the oral formulations.*

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking ZYPREXA as monotherapy or in combination with fluoxetine. If you do not think you are getting better or have any concerns about your condition while taking ZYPREXA, call your doctor. When using ZYPREXA and fluoxetine in combination, also refer to the Patient Counseling Information section of the package insert for 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 ZYPREXA, and should counsel them in its appropriate use. A patient Medication Guide is available for ZYPREXA. 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. When using ZYPREXA and fluoxetine in combination, also refer to the Medication Guide for Symbyax.

### 17.2 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 an increased risk of death. Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with ZYPREXA had a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) compared with placebo.

ZYPREXA is not approved for elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*.

### 17.3 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 ZYPREXA. 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)]*.

### 17.4 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 who have diabetes should follow their doctor's instructions about how often to check their blood sugar while taking ZYPREXA *[see Warnings and Precautions (5.4)]*.

### 17.5 Hyperlipidemia

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

**17.6 Weight Gain**

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

**17.7 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 ZYPREXA, e.g., diazepam or alcohol *[see Warnings and Precautions (5.8) and Drug Interactions (7)]*. 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.

**17.8 Potential for Cognitive and Motor Impairment**

Because ZYPREXA 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 ZYPREXA therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

**17.9 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 (5.13)]*.

**17.10 Concomitant Medication**

Patients should be advised to inform their physicians if they are taking, or plan to take, Symbyax. Patients should also 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 *[see Drug Interactions (7)]*.

**17.11 Alcohol**

Patients should be advised to avoid alcohol while taking ZYPREXA *[see Drug Interactions (7)]*.

**17.12 Phenylketonurics**

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively) *[see Description (11)]*.

**17.13 Use in Specific Populations**

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

Nursing Mothers — Patients should be advised not to breast-feed an infant if they are taking ZYPREXA *[see Use in Specific Populations (8.3)]*.

Pediatric Use — ZYPREXA is indicated for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adolescents 13 to 17 years of age. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin, and hepatic transaminase levels. Patients should be counseled about the potential long-term risks associated with ZYPREXA and advised that these risks may lead them to consider other drugs first *[see Indications and Usage (1.1, 1.2)]*. Safety and effectiveness of ZYPREXA in patients under 13 years of age have not been established. Safety and effectiveness of ZYPREXA and fluoxetine in combination in patients <18 years of age have not been established *[see Warnings and Precautions (5.5, 5.6) and Use in Specific Populations (8.4)]*.

**17.14 Need for Comprehensive Treatment Program in Pediatric Patients**

ZYPREXA is indicated as an integral part of a total treatment program for pediatric patients with schizophrenia and bipolar disorder that may include other measures (psychological, educational, social) for patients with the disorder. Effectiveness and safety of ZYPREXA have not been established in pediatric patients less than 13 years of age. Atypical antipsychotics are not intended for use in the pediatric patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders. Appropriate educational placement is essential and psychosocial intervention is often helpful. The decision to prescribe atypical antipsychotic medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms *[see Indications and Usage (1.3)]*.

Literature revised Month DD, YYYY

**Eli Lilly and Company, Indianapolis, IN 46285, USA**

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**ZYPREXA (olanzapine) Tablet for Oral use**
**ZYPREXA ZYDIS (olanzapine) Tablet, Orally Disintegrating for Oral use**
**ZYPREXA IntraMuscular (olanzapine) Injection, Powder, For Solution for Intramuscular use**

**Initial U.S. Approval: 1996**

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

***See full prescribing information for complete boxed warning.***

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis. (5.1, 5.14, 17.2)**
  **When using ZYPREXA and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.**

### RECENT MAJOR CHANGES

| | |
|---|---|
| Indications and Usage: | |
| Schizophrenia (1.1) | 12/2009 |
| Bipolar I Disorder (Manic or Mixed Episodes) (1.2) | 12/2009 |
| Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder (1.3) | 12/2009 |
| ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania (1.4) | 12/2009 |
| Indications and Usage, *ZYPREXA and Fluoxetine in Combination:* | |
| Depressive Episodes Associated with Bipolar I Disorder (1.5) | 03/2009 |
| Treatment Resistant Depression (1.6) | 03/2009 |
| Dosage and Administration: | |
| Schizophrenia (2.1) | 12/2009 |
| Bipolar I Disorder (Manic or Mixed Episodes) (2.2) | 12/2009 |
| Dosage and Administration, *ZYPREXA and Fluoxetine in Combination:* | |
| Depressive Episodes Associated with Bipolar I Disorder (2.5) | 03/2009 |
| Treatment Resistant Depression (2.6) | 03/2009 |
| Warnings and Precautions: | |
| Hyperglycemia (5.4) | 03/2009 |
| Hyperlipidemia (5.5) | 03/2009 |
| Weight Gain (5.6) | 03/2009 |
| Leukopenia, Neutropenia, and Agranulocytosis (5.9) | 08/2009 |
| Use in Patients with Concomitant Illness (5.14) | 03/2009 |
| Hyperprolactinemia (5.15) | MM/2009 |
| Use in Combination with Fluoxetine, Lithium, or Valproate (5.16) | 03/2009 |
| Laboratory Tests (5.17) | 03/2009 |

### INDICATIONS AND USAGE

ZYPREXA® (olanzapine) is an atypical antipsychotic indicated:

*As oral formulation for the:*

- Treatment of schizophrenia. (1.1)
  - Adults: Efficacy was established in three clinical trials in patients with schizophrenia: two 6-week trials and one maintenance trial. (14.1)
  - Adolescents (ages 13-17): Efficacy was established in one 6-week trial in patients with schizophrenia (14.1). The increased potential (in adolescents compared with adults) for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first in adolescents. (1.1)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. (1.2)
  - Adults: Efficacy was established in three clinical trials in patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one maintenance trial. (14.2)
  - Adolescents (ages 13-17): Efficacy was established in one 3-week trial in patients with manic or mixed episodes associated with bipolar I disorder (14.2). The increased potential (in adolescents compared with adults) for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first in adolescents. (1.2)
- Medication therapy for pediatric patients with schizophrenia or bipolar I disorder should be undertaken only after a thorough diagnostic evaluation and with careful consideration of the potential risks. (1.3)
- Adjunct to valproate or lithium in the treatment of manic or mixed episodes associated with bipolar I disorder. (1.2)
  - Efficacy was established in two 6-week clinical trials in adults (14.2). Maintenance efficacy has not been systematically evaluated.

*As ZYPREXA IntraMuscular for the:*

- Treatment of acute agitation associated with schizophrenia and bipolar I mania. (1.4)
  - Efficacy was established in three 1-day trials in adults. (14.3)

*As ZYPREXA and Fluoxetine in Combination for the:*

- Treatment of depressive episodes associated with bipolar I disorder. (1.5)
  - Efficacy was established with Symbyax (olanzapine and fluoxetine in combination) in adults; refer to the product label for Symbyax.
- Treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode). (1.6)
  - Efficacy was established with Symbyax (olanzapine and fluoxetine in combination) in adults; refer to the product label for Symbyax.

### DOSAGE AND ADMINISTRATION

| | |
|---|---|
| Schizophrenia in adults (2.1) | Oral: Start at 5-10 mg once daily; Target: 10 mg/day within several days |
| Schizophrenia in adolescents (2.1) | Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day |
| Bipolar I Disorder (manic or mixed episodes) in adults (2.2) | Oral: Start at 10 or 15 mg once daily |
| Bipolar I Disorder (manic or mixed episodes) in adolescents (2.2) | Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day |
| Bipolar I Disorder (manic or mixed episodes) with lithium or valproate in adults (2.2) | Oral: Start at 10 mg once daily |
| Agitation associated with Schizophrenia and Bipolar I Mania in adults (2.4) | IM: 10 mg (5 mg or 7.5 mg when clinically warranted) Assess for orthostatic hypotension prior to subsequent dosing (max. 3 doses 2-4 hrs apart) |
| Depressive Episodes associated with Bipolar I Disorder in adults (2.5) | Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily |
| Treatment Resistant Depression in adults (2.6) | Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily |

- Lower starting dose recommended in debilitated or pharmacodynamically sensitive patients or patients with predisposition to hypotensive reactions, or with potential for slowed metabolism. (2.1)
- Olanzapine may be given without regard to meals. (2.1)

*ZYPREXA and Fluoxetine in Combination:*

- Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability. (2.5, 2.6)
- Olanzapine monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder or treatment resistant depression. (2.5, 2.6)
- Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated. (2.5, 2.6)

### DOSAGE FORMS AND STRENGTHS

- Tablets (not scored): 2.5, 5, 7.5, 10, 15, 20 mg (3)
- Orally Disintegrating Tablets (not scored): 5, 10, 15, 20 mg (3)

- Intramuscular Injection: 10 mg vial (3)

**----------CONTRAINDICATIONS----------**

- None with ZYPREXA monotherapy.
- When using ZYPREXA and fluoxetine in combination, also refer to the Contraindications section of the package insert for Symbyax®. (4)
- When using ZYPREXA in combination with lithium or valproate, refer to the Contraindications section of the package inserts for those products. (4)

**----------WARNINGS AND PRECAUTIONS----------**

- *Elderly Patients with Dementia-Related Psychosis:* Increased risk of death and increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack). (5.1)
- *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy; when using in combination with fluoxetine, also refer to the Boxed Warning and Warnings and Precautions sections of the package insert for Symbyax. (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 olanzapine 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)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate. (5.7)
- *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, cerebrovascular disease, and those conditions that could affect hemodynamic responses. (5.8)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Has been reported with antipsychotics, including ZYPREXA. Patients with a history of a clinically significant low white blood cell count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.9)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.11)
- *Potential for Cognitive and Motor Impairment:* Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery. (5.12)
- *Hyperprolactinemia:* May elevate prolactin levels. (5.15)
- *Use in Combination with Fluoxetine, Lithium or Valproate:* Also refer to the package inserts for Symbyax, lithium, or valproate. (5.16)
- *Laboratory Tests:* Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment. (5.17)

**----------ADVERSE REACTIONS----------**

Most common adverse reactions (≥5% and at least twice that for placebo) associated with:

*Oral Olanzapine Monotherapy:*

- Schizophrenia (Adults) – postural hypotension, constipation, weight gain, dizziness, personality disorder, akathisia (6.1)
- Schizophrenia (Adolescents) – sedation, weight increased, headache, increased appetite, dizziness, abdominal pain, pain in extremity, fatigue, dry mouth (6.1)
- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor (6.1)
- Manic or Mixed Episodes, Bipolar I Disorder (Adolescents) – sedation, weight increased, increased appetite, headache, fatigue, dizziness, dry mouth, abdominal pain, pain in extremity (6.1)

*Combination of ZYPREXA and Lithium or Valproate:*

- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia (6.1)

*ZYPREXA and Fluoxetine in Combination:* Also refer to the Adverse Reactions section of the package insert for Symbyax. (6)

*ZYPREXA IntraMuscular for Injection:*

- Agitation with Schizophrenia and Bipolar I Mania (Adults) – somnolence (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----------**

- *Diazepam:* May potentiate orthostatic hypotension. (7.1, 7.2)
- *Alcohol:* May potentiate orthostatic hypotension. (7.1)
- *Carbamazepine:* Increased clearance of olanzapine. (7.1)
- *Fluvoxamine:* May increase olanzapine levels. (7.1)
- *ZYPREXA and Fluoxetine in Combination:* Also refer to the Drug Interactions section of the package insert for Symbyax. (7.1)
- *CNS Acting Drugs:* Caution should be used when taken in combination with other centrally acting drugs and alcohol. (7.2)
- *Antihypertensive Agents:* Enhanced antihypertensive effect. (7.2)
- *Levodopa and Dopamine Agonists:* May antagonize levodopa/dopamine agonists. (7.2)
- *Lorazepam (IM):* Increased somnolence with IM olanzapine. (7.2)
- *Other Concomitant Drug Therapy:* When using olanzapine in combination with lithium or valproate, refer to the Drug Interactions sections of the package insert for those products. (7.2)

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

- *Pregnancy:* ZYPREXA 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 ZYPREXA in children <13 years of age have not been established. (8.4)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide**

**Revised: MM/YYYY**

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*Sections or subsections omitted from the full prescribing information are not listed

## FULL PRESCRIBING INFORMATION

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1, 5.14) and Patient Counseling Information (17.2)]*.**

**When using ZYPREXA and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.**

## 1 INDICATIONS AND USAGE

### 1.1 Schizophrenia

Oral ZYPREXA is indicated for the treatment of schizophrenia. Efficacy was established in three clinical trials in adult patients with schizophrenia: two 6-week trials and one maintenance trial. In adolescent patients with schizophrenia (ages 13-17), efficacy was established in one 6-week trial *[see Clinical Studies (14.1)]*.

When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Warnings and Precautions (5.5, 5.6)]*.

### 1.2 Bipolar I Disorder (Manic or Mixed Episodes)

Monotherapy — Oral ZYPREXA is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. Efficacy was established in three clinical trials in adult patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one monotherapy maintenance trial. In adolescent patients with manic or mixed episodes associated with bipolar I disorder (ages 13-17), efficacy was established in one 3-week trial *[see Clinical Studies (14.2)]*.

When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Warnings and Precautions (5.5, 5.6)]*.

Adjunctive Therapy to Lithium or Valproate — Oral ZYPREXA is indicated for the treatment of manic or mixed episodes associated with bipolar I disorder as an adjunct to lithium or valproate. Efficacy was established in two 6-week clinical trials in adults. The effectiveness of adjunctive therapy for longer-term use has not been systematically evaluated in controlled trials *[see Clinical Studies (14.2)]*.

### 1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder

Pediatric schizophrenia and bipolar I disorder are serious mental disorders; however, diagnosis can be challenging. For pediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, pediatric patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for pediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment for both pediatric schizophrenia and bipolar I disorder should be part of a total treatment program that often includes psychological, educational and social interventions.

### 1.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania

ZYPREXA IntraMuscular is indicated for the treatment of acute agitation associated with schizophrenia and bipolar I mania.

Efficacy was demonstrated in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients with: schizophrenia or bipolar I disorder (manic or mixed episodes) *[see Clinical Studies (14.3)]*.

"Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

### 1.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder

Oral ZYPREXA and fluoxetine in combination is indicated for the treatment of depressive episodes associated with bipolar I disorder, based on clinical studies in adult patients. When using ZYPREXA and fluoxetine in combination, refer to the Clinical Studies section of the package insert for Symbyax.

ZYPREXA monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

### 1.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

Oral ZYPREXA and fluoxetine in combination is indicated for the treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode), based on clinical studies in adult patients. When using ZYPREXA and fluoxetine in combination, refer to the Clinical Studies section of the package insert for Symbyax.

ZYPREXA monotherapy is not indicated for the treatment of treatment resistant depression.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Schizophrenia

**Adults**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical assessment. Olanzapine is not indicated for use in doses above 20 mg/day.

Dosing in Special Populations — The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*. When indicated, dose escalation should be performed with caution in these patients.

Maintenance Treatment — The effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for relapse has been

demonstrated in a placebo-controlled trial *[see Clinical Studies (14.1)]*. The physician who elects to use ZYPREXA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

**Adolescents**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents with schizophrenia was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 12.5 mg/day (mean dose of 11.1 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended.

The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials *[see Clinical Studies (14.1)]*.

Maintenance Treatment — The efficacy of ZYPREXA for the maintenance treatment of schizophrenia in the adolescent population has not been systematically evaluated; however, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

## 2.2 Bipolar I Disorder (Manic or Mixed Episodes)

**Adults**

Dose Selection for Monotherapy — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials *[see Clinical Studies (14.2)]*.

Maintenance Monotherapy — The benefit of maintaining bipolar I patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of 2 weeks, was demonstrated in a controlled trial *[see Clinical Studies (14.2)]*. The physician who elects to use ZYPREXA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Dose Selection for Adjunctive Treatment — When administered as adjunctive treatment to lithium or valproate, oral olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals.

Antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials *[see Clinical Studies (14.2)]*. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

**Adolescents**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents with bipolar I disorder (manic or mixed episodes) was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 10.7 mg/day (mean dose of 8.9 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended.

The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials *[see Clinical Studies (14.2)]*.

Maintenance Treatment — The efficacy of ZYPREXA for the maintenance treatment of bipolar I disorder in the adolescent population has not been evaluated; however, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

## 2.3 Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)

After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

## 2.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania

Dose Selection for Agitated Adult Patients with Schizophrenia and Bipolar I Mania — The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant *[see Clinical Studies (14.3)]*. If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., 3 doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension *[see Warnings and Precautions (5.8)]*. Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended.

If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate *[see Dosage and Administration (2.1, 2.2)]*.

Intramuscular Dosing in Special Populations — A dose of 5 mg/injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg/injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

Administration of ZYPREXA IntraMuscular — ZYPREXA IntraMuscular is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for Preparation of ZYPREXA IntraMuscular with Sterile Water for Injection — Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. ZYPREXA IntraMuscular reconstituted with Sterile Water for Injection should be used immediately (within 1 hour) after reconstitution. *Discard any unused portion.*

The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

| Dose, mg Olanzapine | Volume of Injection, mL |
|---|---|
| 10 | Withdraw total contents of vial |
| 7.5 | 1.5 |
| 5 | 1 |
| 2.5 | 0.5 |

Physical Incompatibility Information — ZYPREXA IntraMuscular should be reconstituted only with Sterile Water for Injection. ZYPREXA IntraMuscular should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed. Lorazepam injection should not be used to reconstitute ZYPREXA IntraMuscular as this combination results in a delayed reconstitution time. ZYPREXA IntraMuscular should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

### 2.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 12.5 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was demonstrated with ZYPREXA and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg.

Safety and efficacy of ZYPREXA and fluoxetine in combination was determined in clinical trials supporting approval of Symbyax (fixed dose combination of ZYPREXA and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. The following table demonstrates the appropriate individual component doses of ZYPREXA and fluoxetine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

**Table 1: Approximate Dose Correspondence Between Symbyax[a] and the Combination of ZYPREXA and Fluoxetine**

| For | Use in Combination | |
|---|---|---|
| Symbyax (mg/day) | ZYPREXA (mg/day) | Fluoxetine (mg/day) |
| 3 mg olanzapine/25 mg fluoxetine | 2.5 | 20 |
| 6 mg olanzapine/25 mg fluoxetine | 5 | 20 |
| 12 mg olanzapine/25 mg fluoxetine | 10+2.5 | 20 |
| 6 mg olanzapine/50 mg fluoxetine | 5 | 40+10 |
| 12 mg olanzapine/50 mg fluoxetine | 10+2.5 | 40+10 |

[a] Symbyax (olanzapine/fluoxetine HCl) is a fixed-dose combination of ZYPREXA and fluoxetine.

While there is no body of evidence to answer the question of how long a patient treated with ZYPREXA and fluoxetine in combination 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.

Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

ZYPREXA monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

### 2.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 20 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was demonstrated with olanzapine and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 18 mg and fluoxetine 25 to 50 mg.

Safety and efficacy of olanzapine in combination with fluoxetine was determined in clinical trials supporting approval of Symbyax (fixed dose combination of olanzapine and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. Table 1 above demonstrates the appropriate individual component doses of ZYPREXA and fluoxetine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

While there is no body of evidence to answer the question of how long a patient treated with ZYPREXA and fluoxetine in combination 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.

Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

ZYPREXA monotherapy is not indicated for treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode).

### 2.7 ZYPREXA and Fluoxetine in Combination: 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. 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. ZYPREXA 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 (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

## 3 DOSAGE FORMS AND STRENGTHS

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. Tablets are not scored. The tablets are available as follows:

| | TABLET STRENGTH | | | | | |
|---|---|---|---|---|---|---|
| | 2.5 mg | 5 mg | 7.5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. Identification | 4112 LILLY 4112 | 4115 LILLY 4115 | 4116 LILLY 4116 | 4117 LILLY 4117 | 4415 LILLY 4415 | 4420 LILLY 4420 |

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. Tablets are not scored. The tablets are available as follows:

| | TABLET STRENGTH | | | |
|---|---|---|---|---|
| ZYPREXA ZYDIS Tablets | 5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4453 | 4454 | 4455 | 4456 |
| Debossed | 5 | 10 | 15 | 20 |

ZYPREXA IntraMuscular is available in 10 mg vial (1s).

## 4 CONTRAINDICATIONS

- None with ZYPREXA monotherapy.
- When using ZYPREXA and fluoxetine in combination, also refer to the Contraindications section of the package insert for Symbyax.
- For specific information about the contraindications of lithium or valproate, refer to the Contraindications section of the package inserts for these other products.

## 5 WARNINGS AND PRECAUTIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Warnings and Precautions section of the package insert for Symbyax.

### 5.1 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. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.14), and Patient Counseling Information (17.2)]*.**

In 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 is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Patient Counseling Information (17.2)]*.

### 5.2 Suicide

The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

### 5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (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 a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported *[see Patient Counseling Information (17.3)]*.

### 5.4 Hyperglycemia

Physicians should consider the risks and benefits when prescribing olanzapine 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 olanzapine should be monitored regularly for worsening of glucose control. Patients starting treatment with olanzapine 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 (17.4)]*.

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. 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.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with a median treatment duration of approximately 3 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). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (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, and/or a baseline fasting glucose

level ≥126 mg/dL). Olanzapine-treated patients had a greater mean HbA1c increase from baseline of 0.04% (median exposure 21 days), compared to a mean HbA1c decrease of 0.06% in placebo-treated subjects (median exposure 17 days).

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). Table 2 shows short-term and long-term changes in fasting glucose levels from adult olanzapine monotherapy studies.

**Table 2: Changes in Fasting Glucose Levels from Adult Olanzapine Monotherapy 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** |
| Fasting Glucose | Normal to High (<100 mg/dL to ≥126 mg/dL) | Olanzapine | 543 | 2.2% | 345 | 12.8% |
| | | Placebo | 293 | 3.4% | NA[a] | NA[a] |
| | Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL) | Olanzapine | 178 | 17.4% | 127 | 26.0% |
| | | Placebo | 96 | 11.5% | NA[a] | NA[a] |

[a] Not Applicable.

The mean change in fasting glucose for 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 have not been established in patients under the age of 13 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 versus -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 exposure | | At least 24 weeks exposure | |
|---|---|---|---|---|---|---|
| **Laboratory Analyte** | **Category Change (at least once) from Baseline** | **Treatment Arm** | **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 olanzapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using olanzapine, is recommended *[see Patient Counseling Information (17.5)]*.

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

Olanzapine Monotherapy in Adults — 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, or patients with high baseline lipid levels.

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. 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 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 4 shows categorical changes in fasting lipids values.

**Table 4: Changes in Fasting Lipids Values from Adult Olanzapine Monotherapy 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** |
| Fasting Triglycerides | Increase by ≥50 mg/dL | Olanzapine | 745 | 39.6% | 487 | 61.4% |
| | | Placebo | 402 | 26.1% | NA[a] | NA[a] |
| | 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] |
| | | | | | | |
| Fasting Total Cholesterol | Increase by ≥40 mg/dL | Olanzapine | 745 | 21.6% | 489 | 32.9% |
| | | Placebo | 402 | 9.5% | NA[a] | NA[a] |
| | 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] |
| | | | | | | |
| Fasting LDL Cholesterol | Increase by ≥30 mg/dL | Olanzapine | 536 | 23.7% | 483 | 39.8% |
| | | Placebo | 304 | 14.1% | NA[a] | NA[a] |
| | 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 mean increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 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 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 5 shows categorical changes in fasting lipids values in adolescents.

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

| | | | Up to 6 weeks exposure | | At least 24 weeks exposure | |
|---|---|---|---|---|---|---|
| **Laboratory Analyte** | **Category Change (at least once) from Baseline** | **Treatment Arm** | **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 (≥90 mg/dL and ≤130 mg/dL to >130 mg/dL) | Olanzapine | 37 | 59.5% | 31 | 64.5% |
| | | 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 olanzapine. Patients receiving olanzapine should receive regular monitoring of weight *[see Patient Counseling Information (17.6)]*.

Olanzapine Monotherapy in Adults — In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg (5.7 lb) compared to an average 0.3 kg (0.6 lb) weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, compared to 3% of placebo-treated patients, with a median exposure of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 0.3% of placebo-treated patients, with a median exposure of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in 0% of placebo-treated patients.

In long-term 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 6 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 6: 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 have not been established in patients under the age of 13 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 7: 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 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 8 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 8: 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 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.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

For specific information about the warnings of lithium or valproate, refer to the Warnings section of the package inserts for these other products.

### 5.8 Orthostatic Hypotension

Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its $\alpha_1$-adrenergic antagonistic properties *[see Patient Counseling Information (17.7)]*.

For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD *[see Dosage and Administration (2)]*. A more gradual titration to the target dose should be considered if hypotension occurs.

Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in nonagitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥30 mmHg) *[see Dosage and Administration (2.4)]*. Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the reactions occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. For intramuscular olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation.

Olanzapine 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, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression *[see Drug Interactions (7)]*. Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine has not been studied and is therefore not recommended. If use of intramuscular olanzapine in combination with parenteral benzodiazepines is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

**5.9 Leukopenia, Neutropenia, and Agranulocytosis**

Class Effect — In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including ZYPREXA. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm$^3$) should discontinue ZYPREXA and have their WBC followed until recovery.

**5.10 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. Olanzapine is not approved for the treatment of patients with Alzheimer's disease.

**5.11 Seizures**

During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine 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. Olanzapine 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 or older.

**5.12 Potential for Cognitive and Motor Impairment**

Somnolence was a commonly reported adverse reaction associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse reaction was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine 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 olanzapine therapy does not affect them adversely *[see Patient Counseling Information (17.8)]*.

**5.13 Body Temperature Regulation**

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine 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 (17.9)]*.

**5.14 Use in Patients with Concomitant Illness**

Clinical experience with olanzapine in patients with certain concomitant systemic illnesses is limited *[see Clinical Pharmacology (12.3)]*.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with olanzapine, olanzapine 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 discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or 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 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 (5.1), and Patient Counseling Information (17.2)]*.

Olanzapine 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 premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients *[see Warnings and Precautions (5.8)]*.

**5.15 Hyperprolactinemia**

As with other drugs that antagonize dopamine $D_2$ receptors, olanzapine elevates prolactin levels, and the elevation persists during chronic 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 which 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 placebo-controlled olanzapine clinical studies (up to 12 weeks), changes from normal to high in prolactin concentrations were observed in 30% of adults treated with olanzapine as compared to 10.5% of adults treated with placebo. In a pooled analysis from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestations included menstrual-related events[1] (2% [49/3240] of females), sexual function-related events[2] (2% [150/8136] of females and males), and breast-related events[3] (0.7% [23/3240] of females, 0.2% [9/4896] of males).

In placebo-controlled olanzapine monotherapy studies in adolescent patients (up to 6 weeks) with schizophrenia or bipolar I disorder (manic or mixed episodes), changes from normal to high in prolactin concentrations were observed in 47% of olanzapine-treated patients compared to 7% of placebo-treated patients. In a pooled analysis from clinical trials including 454 adolescents treated with olanzapine, potentially associated clinical manifestations included menstrual-related events[1] (1% [2/168] of females), sexual function-related events[2] (0.7% [3/454] of females and males), and breast-related events[3] (2% [3/168] of females, 2% [7/286] of males) *[see Use in Specific Populations (8.4)]*.

[1] Based on a search of the following terms: Menstrual-related events include amenorrhoea, hypomenorrhoea, menstruation delayed and oligomenorrhoea.

[2] Based on a search of the following terms: Sexual function-related events include anorgasmia, delayed ejaculation, erectile dysfunction, decreased libido, loss of libido, abnormal orgasm and sexual dysfunction.

[3] Based on a search of the following terms: breast-related events include breast discharge, enlargement or swelling, galactorrhoea, gynaecomastia, and lactation disorder.

### 5.16 Use in Combination with Fluoxetine, Lithium, or Valproate

When using ZYPREXA and fluoxetine in combination, the prescriber should also refer to the Warnings and Precautions section of the package insert for Symbyax. When using ZYPREXA in combination with lithium or valproate, the prescriber should refer to the Warnings and Precautions sections of the package inserts for lithium or valproate *[see Drug Interactions (7)]*.

### 5.17 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 (17.4, 17.5)]*.

## 6 ADVERSE REACTIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Adverse Reactions section of the package insert for Symbyax.

### 6.1 Clinical Trials Experience

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.

**Clinical Trials in Adults**

The information below for olanzapine is derived from a clinical trial database for olanzapine consisting of 8661 adult patients with approximately 4165 patient-years of exposure to oral olanzapine and 722 patients with exposure to intramuscular olanzapine for injection. This database includes: (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine premarketing bipolar I disorder (manic or mixed episodes) trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5788 patients from 88 additional oral olanzapine clinical trials as of December 31, 2001; and (5) 722 patients who participated in intramuscular olanzapine for injection premarketing trials in agitated patients with schizophrenia, bipolar I disorder (manic or mixed episodes), or dementia. In addition, information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar I disorder (manic or mixed episodes) trials with approximately 22 patient-years of exposure, is included below.

The conditions and duration of treatment with olanzapine 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 longer-term

exposure. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse reactions, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar I disorder (manic or mixed episodes) or agitation. However, this information is also generally applicable to bipolar I disorder (manic or mixed episodes) and agitation.

Adverse reactions during exposure were obtained by spontaneous report and recorded by clinical investigators using 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 smaller number of standardized reaction categories. In the tables and tabulations that follow, MedDRA and COSTART Dictionary terminology has been used to classify reported adverse reactions.

The stated frequencies of adverse reactions 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. The reported reactions do not include those reaction terms that were so general as to be uninformative. Reactions listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the reactions occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

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 trials. 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 physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reactions incidence in the population studied.

Incidence of Adverse Reactions in Short-Term, Placebo-Controlled and Combination Trials

The following findings are based on premarketing trials of (1) oral olanzapine for schizophrenia, bipolar I disorder (manic or mixed episodes), a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease, and premarketing combination trials, and (2) intramuscular olanzapine for injection in agitated patients with schizophrenia or bipolar I mania.

*Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials*

Schizophrenia — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (5% for oral olanzapine vs 6% for placebo). However, discontinuations due to increases in ALT were considered to be drug related (2% for oral olanzapine vs 0% for placebo).

Bipolar I Disorder (Manic or Mixed Episodes) Monotherapy — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (2% for oral olanzapine vs 2% for placebo).

Agitation — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (0.4% for intramuscular olanzapine for injection vs 0% for placebo).

*Adverse Reactions Associated with Discontinuation of Treatment in Short-Term Combination Trials*

Bipolar I Disorder (Manic or Mixed Episodes), Olanzapine as Adjunct to Lithium or Valproate — In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 11% for the combination of oral olanzapine with lithium or valproate compared to 2% for patients who remained on lithium or valproate monotherapy. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and peripheral edema (1%).

*Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials*

The most commonly observed adverse reactions associated with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

**Table 9: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Trials — SCHIZOPHRENIA**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine (N=248)** | **Placebo (N=118)** |
| Postural hypotension | 5 | 2 |
| Constipation | 9 | 3 |
| Weight gain | 6 | 1 |
| Dizziness | 11 | 4 |
| Personality disorder[a] | 8 | 4 |
| Akathisia | 5 | 1 |

[a] Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.

**Table 10: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 3-Week and 4-Week Trials — Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine (N=125)** | **Placebo (N=129)** |
| Asthenia | 15 | 6 |
| Dry mouth | 22 | 7 |
| Constipation | 11 | 5 |
| Dyspepsia | 11 | 5 |
| Increased appetite | 6 | 3 |
| Somnolence | 35 | 13 |
| Dizziness | 18 | 6 |
| Tremor | 6 | 3 |

Olanzapine Intramuscular — There was 1 adverse reaction (somnolence) observed at an incidence of 5% or greater among intramuscular olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar I mania was 6% for intramuscular olanzapine for injection and 3% for placebo.

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term, Placebo-Controlled Trials*

Table 11 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with oral olanzapine (doses ≥2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

**Table 11: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials with Oral Olanzapine**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Body System/Adverse Reaction** | **Olanzapine (N=532)** | **Placebo (N=294)** |
| **Body as a Whole** | | |
| Accidental injury | 12 | 8 |
| Asthenia | 10 | 9 |
| Fever | 6 | 2 |
| Back pain | 5 | 2 |
| Chest pain | 3 | 1 |
| **Cardiovascular System** | | |
| Postural hypotension | 3 | 1 |
| Tachycardia | 3 | 1 |
| Hypertension | 2 | 1 |
| **Digestive System** | | |
| Dry mouth | 9 | 5 |
| Constipation | 9 | 4 |
| Dyspepsia | 7 | 5 |
| Vomiting | 4 | 3 |
| Increased appetite | 3 | 2 |
| **Hemic and Lymphatic System** | | |
| Ecchymosis | 5 | 3 |
| **Metabolic and Nutritional Disorders** | | |
| Weight gain | 5 | 3 |
| Peripheral edema | 3 | 1 |
| **Musculoskeletal System** | | |
| Extremity pain (other than joint) | 5 | 3 |
| Joint pain | 5 | 3 |
| **Nervous System** | | |
| Somnolence | 29 | 13 |
| Insomnia | 12 | 11 |
| Dizziness | 11 | 4 |
| Abnormal gait | 6 | 1 |

| | | |
|---|---|---|
| Tremor | 4 | 3 |
| Akathisia | 3 | 2 |
| Hypertonia | 3 | 2 |
| Articulation impairment | 2 | 1 |
| **Respiratory System** | | |
| Rhinitis | 7 | 6 |
| Cough increased | 6 | 3 |
| Pharyngitis | 4 | 3 |
| **Special Senses** | | |
| Amblyopia | 3 | 2 |
| **Urogenital System** | | |
| Urinary incontinence | 2 | 1 |
| Urinary tract infection | 2 | 1 |

*Commonly Observed Adverse Reactions in Short-Term Trials of Oral Olanzapine as Adjunct to Lithium or Valproate*

In the bipolar I disorder (manic or mixed episodes) adjunct placebo-controlled trials, the most commonly observed adverse reactions associated with the combination of olanzapine and lithium or valproate (incidence of ≥5% and at least twice placebo) were:

**Table 12: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Adjunct to Lithium or Valproate Trials — Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine with lithium or valproate (N=229)** | **Placebo with lithium or valproate (N=115)** |
| Dry mouth | 32 | 9 |
| Weight gain | 26 | 7 |
| Increased appetite | 24 | 8 |
| Dizziness | 14 | 7 |
| Back pain | 8 | 4 |
| Constipation | 8 | 4 |
| Speech disorder | 7 | 1 |
| Increased salivation | 6 | 2 |
| Amnesia | 5 | 2 |
| Paresthesia | 5 | 2 |

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term Trials of Olanzapine as Adjunct to Lithium or Valproate*

Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

**Table 13: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials of Oral Olanzapine as Adjunct to Lithium or Valproate**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Body System/Adverse Reaction** | **Olanzapine with lithium or valproate (N=229)** | **Placebo with lithium or valproate (N=115)** |
| **Body as a Whole** | | |
| Asthenia | 18 | 13 |
| Back pain | 8 | 4 |
| Accidental injury | 4 | 2 |
| Chest pain | 3 | 2 |
| **Cardiovascular System** | | |
| Hypertension | 2 | 1 |
| **Digestive System** | | |
| Dry mouth | 32 | 9 |
| Increased appetite | 24 | 8 |
| Thirst | 10 | 6 |
| Constipation | 8 | 4 |
| Increased salivation | 6 | 2 |

| | | |
|---|---|---|
| **Metabolic and Nutritional Disorders** | | |
| Weight gain | 26 | 7 |
| Peripheral edema | 6 | 4 |
| Edema | 2 | 1 |
| **Nervous System** | | |
| Somnolence | 52 | 27 |
| Tremor | 23 | 13 |
| Depression | 18 | 17 |
| Dizziness | 14 | 7 |
| Speech disorder | 7 | 1 |
| Amnesia | 5 | 2 |
| Paresthesia | 5 | 2 |
| Apathy | 4 | 3 |
| Confusion | 4 | 1 |
| Euphoria | 3 | 2 |
| Incoordination | 2 | 0 |
| **Respiratory System** | | |
| Pharyngitis | 4 | 1 |
| Dyspnea | 3 | 1 |
| **Skin and Appendages** | | |
| Sweating | 3 | 1 |
| Acne | 2 | 0 |
| Dry skin | 2 | 0 |
| **Special Senses** | | |
| Amblyopia | 9 | 5 |
| Abnormal vision | 2 | 0 |
| **Urogenital System** | | |
| Dysmenorrhea[a] | 2 | 0 |
| Vaginitis[a] | 2 | 0 |

[a] Denominator used was for females only (olanzapine, N=128; placebo, N=51).

For specific information about the adverse reactions observed with lithium or valproate, refer to the Adverse Reactions section of the package inserts for these other products.

*Adverse Reactions Occurring at an Incidence of 1% or More among Intramuscular Olanzapine for Injection-Treated Patients in Short-Term, Placebo-Controlled Trials*

Table 14 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 1% or more of patients treated with intramuscular olanzapine for injection (dose range of 2.5-10 mg/injection) and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar I mania.

**Table 14: Treatment-Emergent Adverse Reactions: Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trials with Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia or Bipolar I Mania**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Body System/Adverse Reaction** | **Olanzapine (N=415)** | **Placebo (N=150)** |
| **Body as a Whole** | | |
| Asthenia | 2 | 1 |
| **Cardiovascular System** | | |
| Hypotension | 2 | 0 |
| Postural hypotension | 1 | 0 |
| **Nervous System** | | |
| Somnolence | 6 | 3 |
| Dizziness | 4 | 2 |
| Tremor | 1 | 0 |

**Additional Findings Observed in Clinical Trials**

Dose Dependency of Adverse Reactions in Short-Term, Placebo-Controlled Trials

*Extrapyramidal Symptoms:* The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

**Table 15: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | Placebo | Olanzapine 5 ± 2.5 mg/day | Olanzapine 10 ± 2.5 mg/day | Olanzapine 15 ± 2.5 mg/day |
| Parkinsonism[a] | 15 | 14 | 12 | 14 |
| Akathisia[b] | 23 | 16 | 19 | 27 |

[a] Percentage of patients with a Simpson-Angus Scale total score >3.

[b] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

**Table 16: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | Placebo (N=68) | Olanzapine 5 ± 2.5 mg/day (N=65) | Olanzapine 10 ± 2.5 mg/day (N=64) | Olanzapine 15 ± 2.5 mg/day (N=69) |
| Dystonic events[a] | 1 | 3 | 2 | 3 |
| Parkinsonism events[b] | 10 | 8 | 14 | 20 |
| Akathisia events[c] | 1 | 5 | 11 | 10 |
| Dyskinetic events[d] | 4 | 0 | 2 | 1 |
| Residual events[e] | 1 | 2 | 5 | 1 |
| Any extrapyramidal event | 16 | 15 | 25 | 32 |

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[c] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[e] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

The following table enumerates the percentage of adolescent patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy (dose range: 2.5 to 20 mg/day).

**Table 17: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in Placebo-Controlled Clinical Trials of Oral Olanzapine in Schizophrenia and Bipolar I Disorder — Adolescents**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| Categories[a] | Placebo (N=89) | Olanzapine (N=179) |
| Dystonic events | 0 | 1 |
| Parkinsonism events | 2 | 1 |
| Akathisia events | 4 | 6 |
| Dyskinetic events | 0 | 1 |
| Nonspecific events | 0 | 4 |
| Any extrapyramidal event | 6 | 10 |

[a] Categories are based on Standard MedDRA Queries (SMQ) for extrapyramidal symptoms as defined in MedDRA version 12.0.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with placebo in agitation. Patients in each dose group could receive up to 3 injections during the trials *[see Clinical Studies (14.3)]*. Patient assessments were conducted during the 24 hours following the initial dose of intramuscular olanzapine for injection.

**Table 18: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia**

| | Percentage of Patients Reporting Event | | | | |
|---|---|---|---|---|---|
| | Placebo | Olanzapine IM 2.5 mg | Olanzapine IM 5 mg | Olanzapine IM 7.5 mg | Olanzapine IM 10 mg |
| Parkinsonism[a] | 0 | 0 | 0 | 0 | 3 |
| Akathisia[b] | 0 | 0 | 5 | 0 | 0 |

[a] Percentage of patients with a Simpson-Angus Scale total score >3.

[b] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions in the same controlled clinical trial comparing fixed doses of intramuscular olanzapine for injection with placebo in agitated patients with schizophrenia.

**Table 19: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia**

| | Percentage of Patients Reporting Event | | | | |
|---|---|---|---|---|---|
| | Placebo (N=45) | Olanzapine IM 2.5 mg (N=48) | Olanzapine IM 5 mg (N=45) | Olanzapine IM 7.5 mg (N=46) | Olanzapine IM 10 mg (N=46) |
| Dystonic events[a] | 0 | 0 | 0 | 0 | 0 |
| Parkinsonism events[b] | 0 | 4 | 2 | 0 | 0 |
| Akathisia events[c] | 0 | 2 | 0 | 0 | 0 |
| Dyskinetic events[d] | 0 | 0 | 0 | 0 | 0 |
| Residual events[e] | 0 | 0 | 0 | 0 | 0 |
| Any extrapyramidal events | 0 | 4 | 2 | 0 | 0 |

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[c] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[e] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

*Dystonia, Class Effect:* 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 olanzapine use.

*Other Adverse Reactions:* The following table addresses dose relatedness for other adverse reactions using data from a schizophrenia trial involving fixed dosage ranges of oral olanzapine. It enumerates the percentage of patients with treatment-emergent adverse reactions for the 3 fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse reactions for which there was a trend.

**Table 20: Percentage of Patients from a Schizophrenia Trial with Treatment-Emergent Adverse Reactions for the 3 Dose Range Groups and Placebo**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| Adverse Reaction | Placebo (N=68) | Olanzapine 5 ± 2.5 mg/day (N=65) | Olanzapine 10 ± 2.5 mg/day (N=64) | Olanzapine 15 ± 2.5 mg/day (N=69) |
| Asthenia | 15 | 8 | 9 | 20 |
| Dry mouth | 4 | 3 | 5 | 13 |
| Nausea | 9 | 0 | 2 | 9 |
| Somnolence | 16 | 20 | 30 | 39 |
| Tremor | 3 | 0 | 5 | 7 |

Differences among Fixed-Dose Groups 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 oral olanzapine in patients with schizophrenia or schizoaffective disorder, 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/mL (female) or >18.77 ng/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 During the Clinical Trial Evaluation of Oral Olanzapine

Following is a list of treatment-emergent adverse reactions reported by patients treated with oral olanzapine (at multiple doses ≥1 mg/day) 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; rare reactions are those occurring in fewer than 1/1000 patients.

**Body as a Whole** — *Infrequent:* chills, face edema, photosensitivity reaction, suicide attempt[1]; *Rare:* chills and fever, hangover effect, sudden death[1].

**Cardiovascular System** — *Infrequent:* cerebrovascular accident, vasodilatation.

**Digestive System** — *Infrequent:* nausea and vomiting, tongue edema; *Rare:* ileus, intestinal obstruction, liver fatty deposit.

**Hemic and Lymphatic System** — *Infrequent:* leukopenia, thrombocytopenia.

**Metabolic and Nutritional Disorders** — *Infrequent:* alkaline phosphatase increased, bilirubinemia, hypoproteinemia.

**Musculoskeletal System** — *Rare:* osteoporosis.

**Nervous System** — *Infrequent:* ataxia, dysarthria, libido decreased, stupor; *Rare:* coma.

**Respiratory System** — *Infrequent:* epistaxis; *Rare:* lung edema.

**Skin and Appendages** — *Infrequent:* alopecia.

**Special Senses** — *Infrequent:* abnormality of accommodation, dry eyes; *Rare:* mydriasis.

**Urogenital System** — *Infrequent:* amenorrhea[2], breast pain, decreased menstruation, impotence[2], increased menstruation[2], menorrhagia[2], metrorrhagia[2], polyuria[2], urinary frequency, urinary retention, urinary urgency, urination impaired.

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

[2] Adjusted for gender.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Intramuscular Olanzapine for Injection

Following is a list of treatment-emergent adverse reactions reported by patients treated with intramuscular olanzapine for injection (at 1 or more doses ≥2.5 mg/injection) 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) for 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.

**Body as a Whole** — *Frequent:* injection site pain.

**Cardiovascular System** — *Infrequent:* syncope.

**Digestive System** — *Infrequent:* nausea.

**Metabolic and Nutritional Disorders** — *Infrequent:* creatine phosphokinase increased.

Clinical Trials in Adolescent Patients (age 13 to 17 years)

*Commonly Observed Adverse Reactions in Oral Olanzapine Short-Term, Placebo-Controlled Trials*

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 5% or more and reported at least twice as frequently as placebo-treated patients are listed in Table 21.

**Table 21: Treatment-Emergent Adverse Reactions of ≥5% Incidence among Adolescents (13-17 Years Old) with Schizophrenia or Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | 6 Week Trial % Schizophrenia Patients | | 3 Week Trial % Bipolar Patients | |
| Adverse Reactions | Olanzapine (N=72) | Placebo (N=35) | Olanzapine (N=107) | Placebo (N=54) |
| Sedation[a] | 39 | 9 | 48 | 9 |
| Weight increased | 31 | 9 | 29 | 4 |

| | | | | |
|---|---|---|---|---|
| Headache | 17 | 6 | 17 | 17 |
| Increased appetite | 17 | 9 | 29 | 4 |
| Dizziness | 8 | 3 | 7 | 2 |
| Abdominal pain[b] | 6 | 3 | 6 | 7 |
| Pain in extremity | 6 | 3 | 5 | 0 |
| Fatigue | 3 | 3 | 14 | 6 |
| Dry mouth | 4 | 0 | 7 | 0 |

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.

[b] Patients with the following MedDRA terms were counted in this category: abdominal pain, abdominal pain lower, abdominal pain upper.

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term (3-6 weeks), Placebo-Controlled Trials*

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 2% or more and greater than placebo are listed in Table 22.

**Table 22: Treatment-Emergent Adverse Reactions of ≥2% Incidence among Adolescents (13-17 Years Old) (Combined Incidence from Short-Term, Placebo-Controlled Clinical Trials of Schizophrenia or Bipolar I Disorder [Manic or Mixed Episodes])**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine (N=179)** | **Placebo (N=89)** |
| Sedation[a] | 44 | 9 |
| Weight increased | 30 | 6 |
| Increased appetite | 24 | 6 |
| Headache | 17 | 12 |
| Fatigue | 9 | 4 |
| Dizziness | 7 | 2 |
| Dry mouth | 6 | 0 |
| Pain in extremity | 5 | 1 |
| Constipation | 4 | 0 |
| Nasopharyngitis | 4 | 2 |
| Diarrhea | 3 | 0 |
| Restlessness | 3 | 2 |
| Liver enzymes increased[b] | 8 | 1 |
| Dyspepsia | 3 | 1 |
| Epistaxis | 3 | 0 |
| Respiratory tract infection[c] | 3 | 2 |
| Sinusitis | 3 | 0 |
| Arthralgia | 2 | 0 |
| Musculoskeletal stiffness | 2 | 0 |

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.

[b] The terms alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hepatic enzyme were combined under liver enzymes.

[c] Patients with the following MedDRA terms were counted in this category: lower respiratory tract infection, respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection.

### 6.2 Vital Signs and Laboratory Studies

Vital Sign Changes — Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials *[see Warnings and Precautions (5)]*.

Laboratory Changes — An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in ALT, AST, and GGT. In placebo-controlled olanzapine monotherapy studies in adults, 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 to none (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 premarketing database of about 2400 adult 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 2500 adult patients in oral olanzapine clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases.

In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from <3 times the upper limit of normal at baseline to ≥3 times the upper limit of the normal range) were observed in 12% (21/174) of patients exposed to olanzapine compared to 2% (2/87) of the placebo-treated patients. Discontinuation due to transaminase increases occurred in 3.4% (6/179) of patients exposed to olanzapine.

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.

Olanzapine administration was also associated with increases in serum prolactin *[see Warnings and Precautions (5.15)]*, with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models *[see Nonclinical Toxicology (13.2)]*, careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

*Olanzapine Monotherapy in Adolescents:* In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar I disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT (≥3 X ULN in patients with ALT at baseline <3 X ULN), (12.1% vs 2.3%); elevated AST (27.6% vs 3.8%); low total bilirubin (22.1% vs 6.7%); elevated GGT (10.1% vs 1.2%); and elevated prolactin (47.4% vs 6.8%).

ECG Changes — In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc (Fridericia corrected), and PR intervals. Olanzapine use was associated with a mean increase in heart rate compared to placebo (adults: +2.4 beats per minute vs no change with placebo; adolescents: +6.3 beats per minute vs -5.1 beats per minute with placebo). This increase in heart rate may be related to olanzapine's potential for inducing orthostatic changes *[see Warnings and Precautions (5.8)]*.

### 6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZYPREXA. 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 ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, diabetic ketoacidosis, discontinuation reaction (diaphoresis, nausea or vomiting), jaundice, neutropenia, pancreatitis, priapism, rash, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

## 7 DRUG INTERACTIONS

The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies.

### 7.1 Potential for Other Drugs to Affect Olanzapine

Diazepam — The co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Cimetidine and Antacids — Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Inducers of CYP1A2 — Carbamazepine therapy (200 mg bid) causes an approximately 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.

Alcohol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The co-administration of alcohol (i.e., ethanol) with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Inhibitors of CYP1A2

*Fluvoxamine:* Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine Cmax following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

Inhibitors of CYP2D6

*Fluoxetine:* Fluoxetine (60 mg single dose or 60 mg daily dose for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended. When using ZYPREXA and fluoxetine in combination, also refer to the Drug Interactions section of the package insert for Symbyax.

Warfarin — Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics *[see Drug Interactions (7.2)]*.

Inducers of CYP1A2 or Glucuronyl Transferase — Omeprazole and rifampin may cause an increase in olanzapine clearance.

Charcoal — The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

### 7.2 Potential for Olanzapine to Affect Other Drugs

CNS Acting Drugs — Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Antihypertensive Agents — Olanzapine, because of its potential for inducing hypotension, may enhance the effects of certain antihypertensive agents.

Levodopa and Dopamine Agonists — Olanzapine may antagonize the effects of levodopa and dopamine agonists.

Lorazepam (IM) — Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone *[see Warnings and Precautions (5.8)]*.

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium *[see Warnings and Precautions (5.16)]*.

Valproate — Olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate *[see Warnings and Precautions (5.16)]*.

Effect of Olanzapine on Drug Metabolizing Enzymes — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Imipramine — Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

Warfarin — Single doses of olanzapine did not affect the pharmacokinetics of warfarin *[see Drug Interactions (7.1)]*.

Diazepam — Olanzapine did not influence the pharmacokinetics of diazepam or its active metabolite N-desmethyldiazepam. However, diazepam co-administered with olanzapine increased the orthostatic hypotension observed with either drug given alone *[see Drug Interactions (7.1)]*.

Alcohol — Multiple doses of olanzapine did not influence the kinetics of ethanol *[see Drug Interactions (7.1)]*.

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

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

## 8 USE IN SPECIFIC POPULATIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Use in Specific Populations section of the package insert for Symbyax.

### 8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C — 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 maximum recommended human daily oral dose on a $mg/m^2$ basis, respectively) no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a $mg/m^2$ basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a $mg/m^2$ basis). In an oral 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 maximum recommended human daily oral dose on a $mg/m^2$ 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 trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion.

### 8.2 Labor and Delivery

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

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

The safety and effectiveness of oral ZYPREXA in the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder were established in short-term studies in adolescents (ages 13 to 17 years). Use of ZYPREXA in adolescents is supported by evidence from adequate and well-controlled studies of ZYPREXA in which 268 adolescents received ZYPREXA in a range of 2.5 to 20 mg/day *[see Clinical Studies (14.1, 14.2)]*. Recommended starting dose for adolescents is lower than that for adults *[see Dosage and Administration (2.1, 2.2)]*. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic transaminase levels *[see Warnings and Precautions (5.5, 5.6, 5.15, 5.17) and Adverse Reactions (6.2)]*. When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Indications and Usage (1.1, 1.2)]*.

Safety and effectiveness of olanzapine in children <13 years of age have not been established *[see Patient Counseling Information (17.13)]*.

Safety and effectiveness of ZYPREXA and fluoxetine in combination in children and adolescents <18 years of age have not been established.

### 8.5 Geriatric Use

Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to 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 events (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. 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 *[see Boxed Warning, Dosage and Administration (2.1), and Warnings and Precautions (5.1)]*.

Clinical studies of ZYPREXA and fluoxetine in combination did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients.

## 9 DRUG ABUSE AND DEPENDENCE

### 9.3 Dependence

In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily oral dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily oral dose on a $mg/m^2$ basis.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials 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, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

## 10 OVERDOSAGE

### 10.1 Human Experience

In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

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 and 1 patient experiencing 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.

### 10.2 Management of Overdose

The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The administration of activated

charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

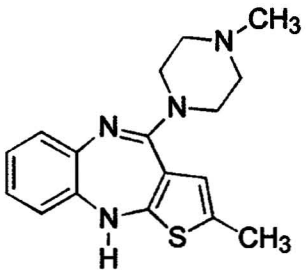
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. 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 beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

For specific information about overdosage with lithium or valproate, refer to the Overdosage section of the package inserts for these products. For specific information about overdosage with olanzapine and fluoxetine in combination, refer to the Overdosage section of the Symbyax package insert.

## 11 DESCRIPTION

ZYPREXA (olanzapine) is an atypical antipsychotic that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-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. The chemical structure is:




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

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 μmol), 5 mg (16 μmol), 7.5 mg (24 μmol), 10 mg (32 μmol), 15 mg (48 μmol), or 20 mg (64 μmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 μmol), 10 mg (32 μmol), 15 mg (48 μmol) or 20 mg (64 μmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

ZYPREXA IntraMuscular (olanzapine for injection) is intended for intramuscular use only.

Each vial provides for the administration of 10 mg (32 μmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT2) antagonism. The mechanism of action of olanzapine in the treatment of acute manic or mixed episodes associated with bipolar I disorder is unknown.

### 12.2 Pharmacodynamics

Olanzapine binds with high affinity to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$ ($K_i$=4, 11, and 5 nM, respectively), dopamine $D_{1-4}$ ($K_i$=11-31 nM), histamine $H_1$ ($K_i$=7 nM), and adrenergic $\alpha_1$ receptors ($K_i$=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ ($K_i$=57 nM) and muscarinic $M_{1-5}$ ($K_i$=73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds weakly to $GABA_A$, BZD, and β-adrenergic receptors ($K_i$>10 μM).

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. Olanzapine's antagonism of histamine $H_1$ receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic $\alpha_1$ receptors may explain the orthostatic hypotension observed with this drug.

### 12.3 Pharmacokinetics

Oral Administration, Monotherapy — Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics 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.

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/mL, binding primarily to albumin and $\alpha_1$-acid glycoprotein.

Metabolism and Elimination — 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 cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, 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.

Intramuscular Administration — ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is similar to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

*Specific Populations*

Renal Impairment — 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 metabolite elimination has not been studied.

Hepatic Impairment — 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 (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Geriatric — In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (≥65 years) than in nonelderly subjects (<65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity *[see Dosage and Administration (2)]*.

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 recommended.

Race — In vivo studies have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine *[see Dosage and Administration (2)]*.

Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents were nonsmokers and this population had a lower average body weight, which resulted in higher average olanzapine exposure compared to adults.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily oral dose on a $mg/m^2$ basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a $mg/m^2$ basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to

0.13-2 and 0.13-4 times the maximum recommended human daily oral dose on a mg/m$^2$ basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in 1 mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a mg/m$^2$ basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily oral dose on a mg/m$^2$ 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 maximum recommended human daily oral dose on a mg/m$^2$ 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 (5.15)]*.

Mutagenesis — 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.

Impairment of Fertility — 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 maximum recommended human daily oral dose on a mg/m$^2$ 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 maximum recommended human daily oral dose on a mg/m$^2$ basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m$^2$ basis); therefore olanzapine may produce a delay in ovulation.

### 13.2 Animal Toxicology and/or Pharmacology

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily oral dose on a mg/m$^2$ basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a mg/m$^2$ basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily oral dose on a mg/m$^2$ basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a mg/m$^2$ basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

## 14 CLINICAL STUDIES

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

### 14.1 Schizophrenia

**Adults**

The efficacy of oral olanzapine in the treatment of schizophrenia was established in 2 short-term (6-week) controlled trials of adult inpatients who met DSM III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in 1 of the 2 trials, but this trial did not compare these 2 drugs on the full range of clinically relevant doses for both.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, 2 more recently developed scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which are embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving 2 fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5 ± 2.5 mg/day, 10 ± 2.5 mg/day, and 15 ± 2.5 mg/day) on a once daily schedule, the 2 highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest

olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high-dose group over the medium-dose group.

(3) In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open-label treatment for at least 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however, criteria were met for stopping the trial early due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months.

Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

**Adolescents**

The efficacy of oral olanzapine in the acute treatment of schizophrenia in adolescents (ages 13 to 17 years) was established in a 6-week double-blind, placebo-controlled, randomized trial of inpatients and outpatients with schizophrenia (n=107) who met diagnostic criteria according to DSM-IV-TR and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL).

The primary rating instrument used for assessing psychiatric signs and symptoms in this trial was the Anchored Version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score.

In this flexible-dose trial, olanzapine 2.5 to 20 mg/day (mean modal dose 12.5 mg/day, mean dose of 11.1 mg/day) was more effective than placebo in the treatment of adolescents diagnosed with schizophrenia, as supported by the statistically significantly greater mean reduction in BPRS-C total score for patients in the olanzapine treatment group than in the placebo group.

While there is no body of evidence available to answer the question of how long the adolescent patient treated with ZYPREXA should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 14.2 Bipolar I Disorder (Manic or Mixed Episodes)

**Adults**

Monotherapy — The efficacy of oral olanzapine in the treatment of manic or mixed episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in adult patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar I disorder who had responded during an initial open-label treatment phase for about 2 weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to ≤12 and HAM-D 21 to ≤8. Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to ≥15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Adjunct to Lithium or Valproate — The efficacy of oral olanzapine with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in 2 controlled trials in patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course. The results of the trials follow:

(1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 μg/mL to 125 μg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 μg/mL to 125 μg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

**Adolescents**

Acute Monotherapy — The efficacy of oral olanzapine in the treatment of acute manic or mixed episodes in adolescents (ages 13 to 17 years) was established in a 3-week, double-blind, placebo-controlled, randomized trial of adolescent inpatients and outpatients who met the diagnostic criteria for manic or mixed episodes associated with bipolar I disorder (with or without psychotic features) according to the DSM-IV-TR (n=161). Diagnosis was confirmed by the K-SADS-PL.

The primary rating instrument used for assessing manic symptoms in this trial was the Adolescent Structured Young-Mania Rating Scale (Y-MRS) total score.

In this flexible-dose trial, olanzapine 2.5 to 20 mg/day (mean modal dose 10.7 mg/day, mean dose of 8.9 mg/day) was more effective than placebo in the treatment of adolescents with manic or mixed episodes associated with bipolar I disorder, as supported by the statistically significantly greater mean reduction in Y-MRS total score for patients in the olanzapine treatment group than in the placebo group.

While there is no body of evidence available to answer the question of how long the adolescent patient treated with ZYPREXA should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 14.3 Agitation Associated with Schizophrenia and Bipolar I Mania

The efficacy of intramuscular olanzapine for injection for the treatment of agitation was established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients from 2 diagnostic groups: schizophrenia and bipolar I disorder (manic or mixed episodes). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar I mania study). Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥14 on the 5 items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least 1 individual item score ≥4 using a 1-7 scoring system (1=absent, 4=moderate, 7=extreme). In the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to 3 injections during the 24 hour IM treatment periods; however, patients could not receive the second injection until after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

(1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270), 4 fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the 3 highest doses. There were no significant pairwise differences for the 7.5 and 10 mg doses over the 5 mg dose.

(2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=311), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

(3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for bipolar I disorder (and currently displaying an acute manic or mixed episode with or without psychotic features) (n=201), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. The tablets are available as follows:

| | TABLET STRENGTH | | | | | |
|---|---|---|---|---|---|---|
| | 2.5 mg | 5 mg | 7.5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4112 | 4115 | 4116 | 4117 | 4415 | 4420 |
| Identification | LILLY | LILLY | LILLY | LILLY | LILLY | LILLY |

| | 4112 | 4115 | 4116 | 4117 | 4415 | 4420 |
|---|---|---|---|---|---|---|
| NDC Codes: | | | | | | |
| Bottles 30 | NDC 0002-4112-30 | NDC 0002-4115-30 | NDC 0002-4116-30 | NDC 0002-4117-30 | NDC 0002-4415-30 | NDC 0002-4420-30 |
| Blisters – ID[a] 100 | NDC 0002-4112-33 | NDC 0002-4115-33 | NDC 0002-4116-33 | NDC 0002-4117-33 | NDC 0002-4415-33 | NDC 0002-4420-33 |
| Bottles 1000 | NDC 0002-4112-04 | NDC 0002-4115-04 | NDC 0002-4116-04 | NDC 0002-4117-04 | NDC 0002-4415-04 | NDC 0002-4420-04 |

[a] Identi-Dose® (unit dose medication, Lilly).

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:

| | TABLET STRENGTH | | | |
|---|---|---|---|---|
| ZYPREXA ZYDIS Tablets[a] | 5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4453 | 4454 | 4455 | 4456 |
| Debossed | 5 | 10 | 15 | 20 |
| NDC Codes: | | | | |
| Dose Pack 30 (Child Resistant) | NDC 0002-4453-85 | NDC 0002-4454-85 | NDC 0002-4455-85 | NDC 0002-4456-85 |

ZYPREXA is a registered trademark of Eli Lilly and Company.
ZYDIS is a registered trademark of Catalent Pharma Solutions.
[a] ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Catalent Pharma Solutions, United Kingdom, SN5 8RU.

ZYPREXA IntraMuscular is available in:

NDC 0002-7597-01 (No. VL7597) – 10 mg vial (1s)

### 16.2 Storage and Handling

Store ZYPREXA tablets, ZYPREXA ZYDIS, and ZYPREXA IntraMuscular vials (before reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP] for up to 1 hour if necessary. *Discard any unused portion of reconstituted ZYPREXA IntraMuscular.* The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect ZYPREXA tablets and ZYPREXA ZYDIS from light and moisture. Protect ZYPREXA IntraMuscular from light, do not freeze.

## 17 PATIENT COUNSELING INFORMATION

*See FDA-approved Medication Guide for the oral formulations.*

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking ZYPREXA as monotherapy or in combination with fluoxetine. If you do not think you are getting better or have any concerns about your condition while taking ZYPREXA, call your doctor. When using ZYPREXA and fluoxetine in combination, also refer to the Patient Counseling Information section of the package insert for 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 ZYPREXA, and should counsel them in its appropriate use. A patient Medication Guide is available for ZYPREXA. 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. When using ZYPREXA and fluoxetine in combination, also refer to the Medication Guide for Symbyax.

### 17.2 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 an increased risk of death. Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with ZYPREXA had a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) compared with placebo.

ZYPREXA is not approved for elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*.

**17.3 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 ZYPREXA. 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)]*.

**17.4 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 who have diabetes should follow their doctor's instructions about how often to check their blood sugar while taking ZYPREXA *[see Warnings and Precautions (5.4)]*.

**17.5 Hyperlipidemia**

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

**17.6 Weight Gain**

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

**17.7 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 ZYPREXA, e.g., diazepam or alcohol *[see Warnings and Precautions (5.8) and Drug Interactions (7)]*. 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.

**17.8 Potential for Cognitive and Motor Impairment**

Because ZYPREXA 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 ZYPREXA therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

**17.9 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 (5.13)]*.

**17.10 Concomitant Medication**

Patients should be advised to inform their physicians if they are taking, or plan to take, Symbyax. Patients should also 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 *[see Drug Interactions (7)]*.

**17.11 Alcohol**

Patients should be advised to avoid alcohol while taking ZYPREXA *[see Drug Interactions (7)]*.

**17.12 Phenylketonurics**

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively) *[see Description (11)]*.

**17.13 Use in Specific Populations**

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

Nursing Mothers — Patients should be advised not to breast-feed an infant if they are taking ZYPREXA *[see Use in Specific Populations (8.3)]*.

Pediatric Use — ZYPREXA is indicated for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adolescents 13 to 17 years of age. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin, and hepatic transaminase levels. Patients should be counseled about the potential long-term risks associated with ZYPREXA and advised that these risks may lead them to consider other drugs first *[see Indications and Usage (1.1, 1.2)]*. Safety and effectiveness of ZYPREXA in patients under 13 years of age have not been established. Safety and effectiveness of ZYPREXA and fluoxetine in combination in patients <18 years of age have not been established *[see Warnings and Precautions (5.5, 5.6) and Use in Specific Populations (8.4)]*.

**17.14 Need for Comprehensive Treatment Program in Pediatric Patients**

ZYPREXA is indicated as an integral part of a total treatment program for pediatric patients with schizophrenia and bipolar disorder that may include other measures (psychological, educational, social) for patients with the disorder. Effectiveness and safety of ZYPREXA have not been established in pediatric patients less than 13 years of age. Atypical antipsychotics are not intended for use in the pediatric patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders. Appropriate educational placement is essential and psychosocial intervention is often helpful. The decision to prescribe atypical

antipsychotic medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms *[see Indications and Usage (1.3)]*.

Literature revised Month DD, YYYY

**Eli Lilly and Company, Indianapolis, IN 46285, USA**

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101 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**ZYPREXA (olanzapine) Tablet for Oral use**
**ZYPREXA ZYDIS (olanzapine) Tablet, Orally Disintegrating for Oral use**
**ZYPREXA IntraMuscular (olanzapine) Injection, Powder, For Solution for Intramuscular use**

**Initial U.S. Approval: 1996**

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

***See full prescribing information for complete boxed warning.***

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis. (5.1, 5.14, 17.2)**
  **When using ZYPREXA and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.**

### ---------- RECENT MAJOR CHANGES ----------

| | |
|---|---|
| Indications and Usage: | |
| Schizophrenia (1.1) | MM/2009 |
| Bipolar I Disorder (Manic or Mixed Episodes) (1.2) | MM/2009 |
| Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder (1.3) | MM/2009 |
| ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania (1.4) | MM/2009 |
| Indications and Usage, *ZYPREXA and Fluoxetine in Combination:* | |
| Depressive Episodes Associated with Bipolar I Disorder (1.5) | 03/2009 |
| Treatment Resistant Depression (1.6) | 03/2009 |
| Dosage and Administration: | |
| Schizophrenia (2.1) | MM/2009 |
| Bipolar I Disorder (Manic or Mixed Episodes) (2.2) | MM/2009 |
| Dosage and Administration, *ZYPREXA and Fluoxetine in Combination:* | |
| Depressive Episodes Associated with Bipolar I Disorder (2.5) | 03/2009 |
| Treatment Resistant Depression (2.6) | 03/2009 |
| Warnings and Precautions: | |
| Hyperglycemia (5.4) | 03/2009 |
| Hyperlipidemia (5.5) | 03/2009 |
| Weight Gain (5.6) | 03/2009 |
| Leukopenia, Neutropenia, and Agranulocytosis (5.9) | 08/2009 |
| Use in Patients with Concomitant Illness (5.14) | 03/2009 |
| Hyperprolactinemia (5.15) | 03/2009 |
| Use in Combination with Fluoxetine, Lithium, or Valproate (5.16) | 03/2009 |
| Laboratory Tests (5.17) | 03/2009 |

### ---------- INDICATIONS AND USAGE ----------

ZYPREXA® (olanzapine) is an atypical antipsychotic indicated:

*As oral formulation for the:*

- Treatment of schizophrenia. (1.1)
  - Adults: Efficacy was established in three clinical trials in patients with schizophrenia: two 6-week trials and one maintenance trial. (14.1)
  - Adolescents (ages 13-17): Efficacy was established in one 6-week trial in patients with schizophrenia (14.1). The increased potential (in adolescents compared with adults) for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first in adolescents. (1.1)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. (1.2)
  - Adults: Efficacy was established in three clinical trials in patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one maintenance trial. (14.2)
  - Adolescents (ages 13-17): Efficacy was established in one 3-week trial in patients with manic or mixed episodes associated with bipolar I disorder (14.2). The increased potential (in adolescents compared with adults) for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first in adolescents. (1.2)
- Medication therapy for pediatric patients with schizophrenia or bipolar I disorder should be undertaken only after a thorough diagnostic evaluation and with careful consideration of the potential risks. (1.3)
- Adjunct to valproate or lithium in the treatment of manic or mixed episodes associated with bipolar I disorder. (1.2)
  - Efficacy was established in two 6-week clinical trials in adults (14.2). Maintenance efficacy has not been systematically evaluated.

*As ZYPREXA IntraMuscular for the:*

- Treatment of acute agitation associated with schizophrenia and bipolar I mania. (1.4)
  - Efficacy was established in three 1-day trials in adults. (14.3)

*As ZYPREXA and Fluoxetine in Combination for the:*

- Treatment of depressive episodes associated with bipolar I disorder. (1.5)
  - Efficacy was established with Symbyax (olanzapine and fluoxetine in combination) in adults; refer to the product label for Symbyax.
- Treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode). (1.6)
  - Efficacy was established with Symbyax (olanzapine and fluoxetine in combination) in adults; refer to the product label for Symbyax.

### ---------- DOSAGE AND ADMINISTRATION ----------

| | |
|---|---|
| Schizophrenia in adults (2.1) | Oral: Start at 5-10 mg once daily; Target: 10 mg/day within several days |
| Schizophrenia in adolescents (2.1) | Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day |
| Bipolar I Disorder (manic or mixed episodes) in adults (2.2) | Oral: Start at 10 or 15 mg once daily |
| Bipolar I Disorder (manic or mixed episodes) in adolescents (2.2) | Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day |
| Bipolar I Disorder (manic or mixed episodes) with lithium or valproate in adults (2.2) | Oral: Start at 10 mg once daily |
| Agitation associated with Schizophrenia and Bipolar I Mania in adults (2.4) | IM: 10 mg (5 mg or 7.5 mg when clinically warranted) Assess for orthostatic hypotension prior to subsequent dosing (max. 3 doses 2-4 hrs apart) |
| Depressive Episodes associated with Bipolar I Disorder in adults (2.5) | Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily |
| Treatment Resistant Depression in adults (2.6) | Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily |

- Lower starting dose recommended in debilitated or pharmacodynamically sensitive patients or patients with predisposition to hypotensive reactions, or with potential for slowed metabolism. (2.1)
- Olanzapine may be given without regard to meals. (2.1)

*ZYPREXA and Fluoxetine in Combination:*

- Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability. (2.5, 2.6)
- Olanzapine monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder or treatment resistant depression. (2.5, 2.6)
- Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated. (2.5, 2.6)

### ---------- DOSAGE FORMS AND STRENGTHS ----------

- Tablets (not scored): 2.5, 5, 7.5, 10, 15, 20 mg (3)
- Orally Disintegrating Tablets (not scored): 5, 10, 15, 20 mg (3)

- Intramuscular Injection: 10 mg vial (3)

**----------CONTRAINDICATIONS----------**

- None with ZYPREXA monotherapy.
- When using ZYPREXA and fluoxetine in combination, also refer to the Contraindications section of the package insert for Symbyax®. (4)
- When using ZYPREXA in combination with lithium or valproate, refer to the Contraindications section of the package inserts for those products. (4)

**----------WARNINGS AND PRECAUTIONS----------**

- *Elderly Patients with Dementia-Related Psychosis:* Increased risk of death and increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack). (5.1)
- *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy; when using in combination with fluoxetine, also refer to the Boxed Warning and Warnings and Precautions sections of the package insert for Symbyax. (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 olanzapine 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)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate. (5.7)
- *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, cerebrovascular disease, and those conditions that could affect hemodynamic responses. (5.8)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Has been reported with antipsychotics, including ZYPREXA. Patients with a history of a clinically significant low white blood cell count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.9)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.11)
- *Potential for Cognitive and Motor Impairment:* Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery. (5.12)
- *Hyperprolactinemia:* May elevate prolactin levels. (5.15)
- *Use in Combination with Fluoxetine, Lithium or Valproate:* Also refer to the package inserts for Symbyax, lithium, or valproate. (5.16)
- *Laboratory Tests:* Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment. (5.17)

**----------ADVERSE REACTIONS----------**

Most common adverse reactions (≥5% and at least twice that for placebo) associated with:

*Oral Olanzapine Monotherapy:*

- Schizophrenia (Adults) – postural hypotension, constipation, weight gain, dizziness, personality disorder, akathisia (6.1)
- Schizophrenia (Adolescents) – sedation, weight increased, headache, increased appetite, dizziness, abdominal pain, pain in extremity, fatigue, dry mouth (6.1)
- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor (6.1)
- Manic or Mixed Episodes, Bipolar I Disorder (Adolescents) – sedation, weight increased, increased appetite, headache, fatigue, dizziness, dry mouth, abdominal pain, pain in extremity (6.1)

*Combination of ZYPREXA and Lithium or Valproate:*

- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia (6.1)

*ZYPREXA and Fluoxetine in Combination:* Also refer to the Adverse Reactions section of the package insert for Symbyax. (6)

*ZYPREXA IntraMuscular for Injection:*

- Agitation with Schizophrenia and Bipolar I Mania (Adults) – somnolence (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----------**

- *Diazepam:* May potentiate orthostatic hypotension. (7.1, 7.2)
- *Alcohol:* May potentiate orthostatic hypotension. (7.1)
- *Carbamazepine:* Increased clearance of olanzapine. (7.1)
- *Fluvoxamine:* May increase olanzapine levels. (7.1)
- *ZYPREXA and Fluoxetine in Combination:* Also refer to the Drug Interactions section of the package insert for Symbyax. (7.1)
- *CNS Acting Drugs:* Caution should be used when taken in combination with other centrally acting drugs and alcohol. (7.2)
- *Antihypertensive Agents:* Enhanced antihypertensive effect. (7.2)
- *Levodopa and Dopamine Agonists:* May antagonize levodopa/dopamine agonists. (7.2)
- *Lorazepam (IM):* Increased somnolence with IM olanzapine. (7.2)
- *Other Concomitant Drug Therapy:* When using olanzapine in combination with lithium or valproate, refer to the Drug Interactions sections of the package insert for those products. (7.2)

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

- *Pregnancy:* ZYPREXA 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 ZYPREXA in children <13 years of age have not been established. (8.4)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide**

**Revised: MM/2009**

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*Sections or subsections omitted from the full prescribing information are not listed

## FULL PRESCRIBING INFORMATION

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1, 5.14) and Patient Counseling Information (17.2)]*.**

**When using ZYPREXA and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.**

## 1 INDICATIONS AND USAGE

### 1.1 Schizophrenia

Oral ZYPREXA is indicated for the treatment of schizophrenia. Efficacy was established in three clinical trials in adult patients with schizophrenia: two 6-week trials and one maintenance trial. In adolescent patients with schizophrenia (ages 13-17), efficacy was established in one 6-week trial *[see Clinical Studies (14.1)]*.

When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Warnings and Precautions (5.5, 5.6)]*.

### 1.2 Bipolar I Disorder (Manic or Mixed Episodes)

Monotherapy — Oral ZYPREXA is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. Efficacy was established in three clinical trials in adult patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one monotherapy maintenance trial. In adolescent patients with manic or mixed episodes associated with bipolar I disorder (ages 13-17), efficacy was established in one 3-week trial *[see Clinical Studies (14.2)]*.

When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Warnings and Precautions (5.5, 5.6)]*.

Adjunctive Therapy to Lithium or Valproate — Oral ZYPREXA is indicated for the treatment of manic or mixed episodes associated with bipolar I disorder as an adjunct to lithium or valproate. Efficacy was established in two 6-week clinical trials in adults. The effectiveness of adjunctive therapy for longer-term use has not been systematically evaluated in controlled trials *[see Clinical Studies (14.2)]*.

### 1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder

Pediatric schizophrenia and bipolar I disorder are serious mental disorders; however, diagnosis can be challenging. For pediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, pediatric patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for pediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment for both pediatric schizophrenia and bipolar I disorder should be part of a total treatment program that often includes psychological, educational and social interventions.

### 1.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania

ZYPREXA IntraMuscular is indicated for the treatment of acute agitation associated with schizophrenia and bipolar I mania.

Efficacy was demonstrated in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients with: schizophrenia or bipolar I disorder (manic or mixed episodes) *[see Clinical Studies (14.3)]*.

"Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

### 1.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder

Oral ZYPREXA and fluoxetine in combination is indicated for the treatment of depressive episodes associated with bipolar I disorder, based on clinical studies in adult patients. When using ZYPREXA and fluoxetine in combination, refer to the Clinical Studies section of the package insert for Symbyax.

ZYPREXA monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

### 1.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

Oral ZYPREXA and fluoxetine in combination is indicated for the treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode), based on clinical studies in adult patients. When using ZYPREXA and fluoxetine in combination, refer to the Clinical Studies section of the package insert for Symbyax.

ZYPREXA monotherapy is not indicated for the treatment of treatment resistant depression.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Schizophrenia

**Adults**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical assessment. Olanzapine is not indicated for use in doses above 20 mg/day.

Dosing in Special Populations — The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*. When indicated, dose escalation should be performed with caution in these patients.

Maintenance Treatment — The effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for relapse has been

demonstrated in a placebo-controlled trial *[see Clinical Studies (14.1)]*. The physician who elects to use ZYPREXA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

**Adolescents**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents with schizophrenia was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 12.5 mg/day (mean dose of 11.1 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended.

The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials *[see Clinical Studies (14.1)]*.

Maintenance Treatment — The efficacy of ZYPREXA for the maintenance treatment of schizophrenia in the adolescent population has not been systematically evaluated; however, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 2.2 Bipolar I Disorder (Manic or Mixed Episodes)

**Adults**

Dose Selection for Monotherapy — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials *[see Clinical Studies (14.2)]*.

Maintenance Monotherapy — The benefit of maintaining bipolar I patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of 2 weeks, was demonstrated in a controlled trial *[see Clinical Studies (14.2)]*. The physician who elects to use ZYPREXA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Dose Selection for Adjunctive Treatment — When administered as adjunctive treatment to lithium or valproate, oral olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals.

Antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials *[see Clinical Studies (14.2)]*. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

**Adolescents**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents with bipolar I disorder (manic or mixed episodes) was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 10.7 mg/day (mean dose of 8.9 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended.

The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials *[see Clinical Studies (14.2)]*.

Maintenance Treatment — The efficacy of ZYPREXA for the maintenance treatment of bipolar I disorder in the adolescent population has not been evaluated; however, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 2.3 Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)

After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

### 2.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania

Dose Selection for Agitated Adult Patients with Schizophrenia and Bipolar I Mania — The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant *[see Clinical Studies (14.3)]*. If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., 3 doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension *[see Warnings and Precautions (5.8)]*. Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended.

If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate *[see Dosage and Administration (2.1, 2.2)]*.

Intramuscular Dosing in Special Populations — A dose of 5 mg/injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg/injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

Administration of ZYPREXA IntraMuscular — ZYPREXA IntraMuscular is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for Preparation of ZYPREXA IntraMuscular with Sterile Water for Injection — Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. ZYPREXA IntraMuscular reconstituted with Sterile Water for Injection should be used immediately (within 1 hour) after reconstitution. *Discard any unused portion.*

The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

| Dose, mg Olanzapine | Volume of Injection, mL |
|---|---|
| 10 | Withdraw total contents of vial |
| 7.5 | 1.5 |
| 5 | 1 |
| 2.5 | 0.5 |

Physical Incompatibility Information — ZYPREXA IntraMuscular should be reconstituted only with Sterile Water for Injection. ZYPREXA IntraMuscular should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed. Lorazepam injection should not be used to reconstitute ZYPREXA IntraMuscular as this combination results in a delayed reconstitution time. ZYPREXA IntraMuscular should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

### 2.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 12.5 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was demonstrated with ZYPREXA and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg.

Safety and efficacy of ZYPREXA and fluoxetine in combination was determined in clinical trials supporting approval of Symbyax (fixed dose combination of ZYPREXA and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. The following table demonstrates the appropriate individual component doses of ZYPREXA and fluoxetine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

**Table 1: Approximate Dose Correspondence Between Symbyax[a] and the Combination of ZYPREXA and Fluoxetine**

| For Symbyax (mg/day) | Use in Combination | |
|---|---|---|
| | ZYPREXA (mg/day) | Fluoxetine (mg/day) |
| 3 mg olanzapine/25 mg fluoxetine | 2.5 | 20 |
| 6 mg olanzapine/25 mg fluoxetine | 5 | 20 |
| 12 mg olanzapine/25 mg fluoxetine | 10+2.5 | 20 |
| 6 mg olanzapine/50 mg fluoxetine | 5 | 40+10 |
| 12 mg olanzapine/50 mg fluoxetine | 10+2.5 | 40+10 |

[a] Symbyax (olanzapine/fluoxetine HCl) is a fixed-dose combination of ZYPREXA and fluoxetine.

While there is no body of evidence to answer the question of how long a patient treated with ZYPREXA and fluoxetine in combination 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.

Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

ZYPREXA monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

### 2.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 20 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was demonstrated with olanzapine and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 18 mg and fluoxetine 25 to 50 mg.

Safety and efficacy of olanzapine in combination with fluoxetine was determined in clinical trials supporting approval of Symbyax (fixed dose combination of olanzapine and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. Table 1 above demonstrates the appropriate individual component doses of ZYPREXA and fluoxetine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

While there is no body of evidence to answer the question of how long a patient treated with ZYPREXA and fluoxetine in combination 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.

Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

ZYPREXA monotherapy is not indicated for treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode).

### 2.7 ZYPREXA and Fluoxetine in Combination: 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. 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. ZYPREXA 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 (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

## 3 DOSAGE FORMS AND STRENGTHS

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. Tablets are not scored. The tablets are available as follows:

| | TABLET STRENGTH | | | | | |
|---|---|---|---|---|---|---|
| | 2.5 mg | 5 mg | 7.5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4112 | 4115 | 4116 | 4117 | 4415 | 4420 |
| Identification | LILLY<br>4112 | LILLY<br>4115 | LILLY<br>4116 | LILLY<br>4117 | LILLY<br>4415 | LILLY<br>4420 |

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. Tablets are not scored. The tablets are available as follows:

| | TABLET STRENGTH | | | |
|---|---|---|---|---|
| ZYPREXA ZYDIS Tablets | 5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4453 | 4454 | 4455 | 4456 |
| Debossed | 5 | 10 | 15 | 20 |

ZYPREXA IntraMuscular is available in 10 mg vial (1s).

## 4 CONTRAINDICATIONS

- None with ZYPREXA monotherapy.
- When using ZYPREXA and fluoxetine in combination, also refer to the Contraindications section of the package insert for Symbyax.
- For specific information about the contraindications of lithium or valproate, refer to the Contraindications section of the package inserts for these other products.

## 5 WARNINGS AND PRECAUTIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Warnings and Precautions section of the package insert for Symbyax.

### 5.1 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. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis** ***[see Boxed Warning, Warnings and Precautions (5.14), and Patient Counseling Information (17.2)].***

In 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 is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Patient Counseling Information (17.2)]*.

### 5.2 Suicide

The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

### 5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (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 a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported *[see Patient Counseling Information (17.3)]*.

### 5.4 Hyperglycemia

Physicians should consider the risks and benefits when prescribing olanzapine 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 olanzapine should be monitored regularly for worsening of glucose control. Patients starting treatment with olanzapine 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 (17.4)]*.

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. 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.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with a median treatment duration of approximately 3 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). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (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, and/or a baseline fasting glucose

level ≥126 mg/dL). Olanzapine-treated patients had a greater mean HbA1c increase from baseline of 0.04% (median exposure 21 days), compared to a mean HbA1c decrease of 0.06% in placebo-treated subjects (median exposure 17 days).

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). Table 2 shows short-term and long-term changes in fasting glucose levels from adult olanzapine monotherapy studies.

**Table 2: Changes in Fasting Glucose Levels from Adult Olanzapine Monotherapy 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** |
| Fasting Glucose | Normal to High (<100 mg/dL to ≥126 mg/dL) | Olanzapine | 543 | 2.2% | 345 | 12.8% |
| | | Placebo | 293 | 3.4% | NA[a] | NA[a] |
| | Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL) | Olanzapine | 178 | 17.4% | 127 | 26.0% |
| | | Placebo | 96 | 11.5% | NA[a] | NA[a] |

[a] Not Applicable.

The mean change in fasting glucose for 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 have not been established in patients under the age of 13 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 versus -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 exposure | | At least 24 weeks exposure | |
|---|---|---|---|---|---|---|
| **Laboratory Analyte** | **Category Change (at least once) from Baseline** | **Treatment Arm** | **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 olanzapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using olanzapine, is recommended *[see Patient Counseling Information (17.5)]*.

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

Olanzapine Monotherapy in Adults — 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, or patients with high baseline lipid levels.

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. 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 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 4 shows categorical changes in fasting lipids values.

**Table 4: Changes in Fasting Lipids Values from Adult Olanzapine Monotherapy 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** |
| Fasting Triglycerides | Increase by ≥50 mg/dL | Olanzapine | 745 | 39.6% | 487 | 61.4% |
| | | Placebo | 402 | 26.1% | NA[a] | NA[a] |
| | 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] |
| Fasting Total Cholesterol | Increase by ≥40 mg/dL | Olanzapine | 745 | 21.6% | 489 | 32.9% |
| | | Placebo | 402 | 9.5% | NA[a] | NA[a] |
| | 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] |
| Fasting LDL Cholesterol | Increase by ≥30 mg/dL | Olanzapine | 536 | 23.7% | 483 | 39.8% |
| | | Placebo | 304 | 14.1% | NA[a] | NA[a] |
| | 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 mean increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 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 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 5 shows categorical changes in fasting lipids values in adolescents.

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

| | | | Up to 6 weeks exposure | | At least 24 weeks exposure | |
|---|---|---|---|---|---|---|
| **Laboratory Analyte** | **Category Change (at least once) from Baseline** | **Treatment Arm** | **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 (≥90 mg/dL and ≤130 mg/dL to >130 mg/dL) | Olanzapine | 37 | 59.5% | 31 | 64.5% |
| | | 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 olanzapine. Patients receiving olanzapine should receive regular monitoring of weight *[see Patient Counseling Information (17.6)]*.

Olanzapine Monotherapy in Adults — In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg (5.7 lb) compared to an average 0.3 kg (0.6 lb) weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, compared to 3% of placebo-treated patients, with a median exposure of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 0.3% of placebo-treated patients, with a median exposure of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in 0% of placebo-treated patients.

In long-term 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 6 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 6: 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 have not been established in patients under the age of 13 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 7: 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 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 8 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 8: 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 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.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

For specific information about the warnings of lithium or valproate, refer to the Warnings section of the package inserts for these other products.

### 5.8 Orthostatic Hypotension

Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its $\alpha_1$-adrenergic antagonistic properties *[see Patient Counseling Information (17.7)]*.

For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD *[see Dosage and Administration (2)]*. A more gradual titration to the target dose should be considered if hypotension occurs.

Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in nonagitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥30 mmHg) *[see Dosage and Administration (2.4)]*. Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the reactions occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. For intramuscular olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation.

Olanzapine 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, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression *[see Drug Interactions (7)]*. Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine has not been studied and is therefore not recommended. If use of intramuscular olanzapine in combination with parenteral benzodiazepines is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

**5.9 Leukopenia, Neutropenia, and Agranulocytosis**

Class Effect — In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including ZYPREXA. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count $<1000/mm^3$) should discontinue ZYPREXA and have their WBC followed until recovery.

**5.10 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. Olanzapine is not approved for the treatment of patients with Alzheimer's disease.

**5.11 Seizures**

During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine 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. Olanzapine 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 or older.

**5.12 Potential for Cognitive and Motor Impairment**

Somnolence was a commonly reported adverse reaction associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse reaction was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine 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 olanzapine therapy does not affect them adversely *[see Patient Counseling Information (17.8)]*.

**5.13 Body Temperature Regulation**

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine 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 (17.9)]*.

**5.14 Use in Patients with Concomitant Illness**

Clinical experience with olanzapine in patients with certain concomitant systemic illnesses is limited *[see Clinical Pharmacology (12.3)]*.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with olanzapine, olanzapine 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 discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or 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 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 (5.1), and Patient Counseling Information (17.2)]*.

Olanzapine 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 premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients *[see Warnings and Precautions (5.8)]*.

**5.15 Hyperprolactinemia**

As with other drugs that antagonize dopamine $D_2$ receptors, olanzapine elevates prolactin levels, and a modest elevation persists during chronic 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 which 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, 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)]*.

### 5.16 Use in Combination with Fluoxetine, Lithium, or Valproate

When using ZYPREXA and fluoxetine in combination, the prescriber should also refer to the Warnings and Precautions section of the package insert for Symbyax. When using ZYPREXA in combination with lithium or valproate, the prescriber should refer to the Warnings and Precautions sections of the package inserts for lithium or valproate *[see Drug Interactions (7)]*.

### 5.17 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 (17.4, 17.5)]*.

## 6 ADVERSE REACTIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Adverse Reactions section of the package insert for Symbyax.

### 6.1 Clinical Trials Experience

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.

**Clinical Trials in Adults**

The information below for olanzapine is derived from a clinical trial database for olanzapine consisting of 8661 adult patients with approximately 4165 patient-years of exposure to oral olanzapine and 722 patients with exposure to intramuscular olanzapine for injection. This database includes: (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine premarketing bipolar I disorder (manic or mixed episodes) trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5788 patients from 88 additional oral olanzapine clinical trials as of December 31, 2001; and (5) 722 patients who participated in intramuscular olanzapine for injection premarketing trials in agitated patients with schizophrenia, bipolar I disorder (manic or mixed episodes), or dementia. In addition, information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar I disorder (manic or mixed episodes) trials with approximately 22 patient-years of exposure, is included below.

The conditions and duration of treatment with olanzapine 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 longer-term exposure. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse reactions, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar I disorder (manic or mixed episodes) or agitation. However, this information is also generally applicable to bipolar I disorder (manic or mixed episodes) and agitation.

Adverse reactions during exposure were obtained by spontaneous report and recorded by clinical investigators using 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 smaller number of standardized reaction categories. In the tables and tabulations that follow, MedDRA and COSTART Dictionary terminology has been used to classify reported adverse reactions.

The stated frequencies of adverse reactions 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. The reported reactions do not include those reaction terms that were so general as to be uninformative. Reactions listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the reactions occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

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 trials. 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 physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reaotions incidence in the population studied.

Incidence of Adverse Reactions in Short-Term, Placebo-Controlled and Combination Trials

The following findings are based on premarketing trials of (1) oral olanzapine for schizophrenia, bipolar I disorder (manic or mixed episodes), a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease, and premarketing combination trials, and (2) intramuscular olanzapine for injection in agitated patients with schizophrenia or bipolar I mania.

*Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials*

Schizophrenia — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (5% for oral olanzapine vs 6% for placebo). However, discontinuations due to increases in ALT were considered to be drug related (2% for oral olanzapine vs 0% for placebo).

Bipolar I Disorder (Manic or Mixed Episodes) Monotherapy — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (2% for oral olanzapine vs 2% for placebo).

Agitation — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (0.4% for intramuscular olanzapine for injection vs 0% for placebo).

*Adverse Reactions Associated with Discontinuation of Treatment in Short-Term Combination Trials*

Bipolar I Disorder (Manic or Mixed Episodes), Olanzapine as Adjunct to Lithium or Valproate — In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 11% for the combination of oral olanzapine with lithium or valproate compared to 2% for patients who remained on lithium or valproate monotherapy. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and peripheral edema (1%).

*Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials*

The most commonly observed adverse reactions associated with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

**Table 9: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Trials — SCHIZOPHRENIA**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine (N=248)** | **Placebo (N=118)** |
| Postural hypotension | 5 | 2 |
| Constipation | 9 | 3 |
| Weight gain | 6 | 1 |
| Dizziness | 11 | 4 |
| Personality disorder[a] | 8 | 4 |
| Akathisia | 5 | 1 |

[a] Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.

**Table 10: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 3-Week and 4-Week Trials — Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine (N=125)** | **Placebo (N=129)** |
| Asthenia | 15 | 6 |
| Dry mouth | 22 | 7 |
| Constipation | 11 | 5 |
| Dyspepsia | 11 | 5 |
| Increased appetite | 6 | 3 |

| | | |
|---|---|---|
| Somnolence | 35 | 13 |
| Dizziness | 18 | 6 |
| Tremor | 6 | 3 |

Olanzapine Intramuscular — There was 1 adverse reaction (somnolence) observed at an incidence of 5% or greater among intramuscular olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar I mania was 6% for intramuscular olanzapine for injection and 3% for placebo.

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term, Placebo-Controlled Trials*

Table 11 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with oral olanzapine (doses ≥2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

**Table 11: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials with Oral Olanzapine**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Body System/Adverse Reaction** | **Olanzapine (N=532)** | **Placebo (N=294)** |
| **Body as a Whole** | | |
| Accidental injury | 12 | 8 |
| Asthenia | 10 | 9 |
| Fever | 6 | 2 |
| Back pain | 5 | 2 |
| Chest pain | 3 | 1 |
| **Cardiovascular System** | | |
| Postural hypotension | 3 | 1 |
| Tachycardia | 3 | 1 |
| Hypertension | 2 | 1 |
| **Digestive System** | | |
| Dry mouth | 9 | 5 |
| Constipation | 9 | 4 |
| Dyspepsia | 7 | 5 |
| Vomiting | 4 | 3 |
| Increased appetite | 3 | 2 |
| **Hemic and Lymphatic System** | | |
| Ecchymosis | 5 | 3 |
| **Metabolic and Nutritional Disorders** | | |
| Weight gain | 5 | 3 |
| Peripheral edema | 3 | 1 |
| **Musculoskeletal System** | | |
| Extremity pain (other than joint) | 5 | 3 |
| Joint pain | 5 | 3 |
| **Nervous System** | | |
| Somnolence | 29 | 13 |
| Insomnia | 12 | 11 |
| Dizziness | 11 | 4 |
| Abnormal gait | 6 | 1 |
| Tremor | 4 | 3 |
| Akathisia | 3 | 2 |
| Hypertonia | 3 | 2 |
| Articulation impairment | 2 | 1 |
| **Respiratory System** | | |
| Rhinitis | 7 | 6 |
| Cough increased | 6 | 3 |
| Pharyngitis | 4 | 3 |
| **Special Senses** | | |
| Amblyopia | 3 | 2 |
| **Urogenital System** | | |

| | | |
|---|---|---|
| Urinary incontinence | 2 | 1 |
| Urinary tract infection | 2 | 1 |

*Commonly Observed Adverse Reactions in Short-Term Trials of Oral Olanzapine as Adjunct to Lithium or Valproate*

In the bipolar I disorder (manic or mixed episodes) adjunct placebo-controlled trials, the most commonly observed adverse reactions associated with the combination of olanzapine and lithium or valproate (incidence of ≥5% and at least twice placebo) were:

**Table 12: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Adjunct to Lithium or Valproate Trials — Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine with lithium or valproate (N=229)** | **Placebo with lithium or valproate (N=115)** |
| Dry mouth | 32 | 9 |
| Weight gain | 26 | 7 |
| Increased appetite | 24 | 8 |
| Dizziness | 14 | 7 |
| Back pain | 8 | 4 |
| Constipation | 8 | 4 |
| Speech disorder | 7 | 1 |
| Increased salivation | 6 | 2 |
| Amnesia | 5 | 2 |
| Paresthesia | 5 | 2 |

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term Trials of Olanzapine as Adjunct to Lithium or Valproate*

Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

**Table 13: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials of Oral Olanzapine as Adjunct to Lithium or Valproate**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Body System/Adverse Reaction** | **Olanzapine with lithium or valproate (N=229)** | **Placebo with lithium or valproate (N=115)** |
| **Body as a Whole** | | |
| Asthenia | 18 | 13 |
| Back pain | 8 | 4 |
| Accidental injury | 4 | 2 |
| Chest pain | 3 | 2 |
| **Cardiovascular System** | | |
| Hypertension | 2 | 1 |
| **Digestive System** | | |
| Dry mouth | 32 | 9 |
| Increased appetite | 24 | 8 |
| Thirst | 10 | 6 |
| Constipation | 8 | 4 |
| Increased salivation | 6 | 2 |
| **Metabolic and Nutritional Disorders** | | |
| Weight gain | 26 | 7 |
| Peripheral edema | 6 | 4 |
| Edema | 2 | 1 |
| **Nervous System** | | |
| Somnolence | 52 | 27 |
| Tremor | 23 | 13 |
| Depression | 18 | 17 |
| Dizziness | 14 | 7 |
| Speech disorder | 7 | 1 |
| Amnesia | 5 | 2 |
| Paresthesia | 5 | 2 |

| | | |
|---|---|---|
| **18** | | |
| Apathy | 4 | 3 |
| Confusion | 4 | 1 |
| Euphoria | 3 | 2 |
| Incoordination | 2 | 0 |
| **Respiratory System** | | |
| Pharyngitis | 4 | 1 |
| Dyspnea | 3 | 1 |
| **Skin and Appendages** | | |
| Sweating | 3 | 1 |
| Acne | 2 | 0 |
| Dry skin | 2 | 0 |
| **Special Senses** | | |
| Amblyopia | 9 | 5 |
| Abnormal vision | 2 | 0 |
| **Urogenital System** | | |
| Dysmenorrhea[a] | 2 | 0 |
| Vaginitis[a] | 2 | 0 |

[a] Denominator used was for females only (olanzapine, N=128; placebo, N=51).

For specific information about the adverse reactions observed with lithium or valproate, refer to the Adverse Reactions section of the package inserts for these other products.

*Adverse Reactions Occurring at an Incidence of 1% or More among Intramuscular Olanzapine for Injection-Treated Patients in Short-Term, Placebo-Controlled Trials*

Table 14 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 1% or more of patients treated with intramuscular olanzapine for injection (dose range of 2.5-10 mg/injection) and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar I mania.

**Table 14: Treatment-Emergent Adverse Reactions: Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trials with Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia or Bipolar I Mania**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Body System/Adverse Reaction** | **Olanzapine (N=415)** | **Placebo (N=150)** |
| **Body as a Whole** | | |
| Asthenia | 2 | 1 |
| **Cardiovascular System** | | |
| Hypotension | 2 | 0 |
| Postural hypotension | 1 | 0 |
| **Nervous System** | | |
| Somnolence | 6 | 3 |
| Dizziness | 4 | 2 |
| Tremor | 1 | 0 |

**Additional Findings Observed in Clinical Trials**

Dose Dependency of Adverse Reactions in Short-Term, Placebo-Controlled Trials

*Extrapyramidal Symptoms:* The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

**Table 15: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | **Placebo** | **Olanzapine 5 ± 2.5 mg/day** | **Olanzapine 10 ± 2.5 mg/day** | **Olanzapine 15 ± 2.5 mg/day** |
| Parkinsonism[a] | 15 | 14 | 12 | 14 |
| Akathisia[b] | 23 | 16 | 19 | 27 |

[a] Percentage of patients with a Simpson-Angus Scale total score >3.

[b] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

**Table 16: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | Placebo (N=68) | Olanzapine 5 ± 2.5 mg/day (N=65) | Olanzapine 10 ± 2.5 mg/day (N=64) | Olanzapine 15 ± 2.5 mg/day (N=69) |
| Dystonic events[a] | 1 | 3 | 2 | 3 |
| Parkinsonism events[b] | 10 | 8 | 14 | 20 |
| Akathisia events[c] | 1 | 5 | 11 | 10 |
| Dyskinetic events[d] | 4 | 0 | 2 | 1 |
| Residual events[e] | 1 | 2 | 5 | 1 |
| Any extrapyramidal event | 16 | 15 | 25 | 32 |

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[c] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[e] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

The following table enumerates the percentage of adolescent patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy (dose range: 2.5 to 20 mg/day).

**Table 17: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in Placebo-Controlled Clinical Trials of Oral Olanzapine in Schizophrenia and Bipolar I Disorder — Adolescents**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| Categories[a] | Placebo (N=89) | Olanzapine (N=179) |
| Dystonic events | 0 | 1 |
| Parkinsonism events | 2 | 1 |
| Akathisia events | 4 | 6 |
| Dyskinetic events | 0 | 1 |
| Nonspecific events | 0 | 4 |
| Any extrapyramidal event | 6 | 10 |

[a] Categories are based on Standard MedDRA Queries (SMQ) for extrapyramidal symptoms as defined in MedDRA version 12.0.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with placebo in agitation. Patients in each dose group could receive up to 3 injections during the trials *[see Clinical Studies (14.3)]*. Patient assessments were conducted during the 24 hours following the initial dose of intramuscular olanzapine for injection.

**Table 18: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia**

| | Percentage of Patients Reporting Event | | | | |
|---|---|---|---|---|---|
| | Placebo | Olanzapine IM 2.5 mg | Olanzapine IM 5 mg | Olanzapine IM 7.5 mg | Olanzapine IM 10 mg |
| Parkinsonism[a] | 0 | 0 | 0 | 0 | 3 |
| Akathisia[b] | 0 | 0 | 5 | 0 | 0 |

[a] Percentage of patients with a Simpson-Angus Scale total score >3.

[b] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions in the same controlled clinical trial comparing fixed doses of intramuscular olanzapine for injection with placebo in agitated patients with schizophrenia.

**Table 19: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia**

| | Percentage of Patients Reporting Event | | | | |
|---|---|---|---|---|---|
| | Placebo (N=45) | Olanzapine IM 2.5 mg (N=48) | Olanzapine IM 5 mg (N=45) | Olanzapine IM 7.5 mg (N=46) | Olanzapine IM 10 mg (N=46) |
| Dystonic events[a] | 0 | 0 | 0 | 0 | 0 |
| Parkinsonism events[b] | 0 | 4 | 2 | 0 | 0 |
| Akathisia events[c] | 0 | 2 | 0 | 0 | 0 |
| Dyskinetic events[d] | 0 | 0 | 0 | 0 | 0 |
| Residual events[e] | 0 | 0 | 0 | 0 | 0 |
| Any extrapyramidal events | 0 | 4 | 2 | 0 | 0 |

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[c] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[e] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

*Dystonia, Class Effect:* 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 olanzapine use.

*Other Adverse Reactions:* The following table addresses dose relatedness for other adverse reactions using data from a schizophrenia trial involving fixed dosage ranges of oral olanzapine. It enumerates the percentage of patients with treatment-emergent adverse reactions for the 3 fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse reactions for which there was a trend.

**Table 20: Percentage of Patients from a Schizophrenia Trial with Treatment-Emergent Adverse Reactions for the 3 Dose Range Groups and Placebo**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| Adverse Reaction | Placebo (N=68) | Olanzapine 5 ± 2.5 mg/day (N=65) | Olanzapine 10 ± 2.5 mg/day (N=64) | Olanzapine 15 ± 2.5 mg/day (N=69) |
| Asthenia | 15 | 8 | 9 | 20 |
| Dry mouth | 4 | 3 | 5 | 13 |
| Nausea | 9 | 0 | 2 | 9 |
| Somnolence | 16 | 20 | 30 | 39 |
| Tremor | 3 | 0 | 5 | 7 |

Differences among Fixed-Dose Groups 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 oral olanzapine in patients with schizophrenia or schizoaffective disorder, 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/mL (female) or >18.77 ng/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 During the Clinical Trial Evaluation of Oral Olanzapine

Following is a list of treatment-emergent adverse reactions reported by patients treated with oral olanzapine (at multiple doses ≥1 mg/day) 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; rare reactions are those occurring in fewer than 1/1000 patients.

**Body as a Whole** — *Infrequent:* chills, face edema, photosensitivity reaction, suicide attempt[1]; *Rare:* chills and fever, hangover effect, sudden death[1].

**Cardiovascular System** — *Infrequent:* cerebrovascular accident, vasodilatation.

**Digestive System** — *Infrequent:* nausea and vomiting, tongue edema; *Rare:* ileus, intestinal obstruction, liver fatty deposit.

**Hemic and Lymphatic System** — *Infrequent:* leukopenia, thrombocytopenia.

**Metabolic and Nutritional Disorders** — *Infrequent:* alkaline phosphatase increased, bilirubinemia, hypoproteinemia.

**Musculoskeletal System** — *Rare:* osteoporosis.

**Nervous System** — *Infrequent:* ataxia, dysarthria, libido decreased, stupor; *Rare:* coma.

**Respiratory System** — *Infrequent:* epistaxis; *Rare:* lung edema.

**Skin and Appendages** — *Infrequent:* alopecia.

**Special Senses** — *Infrequent:* abnormality of accommodation, dry eyes; *Rare:* mydriasis.

**Urogenital System** — *Infrequent:* amenorrhea[2], breast pain, decreased menstruation, impotence[2], increased menstruation[2], menorrhagia[2], metrorrhagia[2], polyuria[2], urinary frequency, urinary retention, urinary urgency, urination impaired.

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

[2] Adjusted for gender.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Intramuscular Olanzapine for Injection

Following is a list of treatment-emergent adverse reactions reported by patients treated with intramuscular olanzapine for injection (at 1 or more doses ≥2.5 mg/injection) 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) for 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.

**Body as a Whole** — *Frequent:* injection site pain.

**Cardiovascular System** — *Infrequent:* syncope.

**Digestive System** — *Infrequent:* nausea.

**Metabolic and Nutritional Disorders** — *Infrequent:* creatine phosphokinase increased.

Clinical Trials in Adolescent Patients (age 13 to 17 years)

*Commonly Observed Adverse Reactions in Oral Olanzapine Short-Term, Placebo-Controlled Trials*

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 5% or more and reported at least twice as frequently as placebo-treated patients are listed in Table 21.

**Table 21: Treatment-Emergent Adverse Reactions of ≥5% Incidence among Adolescents (13-17 Years Old) with Schizophrenia or Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | 6 Week Trial % Schizophrenia Patients | | 3 Week Trial % Bipolar Patients | |
| Adverse Reactions | Olanzapine (N=72) | Placebo (N=35) | Olanzapine (N=107) | Placebo (N=54) |
| Sedation[a] | 39 | 9 | 48 | 9 |
| Weight increased | 31 | 9 | 29 | 4 |
| Headache | 17 | 6 | 17 | 17 |
| Increased appetite | 17 | 9 | 29 | 4 |
| Dizziness | 8 | 3 | 7 | 2 |
| Abdominal pain[b] | 6 | 3 | 6 | 7 |
| Pain in extremity | 6 | 3 | 5 | 0 |
| Fatigue | 3 | 3 | 14 | 6 |
| Dry mouth | 4 | 0 | 7 | 0 |

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.

[b] Patients with the following MedDRA terms were counted in this category: abdominal pain, abdominal pain lower, abdominal pain upper.

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term (3-6 weeks), Placebo-Controlled Trials*

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 2% or more and greater than placebo are listed in Table 22.

**Table 22: Treatment-Emergent Adverse Reactions of ≥2% Incidence among Adolescents (13-17 Years Old) (Combined Incidence from Short-Term, Placebo-Controlled Clinical Trials of Schizophrenia or Bipolar I Disorder [Manic or Mixed Episodes])**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine (N=179)** | **Placebo (N=89)** |
| Sedation[a] | 44 | 9 |
| Weight increased | 30 | 6 |
| Increased appetite | 24 | 6 |
| Headache | 17 | 12 |
| Fatigue | 9 | 4 |
| Dizziness | 7 | 2 |
| Dry mouth | 6 | 0 |
| Pain in extremity | 5 | 1 |
| Constipation | 4 | 0 |
| Nasopharyngitis | 4 | 2 |
| Diarrhea | 3 | 0 |
| Restlessness | 3 | 2 |
| Liver enzymes increased[b] | 8 | 1 |
| Dyspepsia | 3 | 1 |
| Epistaxis | 3 | 0 |
| Respiratory tract infection[c] | 3 | 2 |
| Sinusitis | 3 | 0 |
| Arthralgia | 2 | 0 |
| Musculoskeletal stiffness | 2 | 0 |

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.

[b] The terms alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hepatic enzyme were combined under liver enzymes.

[c] Patients with the following MedDRA terms were counted in this category: lower respiratory tract infection, respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection.

### 6.2 Vital Signs and Laboratory Studies

Vital Sign Changes — Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials *[see Warnings and Precautions (5)]*.

Laboratory Changes — An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in ALT, AST, and GGT. In placebo-controlled olanzapine monotherapy studies in adults, 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 to none (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 premarketing database of about 2400 adult 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 2500 adult patients in oral olanzapine clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases.

In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from <3 times the upper limit of normal at baseline to ≥3 times the upper limit of the normal range) were observed in 12% (21/174) of patients exposed to olanzapine compared to 2% (2/87) of the placebo-treated patients. Discontinuation due to transaminase increases occurred in 3.4% (6/179) of patients exposed to olanzapine.

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.

Olanzapine administration was also associated with increases in serum prolactin *[see Warnings and Precautions (5.15)]*, with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models *[see Nonclinical Toxicology (13.2)]*, careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

*Olanzapine Monotherapy in Adolescents:* In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar I disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT (≥3 X ULN in patients with ALT at baseline <3 X ULN), (12.1% vs 2.3%); elevated AST (27.6% vs 3.8%); low total bilirubin (22.1% vs 6.7%); elevated GGT (10.1% vs 1.2%); and elevated prolactin (47.4% vs 6.8%).

ECG Changes — In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc (Fridericia corrected), and PR intervals. Olanzapine use was associated with a mean increase in heart rate compared to placebo (adults: +2.4 beats per minute vs no change with placebo; adolescents: +6.3 beats per minute vs -5.1 beats per minute with placebo). This increase in heart rate may be related to olanzapine's potential for inducing orthostatic changes *[see Warnings and Precautions (5.8)]*.

### 6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZYPREXA. 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 ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, diabetic ketoacidosis, discontinuation reaction (diaphoresis, nausea or vomiting), jaundice, neutropenia, pancreatitis, priapism, rash, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

## 7 DRUG INTERACTIONS

The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies.

### 7.1 Potential for Other Drugs to Affect Olanzapine

Diazepam — The co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Cimetidine and Antacids — Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Inducers of CYP1A2 — Carbamazepine therapy (200 mg bid) causes an approximately 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.

Alcohol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The co-administration of alcohol (i.e., ethanol) with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Inhibitors of CYP1A2

*Fluvoxamine:* Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine Cmax following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

Inhibitors of CYP2D6

*Fluoxetine:* Fluoxetine (60 mg single dose or 60 mg daily dose for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended. When using ZYPREXA and fluoxetine in combination, also refer to the Drug Interactions section of the package insert for Symbyax.

Warfarin — Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics *[see Drug Interactions (7.2)]*.

Inducers of CYP1A2 or Glucuronyl Transferase — Omeprazole and rifampin may cause an increase in olanzapine clearance.

Charcoal — The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

### 7.2 Potential for Olanzapine to Affect Other Drugs

CNS Acting Drugs — Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Antihypertensive Agents — Olanzapine, because of its potential for inducing hypotension, may enhance the effects of certain antihypertensive agents.

Levodopa and Dopamine Agonists — Olanzapine may antagonize the effects of levodopa and dopamine agonists.

Lorazepam (IM) — Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone *[see Warnings and Precautions (5.8)]*.

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium *[see Warnings and Precautions (5.16)]*.

Valproate — Olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate *[see Warnings and Precautions (5.16)]*.

Effect of Olanzapine on Drug Metabolizing Enzymes — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Imipramine — Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

Warfarin — Single doses of olanzapine did not affect the pharmacokinetics of warfarin *[see Drug Interactions (7.1)]*.

Diazepam — Olanzapine did not influence the pharmacokinetics of diazepam or its active metabolite N-desmethyldiazepam. However, diazepam co-administered with olanzapine increased the orthostatic hypotension observed with either drug given alone *[see Drug Interactions (7.1)]*.

Alcohol — Multiple doses of olanzapine did not influence the kinetics of ethanol *[see Drug Interactions (7.1)]*.

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

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

## 8 USE IN SPECIFIC POPULATIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Use in Specific Populations section of the package insert for Symbyax.

### 8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C — 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 maximum recommended human daily oral dose on a $mg/m^2$ basis, respectively) no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a $mg/m^2$ basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a $mg/m^2$ basis). In an oral 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 maximum recommended human daily oral dose on a $mg/m^2$ 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 trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion.

### 8.2 Labor and Delivery

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

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

The safety and effectiveness of oral ZYPREXA in the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder were established in short-term studies in adolescents (ages 13 to 17 years). Use of ZYPREXA in adolescents is supported by evidence from adequate and well-controlled studies of ZYPREXA in which 268 adolescents received ZYPREXA in a range of 2.5 to 20 mg/day *[see Clinical Studies (14.1, 14.2)]*. Recommended starting dose for adolescents is lower than that for adults *[see Dosage and Administration (2.1, 2.2)]*. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic transaminase levels *[see Warnings and Precautions (5.5, 5.6, 5.15, 5.17) and Adverse Reactions (6.2)]*. When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Indications and Usage (1.1, 1.2)]*.

Safety and effectiveness of olanzapine in children <13 years of age have not been established *[see Patient Counseling Information (17.13)]*.

Safety and effectiveness of ZYPREXA and fluoxetine in combination in children and adolescents <18 years of age have not been established.

### 8.5 Geriatric Use

Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to 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 events (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. 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 *[see Boxed Warning, Dosage and Administration (2.1), and Warnings and Precautions (5.1)]*.

Clinical studies of ZYPREXA and fluoxetine in combination did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients.

## 9 DRUG ABUSE AND DEPENDENCE

### 9.3 Dependence

In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily oral dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily oral dose on a mg/m$^2$ basis.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials 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, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

## 10 OVERDOSAGE

### 10.1 Human Experience

In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

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 and 1 patient experiencing 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.

### 10.2 Management of Overdose

The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

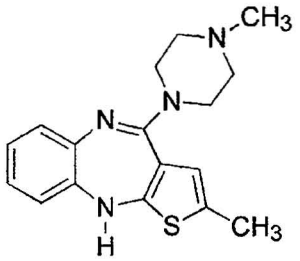
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. 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 beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

For specific information about overdosage with lithium or valproate, refer to the Overdosage section of the package inserts for these products. For specific information about overdosage with olanzapine and fluoxetine in combination, refer to the Overdosage section of the Symbyax package insert.

## 11 DESCRIPTION

ZYPREXA (olanzapine) is an atypical antipsychotic that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-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. The chemical structure is:



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

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 µmol), 5 mg (16 µmol), 7.5 mg (24 µmol), 10 mg (32 µmol), 15 mg (48 µmol), or 20 mg (64 µmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 µmol), 10 mg (32 µmol), 15 mg (48 µmol) or 20 mg (64 µmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

ZYPREXA IntraMuscular (olanzapine for injection) is intended for intramuscular use only.

Each vial provides for the administration of 10 mg (32 µmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT2) antagonism. The mechanism of action of olanzapine in the treatment of acute manic or mixed episodes associated with bipolar I disorder is unknown.

### 12.2 Pharmacodynamics

Olanzapine binds with high affinity to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$ ($K_i$=4, 11, and 5 nM, respectively), dopamine $D_{1-4}$ ($K_i$=11-31 nM), histamine $H_1$ ($K_i$=7 nM), and adrenergic $\alpha_1$ receptors ($K_i$=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ ($K_i$=57 nM) and muscarinic $M_{1-5}$ ($K_i$=73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds weakly to $GABA_A$, BZD, and β-adrenergic receptors ($K_i$>10 µM).

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. Olanzapine's antagonism of histamine $H_1$ receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic $\alpha_1$ receptors may explain the orthostatic hypotension observed with this drug.

### 12.3 Pharmacokinetics

Oral Administration, Monotherapy — Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics 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.

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/mL, binding primarily to albumin and $\alpha_1$-acid glycoprotein.

Metabolism and Elimination — 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 cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, 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.

Intramuscular Administration — ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is similar to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

*Specific Populations*

Renal Impairment — 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 metabolite elimination has not been studied.

Hepatic Impairment — 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 (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Geriatric — In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (≥65 years) than in nonelderly subjects (<65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity *[see Dosage and Administration (2)]*.

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 recommended.

Race — In vivo studies have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine *[see Dosage and Administration (2)]*.

Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents were nonsmokers and this population had a lower average body weight, which resulted in higher average olanzapine exposure compared to adults.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily oral dose on a mg/m$^2$ basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a mg/m$^2$ basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily oral dose on a mg/m$^2$ basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in 1 mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a mg/m$^2$ basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily oral dose on a mg/m$^2$ 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 maximum recommended human daily oral dose on a mg/m$^2$ 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 (5.15)]*.

Mutagenesis — 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.

Impairment of Fertility — 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 maximum recommended human daily oral dose on a $mg/m^2$ 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 maximum recommended human daily oral dose on a $mg/m^2$ basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a $mg/m^2$ basis); therefore olanzapine may produce a delay in ovulation.

### 13.2 Animal Toxicology and/or Pharmacology

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily oral dose on a $mg/m^2$ basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a $mg/m^2$ basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily oral dose on a $mg/m^2$ basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a $mg/m^2$ basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

## 14 CLINICAL STUDIES

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

### 14.1 Schizophrenia

**Adults**

The efficacy of oral olanzapine in the treatment of schizophrenia was established in 2 short-term (6-week) controlled trials of adult inpatients who met DSM III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in 1 of the 2 trials, but this trial did not compare these 2 drugs on the full range of clinically relevant doses for both.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, 2 more recently developed scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which are embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving 2 fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine ($5 \pm 2.5$ mg/day, $10 \pm 2.5$ mg/day, and $15 \pm 2.5$ mg/day) on a once daily schedule, the 2 highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high-dose group over the medium-dose group.

(3) In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open-label treatment for at least 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however, criteria were met for stopping the trial early due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months.

Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

**Adolescents**

The efficacy of oral olanzapine in the acute treatment of schizophrenia in adolescents (ages 13 to 17 years) was established in a 6-week double-blind, placebo-controlled, randomized trial of inpatients and outpatients with schizophrenia (n=107) who met diagnostic criteria according to DSM-IV-TR and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL).

The primary rating instrument used for assessing psychiatric signs and symptoms in this trial was the Anchored Version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score.

In this flexible-dose trial, olanzapine 2.5 to 20 mg/day (mean modal dose 12.5 mg/day, mean dose of 11.1 mg/day) was more effective than placebo in the treatment of adolescents diagnosed with schizophrenia, as supported by the statistically significantly greater mean reduction in BPRS-C total score for patients in the olanzapine treatment group than in the placebo group.

While there is no body of evidence available to answer the question of how long the adolescent patient treated with ZYPREXA should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 14.2 Bipolar I Disorder (Manic or Mixed Episodes)

**Adults**

Monotherapy — The efficacy of oral olanzapine in the treatment of manic or mixed episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in adult patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar I disorder who had responded during an initial open-label treatment phase for about 2 weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to ≤12 and HAM-D 21 to ≤8. Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to ≥15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Adjunct to Lithium or Valproate — The efficacy of oral olanzapine with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in 2 controlled trials in patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course. The results of the trials follow:

(1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

**Adolescents**

Acute Monotherapy — The efficacy of oral olanzapine in the treatment of acute manic or mixed episodes in adolescents (ages 13 to 17 years) was established in a 3-week, double-blind, placebo-controlled, randomized trial of adolescent inpatients and outpatients who met the diagnostic criteria for manic or mixed episodes associated with bipolar I disorder (with or without psychotic features) according to the DSM-IV-TR (n=161). Diagnosis was confirmed by the K-SADS-PL.

The primary rating instrument used for assessing manic symptoms in this trial was the Adolescent Structured Young-Mania Rating Scale (Y-MRS) total score.

In this flexible-dose trial, olanzapine 2.5 to 20 mg/day (mean modal dose 10.7 mg/day, mean dose of 8.9 mg/day) was more effective than placebo in the treatment of adolescents with manic or mixed episodes associated with bipolar I disorder, as supported by the statistically significantly greater mean reduction in Y-MRS total score for patients in the olanzapine treatment group than in the placebo group.

While there is no body of evidence available to answer the question of how long the adolescent patient treated with ZYPREXA should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 14.3 Agitation Associated with Schizophrenia and Bipolar I Mania

The efficacy of intramuscular olanzapine for injection for the treatment of agitation was established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients from 2 diagnostic groups: schizophrenia and bipolar I disorder (manic or mixed episodes). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar I mania study). Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥14 on the 5 items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least 1 individual item score ≥4 using a 1-7 scoring system (1=absent, 4=moderate, 7=extreme). In the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to 3 injections during the 24 hour IM treatment periods; however, patients could not receive the second injection until after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

(1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270), 4 fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the 3 highest doses. There were no significant pairwise differences for the 7.5 and 10 mg doses over the 5 mg dose.

(2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=311), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

(3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for bipolar I disorder (and currently displaying an acute manic or mixed episode with or without psychotic features) (n=201), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. The tablets are available as follows:

| | TABLET STRENGTH | | | | | |
|---|---|---|---|---|---|---|
| | 2.5 mg | 5 mg | 7.5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4112 | 4115 | 4116 | 4117 | 4415 | 4420 |
| Identification | LILLY 4112 | LILLY 4115 | LILLY 4116 | LILLY 4117 | LILLY 4415 | LILLY 4420 |
| NDC Codes: | | | | | | |
| Bottles 30 | NDC 0002-4112-30 | NDC 0002-4115-30 | NDC 0002-4116-30 | NDC 0002-4117-30 | NDC 0002-4415-30 | NDC 0002-4420-30 |
| Blisters – ID[a] 100 | NDC 0002-4112-33 | NDC 0002-4115-33 | NDC 0002-4116-33 | NDC 0002-4117-33 | NDC 0002-4415-33 | NDC 0002-4420-33 |
| Bottles 1000 | NDC 0002-4112-04 | NDC 0002-4115-04 | NDC 0002-4116-04 | NDC 0002-4117-04 | NDC 0002-4415-04 | NDC 0002-4420-04 |

[a] Identi-Dose® (unit dose medication, Lilly).

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:

| | TABLET STRENGTH | | | |
|---|---|---|---|---|
| ZYPREXA ZYDIS Tablets[a] | 5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4453 | 4454 | 4455 | 4456 |
| Debossed | 5 | 10 | 15 | 20 |
| NDC Codes: | | | | |
| Dose Pack 30 (Child Resistant) | NDC 0002-4453-85 | NDC 0002-4454-85 | NDC 0002-4455-85 | NDC 0002-4456-85 |

ZYPREXA is a registered trademark of Eli Lilly and Company.

ZYDIS is a registered trademark of Catalent Pharma Solutions.

[a] ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Catalent Pharma Solutions, United Kingdom, SN5 8RU.

ZYPREXA IntraMuscular is available in:

NDC 0002-7597-01 (No. VL7597) – 10 mg vial (1s)

### 16.2 Storage and Handling

Store ZYPREXA tablets, ZYPREXA ZYDIS, and ZYPREXA IntraMuscular vials (before reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP] for up to 1 hour if necessary. *Discard any unused portion of reconstituted ZYPREXA IntraMuscular.* The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect ZYPREXA tablets and ZYPREXA ZYDIS from light and moisture. Protect ZYPREXA IntraMuscular from light, do not freeze.

## 17 PATIENT COUNSELING INFORMATION

*See FDA-approved Medication Guide for the oral formulations.*

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking ZYPREXA as monotherapy or in combination with fluoxetine. If you do not think you are getting better or have any concerns about your condition while taking ZYPREXA, call your doctor. When using ZYPREXA and fluoxetine in combination, also refer to the Patient Counseling Information section of the package insert for 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 ZYPREXA, and should counsel them in its appropriate use. A patient Medication Guide is available for ZYPREXA. 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. When using ZYPREXA and fluoxetine in combination, also refer to the Medication Guide for Symbyax.

### 17.2 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 an increased risk of death. Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with ZYPREXA had a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) compared with placebo.

ZYPREXA is not approved for elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*.

### 17.3 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 ZYPREXA. 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)]*.

### 17.4 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 who have diabetes should follow their doctor's instructions about how often to check their blood sugar while taking ZYPREXA *[see Warnings and Precautions (5.4)]*.

**17.5 Hyperlipidemia**

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

**17.6 Weight Gain**

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

**17.7 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 ZYPREXA, e.g., diazepam or alcohol *[see Warnings and Precautions (5.8) and Drug Interactions (7)]*. 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.

**17.8 Potential for Cognitive and Motor Impairment**

Because ZYPREXA 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 ZYPREXA therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

**17.9 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 (5.13)]*.

**17.10 Concomitant Medication**

Patients should be advised to inform their physicians if they are taking, or plan to take, Symbyax. Patients should also 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 *[see Drug Interactions (7)]*.

**17.11 Alcohol**

Patients should be advised to avoid alcohol while taking ZYPREXA *[see Drug Interactions (7)]*.

**17.12 Phenylketonurics**

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively) *[see Description (11)]*.

**17.13 Use in Specific Populations**

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

Nursing Mothers — Patients should be advised not to breast-feed an infant if they are taking ZYPREXA *[see Use in Specific Populations (8.3)]*.

Pediatric Use — ZYPREXA is indicated for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adolescents 13 to 17 years of age. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin, and hepatic transaminase levels. Patients should be counseled about the potential long-term risks associated with ZYPREXA and advised that these risks may lead them to consider other drugs first *[see Indications and Usage (1.1, 1.2)]*. Safety and effectiveness of ZYPREXA in patients under 13 years of age have not been established. Safety and effectiveness of ZYPREXA and fluoxetine in combination in patients <18 years of age have not been established *[see Warnings and Precautions (5.5, 5.6) and Use in Specific Populations (8.4)]*.

**17.14 Need for Comprehensive Treatment Program in Pediatric Patients**

ZYPREXA is indicated as an integral part of a total treatment program for pediatric patients with schizophrenia and bipolar disorder that may include other measures (psychological, educational, social) for patients with the disorder. Effectiveness and safety of ZYPREXA have not been established in pediatric patients less than 13 years of age. Atypical antipsychotics are not intended for use in the pediatric patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders. Appropriate educational placement is essential and psychosocial intervention is often helpful. The decision to prescribe atypical antipsychotic medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms *[see Indications and Usage (1.3)]*.

Literature revised Month dd, 2009

**Eli Lilly and Company, Indianapolis, IN 46285, USA**

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NL 6244 AMP 2009DEC02 PRINTED IN USA

# Medication Guide

ZYPREXA® (zy-PREX-a)

(olanzapine)

Tablet

ZYPREXA® ZYDIS® (zy-PREX-a ZY-dis)

(olanzapine)

Tablet, Orally Disintegrating

Read the Medication Guide that comes with ZYPREXA 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 ZYPREXA.

## What is the most important information I should know about ZYPREXA?

**Serious side effects may happen when you take ZYPREXA, including:**

**Increased risk of death in elderly patients with dementia-related psychosis:** Medicines like ZYPREXA can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). ZYPREXA is not approved for treating psychosis in the elderly with dementia.

**High blood sugar (hyperglycemia):** High blood sugar can happen 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 ZYPREXA and during treatment. In people who do not have diabetes, sometimes high blood sugar goes away when ZYPREXA is stopped. People with diabetes and some people who did not have diabetes before taking ZYPREXA need to take medicine for high blood sugar even after they stop taking ZYPREXA.

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

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

- 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)** may happen in people treated with ZYPREXA, especially in teenagers (13-17 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 ZYPREXA and during treatment.

**Increase in weight (weight gain):** Weight gain is very common in people who take ZYPREXA. Teenagers (13-17 years old) are more likely to gain weight and to gain more weight than adults. Some people may gain a lot of weight while taking ZYPREXA, 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.

**Increased risk in teenagers (13-17 years old):** Possible serious risks of weight gain and increases in cholesterol and triglycerides are more common in teenagers than in adults. You and your doctor should decide if other available treatments should be used first. Before your teenager takes ZYPREXA, talk with your doctor about the possible long-term risks of teenagers taking ZYPREXA.

## What is ZYPREXA?

**ZYPREXA is a prescription medicine used to treat:**

- schizophrenia in people age 13 or older.
- bipolar disorder, including:
  - manic or mixed episodes that happen with bipolar I disorder in people age 13 or older.
  - manic or mixed episodes that happen with bipolar I disorder, when used with the medicine lithium or valproate, in adults.
  - long-term treatment of bipolar I disorder in adults.
- episodes of depression that happen with bipolar I disorder, when used with the medicine fluoxetine (Prozac®), in adults.
- episodes of depression that do not get better after 2 other medicines, also called treatment resistant depression, when used with the medicine fluoxetine (Prozac), in adults.

ZYPREXA has not been approved for use in children under 13 years of age.

The symptoms of schizophrenia include hearing voices, seeing things that are not there, having beliefs that are not true, and being suspicious or withdrawn.

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.

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.

Some of your symptoms may improve with treatment. If you do not think you are getting better, call your doctor.

## What should I tell my doctor before taking ZYPREXA?

ZYPREXA may not be right for you. Before starting ZYPREXA, tell your doctor if you have or had:

- heart problems
- seizures
- 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)
- Alzheimer's disease
- narrow-angle glaucoma
- enlarged prostate in men
- bowel obstruction
- phenylketonuria, because ZYPREXA ZYDIS contains phenylalanine

- breast cancer
- thoughts of suicide or hurting yourself
- any other medical condition
- are pregnant or plan to become pregnant. It is not known if ZYPREXA will harm your unborn baby.
- are breast-feeding or plan to breast-feed. ZYPREXA can pass into your breast milk and may harm your baby. You should not breast-feed while taking ZYPREXA. Talk to your doctor about the best way to feed your baby if you take ZYPREXA.

Tell your doctor if you exercise a lot or are in hot places often.

The symptoms of bipolar I disorder, treatment resistant depression, or schizophrenia may include **thoughts of suicide** or of hurting yourself or others. If you have these thoughts at any time, tell your doctor or go to an emergency room right away.

**Tell your doctor about all the medicines that you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. ZYPREXA 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 ZYPREXA with your other medicines. Do not start or stop any medicine while taking ZYPREXA without talking to your doctor first.

## How should I take ZYPREXA?

- Take ZYPREXA exactly as prescribed. Your doctor may need to change (adjust) the dose of ZYPREXA until it is right for you.
- If you miss a dose of ZYPREXA, take the missed dose as soon as you remember. If it is almost time for the next dose, just skip the missed dose and take your next dose at the regular time. Do not take two doses of ZYPREXA at the same time.
- **To prevent serious side effects, do not stop taking ZYPREXA suddenly. If you need to stop taking ZYPREXA, your doctor can tell you how to safely stop taking it.**
- **If you take too much ZYPREXA, call your doctor or poison control center at 1-800-222-1212 right away, or get emergency treatment.**
- ZYPREXA can be taken with or without food.
- ZYPREXA is usually taken one time each day.
- Take ZYPREXA ZYDIS as follows:
  - Be sure that your hands are dry.
  - Open the sachet and peel back the foil on the blister. Do not push the tablet through the foil.
  - As soon as you open the blister, remove the tablet and put it into your mouth.
  - The tablet will disintegrate quickly in your saliva so that you can easily swallow it with or without drinking liquid.
- Call your doctor if you do not think you are getting better or have any concerns about your condition while taking ZYPREXA.

## What should I avoid while taking ZYPREXA?

- ZYPREXA 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 ZYPREXA affects you.
- Avoid drinking alcohol while taking ZYPREXA. Drinking alcohol while you take ZYPREXA may make you sleepier than if you take ZYPREXA alone.

## What are the possible side effects of ZYPREXA?

**Serious side effects may happen when you take ZYPREXA, including:**

- **See "What is the most important information I should know about ZYPREXA?", which describes the increased risk of death in elderly people with dementia-related psychosis and the risks of high blood sugar, high cholesterol and triglyceride levels, and weight gain.**
- **Increased incidence of stroke or "mini-strokes" called transient ischemic attacks (TIAs) in elderly people with dementia-related psychosis** (elderly people who have lost touch with reality due to confusion and memory loss). ZYPREXA is not approved for these patients.
- **Neuroleptic Malignant Syndrome (NMS):** NMS is a rare but very serious condition that can happen in people who take antipsychotic medicines, including ZYPREXA. NMS can cause death and must be treated in a hospital. Call your doctor right away if you become severely ill and have any 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 can not control. These movements usually affect the face and tongue. Tardive dyskinesia may not go away, even if you stop taking ZYPREXA. It may also start after you stop taking ZYPREXA. Tell your doctor if you get any body movements that you can not control.
- **Decreased blood pressure when you change positions, with symptoms of dizziness, fast or slow heartbeat, or fainting.**
- **Difficulty swallowing, that can cause food or liquid to get into your lungs.**
- **Seizures: Tell your doctor if you have a seizure during treatment with ZYPREXA.**
- **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 any 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 side effects of ZYPREXA include:** lack of energy, dry mouth, increased appetite, sleepiness, tremor (shakes), having hard or infrequent stools, dizziness, changes in behavior, or restlessness.

**Other common side effects in teenagers (13-17 years old) include:** headache, stomach-area (abdominal) pain, pain in your arms or legs, or tiredness. Teenagers experienced greater increases in prolactin, liver enzymes, and sleepiness, as compared with adults.

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 ZYPREXA. 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 ZYPREXA?

- Store ZYPREXA at room temperature, between 68°F to 77°F (20°C to 25°C).

- Keep ZYPREXA away from light.
- Keep ZYPREXA dry and away from moisture.

**Keep ZYPREXA and all medicines out of the reach of children.**

## General information about ZYPREXA

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

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

## What are the ingredients in ZYPREXA?

**Active ingredient:** olanzapine

**Inactive ingredients:**

**Tablets** — carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains: Titanium Dioxide, FD&C Blue No. 2 Aluminum Lake, or Synthetic Red Iron Oxide.

**ZYDIS** — gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

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

Medication Guide revised Month dd, 2009

**Eli Lilly and Company**
**Indianapolis, IN 46285, USA**

**www.zyprexa.com**

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NL 6921 AMP 2009DEC02 PRINTED IN USA

**NDA 20-592, ZYPREXA (olanzapine) Tablet for Oral Use**
**NDA 21-086, ZYPREXA ZYDIS (olanzapine) Tablet, Orally Disintegrating for Oral Use**

# RISK EVALUATION AND MITIGATION STRATEGY (REMS)

## I. Goals(s)

The goal of the REMS is to inform patients of the serious risks associated with the use of Zyprexa (olanzapine) Tablet for Oral Use and Tablet, Orally Disintegrating for Oral Use, including the risks of hyperglycemia, hyperlipidemia, and weight gain.

## II. REMS Elements

### A. Medication Guide
The Medication Guide will be dispensed with each Zyprexa prescription in accordance with 21 CFR 208.24.

### B. Communication Plan
This REMS for Zyprexa does not include a Communication Plan.

### C. Elements to Assure Safe Use
This REMS for Zyprexa does not include elements to assure safe use.

### D. Implementation System
Because this REMS for Zyprexa does not include elements to assure safe use, an implementation system is not required.

### E. Timetable for Submission of Assessments
The Timetable for Assessments is as follows:

- The first assessment is due 18 months from the original approval date of the REMS (September 19, 2010).
  The second assessment is due 3 years from the original approval date of the REMS (March 19, 2012).
- The third assessment is due 7 years from the original approval date of the REMS (March 19, 2016).

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Eli Lilly and Company will submit each assessment so it will be received by the FDA on or before the due dates listed above.

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**020592 / S-035, 039, 040, 041, 049,053, 055**

**021086 / S-21, 031, 032, 034**

**021253 / S-037, 039, 043**

## OFFICER/EMPLOYEE LIST

## Officer/Employee List
## Application: 20-592 S040/S041: Zyprexa
## Pediatric Schizophrenia/BiPolar

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Cara Alfaro
Doris Bates
Mary Dempsey
Ida-Lina Diak
Jessica Diaz
Jodi Duckhorn
Fanhui Kong
Thomas Laughren
Mitchell Mathis
Marilyn Pitts
Sarah Simon
Ellis Unger
James Vidra
Peiling Yang

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**020592 / S-035, 039, 040, 041, 049,053, 055**

**021086 / S-21, 031, 032, 034**

**021253 / S-037, 039, 043**

# MEDICAL REVIEW(S)

**Review and Evaluation of Clinical Data**
**NDA 020592, NDA 021086, NDA 021253**

| | |
|---|---|
| **Sponsor:** | Eli Lilly and Company |
| **Drug:** | Zyprexa® (olanzapine) |
| **Material Submitted:** | NDA 020592/053, NDA 021253/039<br>NDA 021086/032 |
| **Correspondence Date:** | 10/23/2009 |
| **Date Received:** | 10/26/2009 |

## I. Background

This submission dated October 23, 2009, NDA 20592/053 (eCTD Sequence No. 0042), provides for a Prior Approval Labeling Supplement for Zyprexa oral tablets and intramuscular injection. The sponsor proposed changes include revisions to laboratory and clinical findings regarding liver enzyme elevations and neutropenia in **Section 6.2 Vital Signs and Laboratory Studies**. It also provides new language regarding cardiac death in the Highlights Section of the USPI. The safety team in the DPP will review the cardiac death issue separately. Therefore, this review will only focus on the revisions in Section 6.2 Vital Signs and Laboratory Studies.

## II. Summary of Proposed Changes in Section 6.2 Vital Signs and Laboratory Studies

### Aminotransferase

Changing the Incidence Rates of Aminotransferase Elevations

The sponsor stated that they have (b) (4) reasons to change the incidence rates of aminotransferase elevation in the US product label: (b) (4)

(b) (4)

(b) (4)

(b) (4)

Adding New Additional Analysis Results of Aminotransferase to the Labeling

The sponsor is proposing to add to the labeling the new analysis results which include the incidence rates of patients with ALT elevations ≥5x ULN, (b) (4), and the incidence rates of meeting criteria for Hy's rule. They also reviewed and added the data on AEs and ALT values for patients with ALT elevations at least 3x ULN.

(b) (4)

The sponsor reviewed the recently published FDA's Guidance for Industry: Drug-Induced Liver Injury which listed the specific criteria for discontinuation of treatment due to liver injury. (b) (4) . They concluded that they did not find any subjects who met the discontinuation criteria listed in the FDA guidance. (b) (4)

**Neutropenia**

(b) (4)

neutropenia, and agranulocytosis was added to the US product label on 31 August 2009 (Section 5.9 titled Leukopenia, Neutropenia, and Agranulocytosis). The warning/precaution supersedes information included in (b) (4).

**III. Review of Proposed Labeling Revisions**

The changes proposed by the sponsor in section 6.2 of Zyprexa labeling are identified as follows: deletions are identified by strikethrough, additions are identified by underlining.

**Section 6.2:** (b) (4) **:**

(b) (4)

The sponsor moved the original premarketing data from the 3rd paragraph to the first paragraph, and added the new criteria they used in the analyses of ALT elevation: (change from <3 times the upper limit of normal [ULN] at baseline to ≥3 times ULN). They corrected the incidence rates according to the new analysis results using the new criteria and a larger data set which included additional trials. The new incidence rates are supported by the following table.

**Table 1.5. Incidence of ALT Abnormalities Using 3X Upper Limit of the Central Lab Reference Range**
**Adult Placebo-Controlled Olanzapine Integrated Database**
**Double-Blind Acute and Extension Phases**

| Therapy | N | n | % |
|---|---|---|---|
| Olz | 1426 | 77 | 5.4% |
| Placebo | 1187 | 10 | 0.8% |

N = The number of patients with no abnormal baseline values and at least one post-baseline value.
n = The number of patients with no abnormal baseline values and at least one abnormal post-baseline value.
An abnormal value is defined as a value >= 3 times the upper limit of the central lab reference range.
Fixed dose olanzapine arms < 5 mg were excluded from this analysis.
Studies included in the analysis: HBBD, HBBI, HGAD, HGAP, HGBH, HGEH, HGGA, HGGF, HGGW, HGGY, HGKK, HGKL, HGKQ

They added the analysis result of incidence rate of ALT ≥5x ULN, which is shown in the table below:

(b) (4)

[redacted]

The sponsor added the following statement:
"ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine or discontinued olanzapine".

I have reviewed all the ALT Lab values for patients with ALT abnormalities >= 3x, 5x, or 10x ULN in the adult placebo-controlled olanzapine integrated database. There were a total of 87 patients who had at least one elevated post-baseline ALT value in this database. Seventy-seven were from the olanzapine monotherapy group and 10 were from the placebo group. Most patients had ALT normalized or decreasing at the last follow up except 5 patients who did not have further follow up. All of these 5 patients discontinued from the treatment. The table below listed the information for these 5 patients.

| Patient ID | Indication | Olanzapine dosage | Reason for discontinuation | Date last study drug taken | Last Lab Sample date | Last ALT result |
|---|---|---|---|---|---|---|
| HGGW-022-2060 | Bipolar Mania | No data | Lack of efficacy, MD and patient's perception | 1998-06-07 | 1998-06-09 | 409 H (>=10X) |
| HGKQ-2-203 | Bipolar Mania | 15mg | Adverse Event - Blood creatine phosphokinase increased | 2005-02-03 | 2005-02-03 | 347 H (>=5X) |
| HGKQ-84-8403 | Bipolar Mania | 10mg | Adverse Event - Hepatitis toxic | 2005-10-01 | 2005-09-27 | 229 H (>=5X) |
| HGBH-334-3347 | Schizophrenia | 5mg | Patient moved | 1997-03-04 | 1997-03-05 | 517 H (>=10X) |
| HGBH-355-3551 | Schizophrenia | 5mg | Personal conflict | 1995-07-17 | 1995-07-18 | 186 H (>=3X) |

Based on my review, the statement "ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine or discontinued olanzapine" is accurate.

The sponsor also added the following statement in the same paragraph:
"No (b) (4) patient (b) with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule."

The sponsor listed AEs for adult patients with ALT abnormality ≥3x ULN in the submission. Among all of the patients, four had SAEs which were believed to be related to aminotransferase elevations but not jaundice.

Patient (ID: HGAD-011-1526) had increased GGT and SGPT.
Patient (ID: HGAD-015-1704) had increased SGPT.
Patient (ID: HGAD-020-1951) had increased SGPT.
Patient (ID: HGBH-325-3250) had increased ALT.

The sponsor did not include the actual GGT and SGPT lab results in the submission. However, all of these patients' ALT values either returned to normal or were decreasing at the last follow up. Therefore, I believe the statement that "No (b) (4) patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule " is also accurate.

The sponsor deleted the following sentences. This is acceptable.

(b) (4)

The sponsor also deleted the following statement regarding the discontinuation treatment due to transaminase increases.

~~"Among 2500 adult patients in oral olanzapine clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases"~~

The sponsor has examined the cases of discontinuation due to transaminase increases. There were a total of 23 adult cases from the premarketing database and 8 cases from the adolescent database that discontinued from the treatment due to transaminase increases. The following table listed the highest transaminase values of all the discontinuation cases.

**Table 1.12. Cases of Discontinuations due to Elevated Aminotransferases Adult and Adolescent Patients Exposed to Olanzapine**

| Patient | Reason for Discontinuation | Highest Aminotransferases ALT | AST | GGT | Additional Labs/Information/Outcome |
|---|---|---|---|---|---|
| **Adult Patients** | | | | | |
| HGAD 011-1526 | ALT increased | 237 U/L | 102 U/L | NR | DC from study. Approximately 4 months after DC, LFTs remained elevated, but not increasing. |
| HGAD 014-1651 | ALT increased | 187 U/L | 82 U/L | NR | DC from study. Hx of elevated LFTs 2 months prior to entering study; also, Hx of heroin use. Hepatitis C was diagnosed at follow-up. |
| HGAD 015-1701 | ALT increased | 239 U/L (BL 12 U/L) | 94 U/L | NR | DC from study. Four days after DC, ALT remained elevated, AST was approaching normal limits. |
| HGAD 015-1704 | ALT increased | 394 U/L | 172 U/L | NR | DC from study. Values returned to within normal limits 18 days after DC. |
| HGAD 019-1870 | ALT increased | 685 U/L (BL 48 U/L) | 225 U/L (BL 29 U/L) | NR | DC from study. Follow-up continued until values returned to normal. ALT in 20 days; AST in 13 days. |
| HGAD 019-1878 | ALT increased | 181 U/L | NR | NR | DC from study. Follow-up 15 days after DC, ALT within normal limits. |
| E003 151-1511 | ALT increased | 109 IU/L | NR | NR | DC from study. No follow-up reported. |
| E003 152-1527 | ALT increased | 102 IU/L | NR | NR | DC from study. Follow-up: 8 days after DC - ALT 51 IU/L; 29 days after DC - ALT 33 IU/L |
| E003 404-4070 | ALT increased | 86 IU/L | NR | NR | DC from study. Follow-up 13 days after DC - ALT 30 IU/L. |
| E003 602-6033 | ALT increased | 171 U/L | NR | NR | DC from study. Follow-up 4 days after DC - ALT 38 IU/L. |
| E003 724-7270 | ALT increased | 165 U/L | NR | NR | DC from study. Follow-up 21 days after DC – ALT 84 U/L |
| E003 802-8033 | ALT increased | 315 IU/L | 113 IU/L | NR | DC from study. Elevated LFTs spontaneously returned to normal. |
| E003 902-9023 | ALT increased | 228 U/L (BL 9 U/L) | NR | NR | DC from study. Follow- up 2 weeks after DC - ALT 29 U/L. |
| E003 941-9413 | ALT increased | 170 IU/L | 98 IU/L | 75 IU/L | DC from study. No follow-up reported. |

(continued)

**Table 1.12. Cases of Discontinuations due to Elevated Aminotransferases Adult and Adolescent Patients Exposed to Olanzapine (continued)**

| Patient | Reason for Discontinuation | Highest Aminotransferases ALT | AST | GGT | Additional Labs/Information/Outcome |
|---|---|---|---|---|---|
| **Adult Patients, continued** | | | | | |
| HGAJ 325-2955 | ALT increased | 376 U/L (BL 35 U/L) | 150 U/L | NR | DC from study. Positive Hepatitis A antibody after DC. |
| E003 151-1508 | GGT increased | 300 U/L | 142 U/L | 118 U/L | DC from study. No follow-up reported. |
| E003 401-4002 | GGT increased | 48 IU/L | 20 IU/L | 50 IU/L | Also Tbili: 2.907 micromoles/L (WNL). DC from study. Received alternative neuroleptic. Increased liver enzymes did not return to normal. |
| E003 702-7026 | GGT increased | 206 IU/L (BL 95 U/L) | 145 IU/L | 293 IU/L | Also: Alk phos: 327 (IU/L). Elevated liver enzymes at Visit 1. DC from study after several increases in LFTs. Patient refused further blood tests. |
| HGAJ 062-1080 | GGT increased | NR | 109 U/L | 287 U/L (BL 71 U/L) | DC from study. Probable chronic viral hepatis. no clinical symptoms from the elevated hepatic enzymes. |
| HGAJ 021-1247 | LFT abnormal | 304 U/L (BL 14 U/L) | 553 U/L (BL 21 U/L) | 610 U/L (BL 21 U/L) | Also: Alk Phos:163 U/L . DC from study. Increase in alcohol intake for 3 months prior to DC from study |
| HGAJ 029-0173 | LFT abnormal | 396 U/L (BL 38 U/L) | 148 U/L | NR | DC from study. Hepatitis C antibody tests performed after DC from study were found to be reactive although the patient continued to be asymptomatic. |
| HGAJ 816-6514 | LFT abnormal | 107 U/L | NR | 328 U/L | Also: Alk Phos: 184 U/L. Significant hx of liver disease (jaundice) of unknown origin. DC from study. |
| HGAP 005-1210 | LFT abnormal | 412 U/L | 150 U/L | NR | ALT and AST elevated prior to entering study. DC from study. Follow-up 2 months after DC. ALT: 122 U/L. Follow-up 46 days after DC. AST: 58 U/L. |

(continued)

**Table 1.12. Cases of Discontinuations due to Elevated Aminotransferases Adult and Adolescent Patients Exposed to Olanzapine (concluded)**

| Patient | Reason for Discontinuation | Highest Aminotransferases ALT | AST | GGT | Additional Labs/Information/Outcome |
|---|---|---|---|---|---|
| **Adolescent Patients** | | | | | |
| HGIN 007-0703 | ALT increased | 231 U/L (BL 17 U/L) | 142 U/L | 34 U/L | DC from study. Follow up 22 days weeks after DC - ALT: 18 U/L. Follow-up 6 days after DC, AST: 33 U/L |
| HGIN 010-1001 | LFT abnormal | 597 U/L (BL 22 U/L) | 410 U/L (BL 26 U/L) | 129 U/L (BL 23 U/L) | DC from study. Follow up 20 days after DC, different lab ALT: 82 U/L (21-27 U/L, AST: 43 U/L (17-59 U/L). |
| HGIN 021-2103 | Transaminases increased | 396 U/L (BL 16 U/L) | 136 U/L (BL 20 U/L) | 63 U/L | DC from study. Follow up 14 days after DC ALT: 43 U/L, AST: 25 U/L. |
| HGIN 910-9110 | AST increased | 321 U/L | 190 U/L (BL 66 U/L) | NR | DC from study. Follow up 21 days after DC, AST and ALT: normal. |
| HGIN 920-9202 | ALT increased | 393 U/L (BL 13 U/L) | 179 U/L (BL 13 U/L) | 82 U/L (BL 22 U/L) | DC from study. Follow up 22 days after DC, ALT: 20 U/L. |
| HGIU 012-1203 | Hepatic enzyme increased | 325 U/L | 148 U/L | 53 U/L | DC from study. Follow up 7 days after DC, liver enzymes were within normal limits. |
| HGIU 020-2007 | LFT abnormal | 330 U/L | 204 U/L | NR | DC from study in open-label phase. Follow up 6 days after DC, AST: normal, ALT: decreasing but still above normal limit. |
| HGIU 720-7217 | Hepatic enzyme increased | 125 U/L | 103 U/L | NR | DC from study in open-label phase. Follow up 56 days after DC, liver enzymes were within normal limits. |

Abbreviations: Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DC = discontinued; GGT = gamma glutamyl transferase; Hx = history of; LDH = lactate dehydrogenase; LFT = liver function transaminase; NR = not reported; WNL = with no limits.

The sponsor further reviewed the recently published FDA's Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation (07/2009), which listed the following specific criteria for discontinuation of treatment due to transaminase increases:

- ALT or AST >8x ULN
- ALT or AST >5x ULN for more than 2 weeks
- ALT or AST >3x ULN and (TBL >2x ULN or INR >1.5)
- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

As you can see from the yellow highlight in the table above, four adult cases and 3 adolescent cases had ALT >8x ULN and therefore these cases have met the criteria for discontinuation of treatment due to transaminase increases. However, since the readings in the table were the highest ALT values during the studies, it is not clear if these were the readings when patients were discontinued. One patient, HGAJ 029-0173, was tested hepatitis C antibody positive after discontinuation.

Since at least the majority of cases did not meet the criteria specified in the FDA guidance regarding drug-induced liver injury, I consider it is acceptable for the sponsor to delete the language regarding the drug discontinuation due to aminotransferase increase.

## Section 6.2: Aminotransferase - Olanzapine Monotherapy in Adolescents:

22

*Olanzapine Monotherapy in Adolescents:* In placebo-controlled clinical trials of adolescent patients with Schizophrenia or Bipolar I Disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT (≥3-X ULN in patients with ALT at baseline <3-X ULN), (12 (b)(4)% vs 2 (b)(4)%); elevated AST ( (b)(4)8% vs (b)(4)4%); low total bilirubin (22 (b)(4)% vs (b)(4)7%); elevated GGT (10 (b)(4)% vs 1 (b)(4)%); and elevated prolactin (47 (b)(4)% vs (b)(4)7%).

In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from <3 times ULN at baseline to ≥3 times ULN) were observed in 12% (22/192) of patients exposed to olanzapine compared to 2% (2/109) of patients exposed to placebo. Reg Resp Table 1.9. ALT elevations ≥5 times ULN were observed in 4% (8/192) of olanzapine-treated patients, compared to 1% (1/109) of placebo-treated patients. Reg Resp Table 1.10. ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine or discontinued olanzapine. Reg Resp Attachment 3. No adolescent patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule. Reg Resp Table 1.11. Reg Resp Attachment 4.

In the first paragraph, the sponsor rounded up the incidence rates for elevated ALT, AST, low total bilirubin, GGT and prolactin. This is acceptable.

In the 2nd paragraph, the sponsor specified the incidence rates of ALT elevations ≥3x ULN and ≥5x ULN. This is supported by the following tables.

**Table 1.9. Incidence of ALT Abnormalities Using 3X Upper Limit of the Central Lab Reference Range**
**Adolescent Placebo-Controlled Olanzapine Integrated Database**
**Double-Blind Acute and Extension Phases**

| Therapy | N | n | % |
|---|---|---|---|
| Olz | 192 | 22 | 11.5% |
| Placebo | 109 | 2 | 1.8% |

N = The number of patients with no abnormal baseline values and at least one post-baseline value.
n = The number of patients with no abnormal baseline values and at least one abnormal post-baseline value.
An abnormal value is defined as a value >= 3 times the upper limit of the central lab reference range.
Fixed dose olanzapine arms < 5 mg were excluded from this analysis.
Studies included in the analysis: HGGF, HGIN, HGIU, HGKL

**Table 1.10. Incidence of ALT Abnormalities Using 5X Upper Limit of the Central Lab Reference Range**
**Adolescent Placebo-Controlled Olanzapine Integrated Database**
**Double-Blind Acute and Extension Phases**

| Therapy | N | n | % |
|---|---|---|---|
| Olz | 192 | 8 | 4.2% |
| Placebo | 109 | 1 | 0.9% |

N = The number of patients with no abnormal baseline values and at least one post-baseline value.
n = The number of patients with no abnormal baseline values and at least one abnormal post-baseline value.
An abnormal value is defined as a value >= 5 times the upper limit of the central lab reference range.
Fixed dose olanzapine arms < 5 mg were excluded from this analysis.
Studies included in the analysis: HGGF, HGIN, HGIU, HGKL

I have reviewed all ALT Lab values for patients with ALT abnormalities >= 3, 5, or 10x ULN in adolescent placebo-controlled olanzapine integrated database in the submission. All ALT values were normalized or decreasing at the last follow up. I also have reviewed all the AEs for adolescent patients with ALT abnormality ≥3x ULN. There were no SAEs related to aminotransferase elevations or jaundice. Therefore, the statement in the 2nd paragraph is accurate. These changes are acceptable.

**Section 6.2: Neutropenia**

(b) (4)

(b) (4)

. This is acceptable.

**III. Conclusions and Recommendations**

The sponsor proposed changes are acceptable. I recommend that these labeling supplements to be approved.

Jenn Sellers, M.D., Ph.D., FAAP
May 6, 2010

cc: NDA
Laughren, T/Mathis, M/David, P/Kiedrow, K/Zhang, J

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-20592 | SUPPL-53 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |
| NDA-21253 | SUPPL-39 | ELI LILLY AND CO | ZYPREXA IM (OLANZAPINE) 10MG VIALS INJ |
| NDA-21086 | SUPPL-32 | ELI LILLY AND CO | ZYPREXA ZYDIS(OLANZAPINE)5/10/15/20/ MGTS |

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JENN W SELLERS
05/06/2010

JING ZHANG
05/06/2010

**Review and Evaluation of Clinical Data**

**NDA 20-592, 21-086, 21-253**

| | |
|---|---|
| Sponsor: | Eli Lilly and Company |
| Drug | Zyprexa (olanzapine) oral tablets, TS, injection. |
| Material Submitted: | N 20592/-035, -040; |
| Related NDAs: | N 21086/-(b) (4); 21253/-(b) (4); |
| Correspondence Date: | 1 Sep 2009, 6 Oct 2009 |

## I. Background

This submission provides for Prior Approval labeling supplement for Zyprexa to include updated language regarding hyperprolactinemia. This review encompasses two submissions, eCTD 0035 submitted 1 Sep 2009 and eCTD 0040 submitted 6 Oct 2009.

The submission 0035 includes results from an updated analyses of prolactin data collected during placebo controlled trials in adults and adolescents with schizophrenia and other psychiatric disorders treated with olanzapine monotherapy. This was done in Q1-Q2 2009 by Eli Lilly. This was done as the number of exposures in this database has more than doubled since the approval of olanzapine in 1996.

This submission also includes results from an analysis of the clinical manifestations potentially associated with hyperprolactinemia using comprehensive groupings (breast-, menstrual-, and sexual- function related).

In submission 0040, the sponsor requested to delete the term (b) (4) in paragraph 1 of the section on hyperprolactinemia of Zyprexa labeling.

## II. Clinical Data and Analyses

Data from two adult databases were used to present hyperprolactinemia related AEs in the proposed Zyprexa labeling: the Adult Olanzapine Monotherapy Placebo-Controlled Database and the Olanzapine Adult Overall Database.

The placebo-controlled database was used to analyze the incidence and frequencies of hyperprolactinemia and the Olanzapine Adult Overall Database was used to analyze categorized hyperprolactin associated AEs.

For adolescents, data from 4 studies in the olanzapine Adolescent Overall Database was used to analyze both the incidence and frequencies of hyperprolactinemia and also categorized hyperprolactin associated AE's.

Analyses included

- incidence of treatment-emergent high prolactin values anytime during the study (provided for adults only, as incidence for adolescents remains unchanged in the USPI)

- incidence of treatment-emergent adverse events by category

- frequencies of treatment-emergent adverse events by category.

Because laboratories with disparate reference ranges were used to assay prolactin in studies evaluated, prolactin data were normalized for pooling and analysis. Normalization involved the use of a conversion factor that is both lab-specific and analyte-specific for the purpose of analyzing data across studies. The number of patients with normal baseline and at least one treatment-emergent high prolactin value at any time during the placebo-controlled period was summarized by treatment.

The sponsor looked at the incidence and frequencies of possible prolactin-related, treatment emergent adverse events by categories (Table 1). The terms included were chosen from a list of prolactin-related MedDRA preferred terms (version 12).

**Table 1**: MedRA Preferred Term Categories for Potential Clinical Manifestations Associated with Prolactin Elevations.

| Sexual Function-Related Preferred Terms | Menstrual-Related Preferred Terms | Breast-Related Preferred Terms |
|---|---|---|
| Anorgasmia | Amenorrhoea | Breast discharge |
| Ejaculation delayed | Hypomenorrhoea | Breast enlargement |
| Erectile dysfunction | Menstruation delayed | Breast swelling |
| Libido decreased | Oligomenorrhoea | Galactorrhoea |
| Loss of libido | | Gynaecomastia |
| Orgasm abnormal | | Lactation disorder |
| Sexual dysfunction | | |

The number of possible prolactin-related, treatment emergent adverse events were summarized from a list of prolactin-related MedRA Preferred Terms. Hyperprolactinemia may also be associated with infertility, oligospermia, osteopenia, and osteoporosis. However, these conditions may take months to years to appear, and since the median exposure was 97 days in the olanzapine adult database and 88 days in the adolescent database, these terms were excluded.

Adult Olanzapine Placebo-Controlled Database

The current adult olanzapine monotherapy placebo-controlled database consists of 14 studies including 2118 olanzapine treated and 1467 placebo-treated patients, with exposure up to 52 weeks. For the current proposed changes to the USPI, analyses were performed on the data from only 9 studies (Table 2) included in the adult olanzapine placebo-controlled database, as the others did not contain prolactin measurements. This

subset of the larger database included data from 1471 olanzapine-treated and 918 placebo-treated patients. For both databases, the mean ages were 38 and 37 years.

Table 2: Subset of 9 trials from the Olanzapine Adult Placebo-Controlled Database

| Study | Formulation | Indication | OLZ Dose(s) or Dose Range | Placebo-Controlled Duration (weeks) |
|---|---|---|---|---|
| F1D-MC-HGAD | Oral | Schizophrenia | 2.5 to 17.5 | 6 |
| F1D-MC-HGAP | Oral | Schizophrenia | 1, 10 | 6 |
| F1D-MC-HGGA | Oral | Psychotic depression | 5 to 20 | 8 |
| F1D-MC-HGJZ | Depot | Schizophrenia | 210 mg/2 wk 300 mg/2 wk 405 mg/4 wk | 8 |
| F1D-MC-HGKK | Oral | Borderline personality disorder | 2.5, 5-10 | 12 |
| F1D-MC-HGKL | Oral | Borderline personality disorder | 2.5 to 20 | 12 |
| F1D-MC-HGKQ | Oral | Bipolar mania | 5 to 20 | 3 |
| H8Y-BD-HBBD | Oral | Schizophrenia | 15 | 4 |
| H8Y-MC-HBBI | Oral | Schizophrenia | 15 | 4 |

Using the subset of 9 adult trials, Table 3 summarizes the incidence of patients with treatment-emergent high prolactin values at any time. Differences were shown between different treatment groups, with 30.3% of olanzapine treated patients and 10.5% of placebo-treated patients having high prolactin values.

Table 3: Treatment Emergent High prolactin Values Anytime in Adult Olanzapine Placebo-Controlled Database

| Treatment | N | n | (%)[a] | P-value[b] |
|---|---|---|---|---|
| Olanzapine | 943 | 286 | 30.3% | <.001 |
| Placebo | 582 | 61 | 10.5% | |

N= number of subjects with a normal baseline and at least one post baseline result.
n= number of subjects with an abnormal post-baseline result at anytime.

Olanzapine Adult Overall Database

To examine the incidence of treatment emergent adverse events that may possibly be related to increases in prolactin levels by category, the olanzapine adult overall database was used. This integrated database has 84 studies that were conducted in adults with a diagnosis of schizophrenia or bipolar disorder, and studies that administered doses approved in the label (5 mg to 20 mg/day). (Table 4)

Table 4: Studies included in the Olanzapine Adult Overall Database

| Studies | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| B003 | HGAD | HGAJ | HGAP | HGBB | HGBF | HGBG | HGBH | HGBI | HGBJ |
| HGBK | HGBL | HGBM | HGBO | HGBQ | HGBR | HGBS | HGBU | HGBX | HGCA |
| HGCF | HGCG | HGCH | HGCJ | HGCK | HGCL | HGCM | HGCO | HGCP | HGCQ |
| HGCU | HGCV | HGCX | HGCY | HGCZ | HGDB | HGDD | HGDG | HGDH | HGDI |
| HGDM | HGDQ | HGDT | HGDU | HGDV | HGDY | HGDZ | HGEB | HGEC | HGEF |
| HGEH | HGEJ | HGEP | HGEQ | HGER | HGES | HGET | HGEZ | HGFH | HGFM |
| HGFT | HGFW | HGGD | HGGF | HGGI | HGGN | HGGW | HGGY | HGHD | HGHG |
| HGHH | HGHJ | HGHL | HGHO | HGHQ | HGHR | HGIA | HGIJ | HGIY | HGJB |
| HGJT | HGJU | LOBU | P022 | | | | | | |

This 84- study database includes data from 8136 olanzapine-treated subjects, with a median exposure of 97 days. Table 5 summarizes possible prolactin-related TEAE's by category and gender.

Table 5: Frequencies of possible prolactin-related treatment emergent adverse events by category and gender.

| Category | Males (N=4896) n (%) | Females (N=3240) n (%) | Total (N=8136) n (%) | CIOMS Frequency (Based on Total) |
|---|---|---|---|---|
| Breast-related | 9 (0.2%) | 23 (0.7%) | 32 (0.4%) | Uncommon |
| Menstrual-related | | 49 (2%) | 49 (2%)* | Common |
| Sexual function-related | 117 (2%) | 33 (1%) | 150 (2%) | Common |

Olanzapine Adolescent Overall Database

For analyses of prolactin related AE's in adolescents, there were 4 studies that are included in the Olanzapine Adolescent Overall Database. This integrated database contains data for 454 patients aged 13 through 18 years (Table 6).

Table 6: Studies in the Olanzapine Adolescent Overall Database

| Study | Formulation | Indication | OLZ Dose(s) or Dose Range | Duration (weeks) |
|---|---|---|---|---|
| F1D-MC-HGIN | Oral | Schizophrenia | 2.5 to 20 mg/day | 6 weeks DB, 26 weeks OL |
| F1D-MC-HGIU | Oral | Bipolar mania | 2.5 to 20 mg/day | 3 weeks DB, 26 weeks OL |
| F1D-MC-HGMF | Oral | Schizophrenia or bipolar disorder | 2.5 to 20 mg/day | 4.5 weeks OL |
| F1D-SB-LOAY | Oral | Schizophrenia, schizoaffective, and schizophreniform disorders | 5 to 20 mg/day | 6 weeks DB; 24 weeks OL |

Analyses of data from the 4 adolescent studies showed that there is no change in the incidence of treatment-emergent high prolactin values for adolescents treated with olanzapine compared to that in the currently approved Zyprexa labeling.

Table 7 summarizes possible prolactin-related TEAEs by category and gender.

Table 7: Prolactin-Related TEAE's by Category and Gender in Adolescents.

| Category | Males (N=286) n (%) | Females (N=168) n (%) | Total (N=454) n (%) | CIOMS Frequency (Based on Totals) |
|---|---|---|---|---|
| Breast-related | 7 (2%) | 3 (2%) | 10 (2%) | Common |
| Menstrual-related | | 2 (1%) | 2 (1%)* | Common |
| Sexual function-related | 3 (1%) | | 3 (0.7%) | Uncommon |

## III. Proposed Labeling Revisions

The changes proposed by the sponsor in section 5.15 of Zyprexa labeling are identified as follows: deletions are identified by ~~strikethrough~~ and additions by use of underline. The additions proposed by the reviewer are identified by additions

(b) (4)

**IV. Conclusions and Recommendations**

The sponsor has included updated results from analyses of prolactin data. These analyses were conducted in 2009. They also propose including prolactin-related treatment adverse effects summarized by categories of sexual function-, menstrual- and breast-related terms. These additions are more clinically relevant compared to the previous label which only had manifestations related to the breast. It recognizes that prolactin increases affect organ systems other than the breast.

However, the terms of menstrual-related, sexual function related and breast related events are non-specific. I recommend a foot note at the end of the hyperprolactinemia section to give more explanation for what is included in these categaries. For example, breast-related events include breast discharge, enlargement and swelling, galactorrhoea, gynaecomastia and lactation disorders.

The elimination of the term '(b) (4)' in section 5.15 paragraph 1 also is appropriate.

The sponsor notes in their regulatory response document that they propose to change section 5.14. However, they actually propose to change 5.15, which is the section on hyperprolactinemia.

I recommend that this labeling revision be approved with the minor changes proposed by us.

---

Maju Mathews, MD, MRCPsych, Dip Psych.
Medical Officer Reviewer
FDA CDER ODE1 DPP HFD 130
12/16/2009

Cc: Laughren, T/Mathis, M/David, P/Kiedrow, K/Zhang,J

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-20592 | SUPPL-52 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |
| NDA-21086 | SUPPL-31 | ELI LILLY AND CO | ZYPREXA ZYDIS(OLANZAPINE)5/10/15/20/ MGTS |
| NDA-21253 | SUPPL-37 | ELI LILLY AND CO | ZYPREXA IM (OLANZAPINE) 10MG VIALS INJ |

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MAJU MATHEWS
12/17/2009

JING ZHANG
12/17/2009

**Review and Evaluation of Clinical Data**
**NDA #20-592, 21-086, 18-936**

| | |
|---|---|
| **NDA#:** | 20-592/S039, 21-086/S021, & 18-936/S077 |
| **Sponsor:** | Eli Lilly and Company |
| **Drug:** | Zyprexa tablet, Zydis, & Prozac |
| **Material Submitted:** | Resubmission of Response to Approvable Letter |
| **Date Submitted:** | 4 February 2008 |
| **Proposed Indication:** | Treatment Resistant Depression |
| **Intended Population:** | Adults |
| **Related Supplements:** | N21-520/S012 |
| **Medical Reviewer:** | Jing Zhang, MD. PhD. |

On 28 September 2006, Lilly submitted a supplemental New Drug Application (sNDA) for the use of fluoxetine in combination with olanzapine for the treatment of treatment-resistant depression (TRD). FDA issued a Refuse to File for these applications on 27 November 2006. Lilly responded with a briefing document, dated 4 January 2007. After review of this document and further evaluation from the FDA, these applications were considered re-filed on 5 January 2007. Revised labeling, in accordance with that described in the 4 January 2007 briefing document, was submitted to FDA on 21 March 2007.

The FDA sent an Approvable Letter dated 21 September 2007 regarding these sNDAs. This letter indicated that FDA had completed their review of these applications and that they are approvable. Before these applications may be approved, the following deficiency must be addressed:

> "Clinical studies for the TRD indication were submitted to the Symbyax (olanzapine/fluoxetine) application, NDA 21-520/s012. The addition of TRD language to each of the individual components is dependent on this application. Therefore, we cannot approve these applications until we take an approval action on NDA 21-520/s012 (Symbyax for treatment resistant depression)."

Lilly re-submitted these applications on 4 February 2008 in response to the Approvable Letter dated on 27 September 2007. After extensive reviewing risks of hyperglycemia, hyperlipidemia, and weight gain associated with Zyprexa and olanzapine/fluoxetine combination (OFC) by a safety team in FDA, numerous changes on Zyprexa and Symbyax labelings had been recommended. Currently the FDA is in the processing to approve sNDA 21,520/S-012, Symbyax for treatment resistant depression in adults. The deficiency listed above has been addressed. It is recommended that these applications be approved.

Jing Zhang, MD. PhD.
July 23, 2008

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

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/s/
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Jing Zhang
7/23/2008 09:30:45 PM
MEDICAL OFFICER

Gwen Zornberg
7/24/2008 06:59:14 AM
MEDICAL OFFICER
I concur with Dr. Zhang's recommendation of an Approval action for these supplements submitted by Lilly.

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA<br>(Complete Response to Approvable Action) |
| Submission Number | 020592 |
| Submission Code | SE5 040/041 |
| Letter Date | 2/5/2008 |
| Stamp Date | 2/5/2008 |
| PDUFA Goal Date | 8/5/2008 |
| Reviewer Name | Cara Alfaro, Pharm.D. |
| Review Completion Date | 7/14/2008 |
| Established Name | Olanzapine |
| Trade Name | Zyprexa |
| Therapeutic Class | Antipsychotic |
| Applicant | Eli Lilly & Co |
| Priority Designation | S |
| Formulation | Oral tablets |
| Dosing Regimen | 2.5 – 5 mg starting, maximum dose 20 mg/day |
| Indications | Treatment of Bipolar I Disorder (040) and Schizophrenia (041) |
| Intended Population | Adolescents |

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# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

This is a review of the complete response to the approvable action taken on 4/30/07 for NDAs 20-592 SE5-040 "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents" and SE5-041 "treatment of schizophrenia in adolescents". It is recommended that the Division take an approvable action on these supplements and that olanzapine be considered as second line treatment for bipolar disorder and schizophrenia in the adolescent population.

The Sponsor responded to all additional requests for information pertaining to pivotal trials HGIU (bipolar disorder) and HGIN (schizophrenia) outlined in the 4/30/2007 approvable letter (other requests for additional safety data in adults and adolescents were also submitted and reviewed by another clinical reviewer). A review of these data did not reveal new safety risks or significant changes to already known safety risks that warranted significant changes to proposed product labeling beyond the changes suggested in the approvable letter. However, it is recommended that gynecomastia and galactorrhea be included as adverse events in product labeling as they appear to occur more frequently in the adolescent population compared to adults. The Sponsor also adequately addressed the disparity in the efficacy signal primarily driven by the differential placebo response between the United States and Russian sites in study HGIN (schizophrenia).

The recommendation for an approvable action (rather than an approval action) is based on the need for the development of a medication guide discussing significant adverse events in adolescents (b) (4) Though these adverse events are well known for olanzapine, they occur much more frequently in the adolescent population. Weight gain, hyperglycemia, and hyperlipidemia are significant risk factors for cardiovascular morbidity, especially in disease states such as schizophrenia or bipolar disorder in which it is likely that patients will be taking these medications chronically.

Given these safety concerns, it is recommended that olanzapine be considered as second line therapy for the treatment of bipolar disorder and schizophrenia in the adolescent population. Recently two other antipsychotics, risperidone and aripiprazole, received approval for treatment of bipolar disorder and schizophrenia in adolescents. In comparison to olanzapine, these antipsychotics are not associated with the same magnitude of risk with regard to weight gain, hyperglycemia and hyperlipidemia.

## 1.2 Recommendation on Postmarketing Actions

### 1.2.1 Risk Management Activity

The Sponsor submitted a "risk management plan" document, however, it was not a typical risk management plan. The Sponsor has proposed education, labeling changes and some further clinical trials to address the safety risks of olanzapine in both adults and adolescents.

### 1.2.2 Required Phase 4 Commitments

The Sponsor is planning to conduct a 52-week open-label safety study (Study F1D-MC-HGMX) in adolescent subjects with bipolar disorder or schizophrenia (see Section 7 of review - Studies to be Conducted In Adolescents ). This study is being considered as a Phase 4 commitment. As of this time, the protocol for this study has not been submitted.
No additional Phase 4 commitments are recommended.

# 2 INTRODUCTION AND BACKGROUND

On 10/30/06, Eli Lilly and Company submitted NDA 20-592 SE5-040 and SE5-041 to support the indications "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents" and "treatment of schizophrenia in adolescents" respectively. An approvable action was taken 4/30/2007 and the Sponsor was asked to submit additional safety analyses as well as further exploration of the disparity in efficacy results between the US and Russian sites (largely driven by a very low placebo response in the Russian sites) in the pivotal adolescent schizophrenia trial (HGIN). The Sponsor was also asked to submit updated information on risks of weight gain, hyperglycemia and hyperlipidemia that would be reflected not only in Zyprexa labeling, but also in Symbyax labeling.

The Sponsor submitted a response on 8/30/2007, this response was considered incomplete (letter date 9/13/2007) since the submission did not include all requested data regarding the risks of weight gain, hyperglycemia and hyperlipidemia. The Sponsor submitted a response on 2/5/2008 and it was considered a complete response. For the purposes of this review, this reviewer is addressing the portions of the complete response pertaining to SE5-040 and SE5-041, specifically the questions posed to the Sponsor for issues relating to the pivotal trials for the bipolar and schizophrenia adolescent trials. Another clinical reviewer (Evelyn Mentari, M.D.) will be reviewing the requested safety information relating to risks of weight gain, hyperglycemia and hyperlipidemia for both adult and adolescent populations.

## 2.1 Brief Overview of Pivotal Trials HGIU and HGIN

Study HGIU was the pivotal trial for establishing efficacy and safety for the indication "treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with bipolar I disorder. The study consisted of a 3-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 107), or placebo (n = 54).

Study HGIN was the pivotal trial for establishing efficacy and safety for the indication "treatment of schizophrenia in adolescent patients". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with schizophrenia. The study consisted of a 6-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 72), or placebo (n = 35).

## 2.2 Summary Table of Clinical Trials in Original Submission

This summary table is included in this review as some of the Sponsor's responses included additional data from some of the supportive trials.

| Study | Description | Length | Age Range (years) | Number of Patients |
|---|---|---|---|---|
| HGIN | MC, DB, PC study in adolescent patients with schizophrenia.<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S. and Russia sites | 6 weeks DB<br>26 weeks OL extension | 13 to 17 | 107<br>(n = 72 olanzapine, n = 35 placebo) |
| HGIU | MC, DB, PC study in adolescent patients with mixed/manic episode of bipolar I disorder.<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S., Puerto Rico | 3 weeks DB<br>26 weeks OL extension | 13 – 17 | 161<br>(n = 107 olanzapine, n = 54 placebo) |
| LOAY | OL study in patients with schizophrenia, schizoaffective, and schizophreniform disorders<br>Flexible dose olanzapine (5 – 20 mg)<br>German sites | 24 weeks | 12 – 21 | 96<br>(n = 89, 13-17 years) |
| HGMF | OL study in adolescent patients with schizophrenia or bipolar I disorder<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S., Puerto Rico, Russia | 4.5 weeks | 13 – 17 | 107<br>(n = 37 schizophrenia, n = 70 bipolar) |
| HGCS | OL study in adolescent patients with schizophrenia<br>Dosing: 2.5 to 20 mg/day<br>Single site | 8 weeks | 10 – 18 | 8 |
| HGCR | DB study in adolescent patients with schizophrenia, haloperidol as active comparator<br>Dosing: 2.5 qod – 20 mg/day<br>Single site | 8 weeks | 12 – 16 | 2 |
| HGGC | OL study in children and adolescents with bipolar disorder<br>Dosing: 2.5 to 20 mg/day<br>Single site (U.S.) | 8 weeks | 5 – 14 | 23 |

# 3. REQUESTS FOR INFORMATION

This section includes the requests for information that were outlined in the 4/30/2007 approvable letter, the Sponsor's response and reviewer's comments.

Table 3.1, below, is from the original NDA submission and defines the different databases used to address various safety signals. Some of the requests for information asked for reanalysis in the Overall Olanzapine Exposure Database.

Table 3.1. Sponsor's Table – Databases for Summary of Clinical Safety

**Table 2.7.4.1. Databases for Summary of Clinical Safety**

| Database | Indication | Studies Used | Number of Patients |
|---|---|---|---|
| Acute Placebo-Controlled Databases | Schizophrenia | HGIN | N=107 (Olz=72, Pla=35) |
| | Bipolar | HGIU | N=161 (Olz=107, Pla=54) |
| | Combined | HGIN, HGIU | N=268 (Olz=179, Pla=89) |
| Overall Olanzapine Exposure Databases | Schizophrenia | HGIN, LOAY, HGMF[a] | N=227 |
| | Bipolar | HGIU, HGMF[a] | N=227 |
| | Combined | HGIN, HGIU, LOAY, HGMF | N=454 |

a Because Study HGMF enrolled patients with schizophrenia or bipolar disorder, some patients from Study HGMF were included in the Overall Olanzapine Exposure Bipolar Database and some patients from Study HGMF were included in the Overall Olanzapine Exposure Schizophrenia Database.

## 3.1 Prolactin

*Division Request #1*

For the acute phases of HGIU and HGIN, many patients have elevated prolactin at baseline, therefore the change from baseline to endpoint analyses can be difficult to interpret. Please provide additional analyses for the change from baseline to endpoint on the subset of patients with baseline prolactin within the normal range. Please also provide a separate analysis for gender and age.

*Data Submitted in the Original Submission*

Prolactin reference ranges for adolescents (13 – 17 years) in study HGIN and HGIU[1]: males = 2.8 – 11 ng/ml; females = 3.2 – 20 ng/ml

In the original analysis of the HGIN + HGIU acute studies, the following change from baseline to endpoint in prolactin concentrations were provided (Table 3.1.1). However, this analysis included subjects with abnormal (usually elevated due to prior therapies) prolactin concentrations making a change from baseline difficult to interpret.

[1] Covance did not have pediatric reference ranges for prolactin. The Sponsor obtained these reference ranges from the Tietz Textbook of Clinical Chemistry (Burtis CA and Ashwood ER 1999).

Table 3.1.1. Prolactin: Change from Baseline To Endpoint, All Subjects (HGIN + HGIU)

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | **Mean** | Std | LS Mean Change | LS Mean Difference | P-value |
| Prolactin (mcg/L) | Olanzapine | 163 | 14.06 | 9.92 | **11.44** | 14.52 | 10.51 | | |
| | Placebo | 80 | 14.95 | 11.86 | **-0.16** | 10.69 | -1.15 | 11.66 | < 0.001 |

The Sponsor also included a prolactin analysis by gender since it is well established that females have a more pronounced elevation in prolactin concentration with antipsychotic therapy.

Table 3.1.2. Prolactin Analysis by Gender

| Laboratory Evaluations | Gender | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value | **P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PROLACTIN | Female | Olz | 63 | 15.87 | 10.06 | 15.63 | 16.86 | 14.26 | 14.25 | <.001 | .236 |
| | | Placebo | 37 | 15.25 | 7.59 | 1.35 | 9.20 | 0.00 | | | |
| | Male | Olz | 100 | 12.92 | 9.71 | 8.80 | 12.20 | 8.70 | 10.12 | <.001 | |
| | | Placebo | 43 | 14.70 | 14.67 | -1.46 | 11.78 | -1.42 | | | |

In the original analysis, the Sponsor did not provide a prolactin analysis by age.

*Sponsor's Response*
Seventy percent of olanzapine-treated subjects (114/163) and 71% of placebo-treated subjects (57/80) had normal baseline prolactin concentrations. Table 3.1.3 provides the reanalysis by the Sponsor including only those subjects with normal baseline prolactin levels.

Table 3.1.3. Prolactin: Change from Baseline To Endpoint, Subjects with Normal Baseline Prolactin (HGIN + HGIU)

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | **Mean** | Std | LS Mean Change | LS Mean Difference | P-value |
| Prolactin (mcg/L) | Olanzapine | 114 | 11.72 | 6.63 | **12.98** | 11.93 | 12.24 | | |
| | Placebo | 57 | 12.07 | 6.34 | **2.32** | 7.30 | 1.48 | 10.76 | < 0.001 |

From Sponsor table APP.1.1 in Regulatory Response document

Table 3.1.4. Prolactin Analysis by Gender and Age, Subjects with Normal Baseline Prolactin (HGIN + HGIU)

| Laboratory Evaluations | Subgroup | Group | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value | **P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PROLACTIN | Gender | Female | Olz | 47 | 14.65 | 8.68 | 15.14 | 15.25 | 12.66 | 11.96 | <.001 | .574 |
| | | | Placebo | 29 | 15.14 | 7.21 | 3.19 | 8.98 | 0.70 | | | |
| | | Male | Olz | 67 | 9.67 | 3.53 | 11.47 | 8.72 | 11.57 | 10.01 | <.001 | |
| | | | Placebo | 28 | 8.90 | 2.99 | 1.41 | 5.01 | 1.56 | | | |
| | Age | <15 | Olz | 46 | 12.02 | 6.37 | 14.70 | 13.60 | 11.15 | 14.86 | <.001 | .080 |
| | | | Placebo | 18 | 10.97 | 2.98 | -0.22 | 3.72 | -3.71 | | | |
| | | >=15 | Olz | 68 | 11.52 | 6.84 | 11.82 | 10.61 | 11.76 | 8.53 | <.001 | |
| | | | Placebo | 39 | 12.58 | 7.38 | 3.49 | 8.24 | 3.23 | | | |

*Reviewer Comments*
In the reanalysis including only those subjects with normal baseline prolactin (Table 3.1.3), the change from baseline to endpoint in olanzapine-treated subjects is slightly greater (12.98 mcg/L) compared to the original analysis (11.44 mcg/L). However, change from baseline to endpoint in placebo-treated subjects was also greater (2.32 mcg/L) compared to the original analysis (-0.16 mcg/L) such that the LS mean difference is lower in this analysis (10.76) compared to the original analysis (11.66). Both analyses found these differences between treatment groups to be statistically significant ($p < 0.001$).

For the gender analysis, the results from this reanalysis including only those subjects with normal baseline prolactin concentrations was similar to the original analysis; however, the change from baseline to endpoint in olanzapine-treated males was higher in this analysis (11.47 mcg/L) compared to the original analysis (8.80 mcg/L). The LS mean differences in this analysis were less than the original analysis primarily due to an increase in change from baseline to endpoint in placebo-treated subjects. The overall results are essentially the same – no differential gender effects were noted; olanzapine increases prolactin concentrations to the same degree in both male and female adolescents.

The Sponsor had not provided an age subgroup analysis in the original submission. This analysis (including only those subjects with normal baseline prolactin concentrations) found a statistically significant ($p = 0.08$) increase in prolactin concentrations in olanzapine-treated subjects < 15 years old compared to subjects ≥ 15 years old. Mean change from baseline to endpoint for olanzapine-treated subjects < 15 years old was 14.7 mcg/L compared to 11.82 mcg/L in subjects ≥ 15 years old. It does appear, however, that the statistical differences may have been driven by differences in the placebo-treated subjects: change in prolactin for subjects < 15 years old was -0.22 mcg/L compared to 3.49 mcg/L for subjects ≥ 15 years old.

*Division Request #2*
Table APP.2.7.4.24 in summary-clin-safe-app provides prolactin data over time for the overall combined database. Please provide a similar table for only those patients who completed 19-32

weeks in the study (n = 83 bipolar, n = 93 schizophrenia) – e.g. provide baseline, 1-6 week, 7-18 week and 19-32 week data for only those patients completing 19-32 weeks.

*Data Submitted in the Original Submission*
In the original submission, the Sponsor had included prolactin concentrations for all subjects in the Overall Olanzapine Exposure Combined Database (see Table 3.1.5). However, it was difficult to evaluate patterns over time in subjects completing the trials since these data also included subjects who dropped out over the course of these trials. Therefore, the Sponsor was asked to provide these data only for subjects completing these trials in order to evaluate a potential pattern in prolactin concentration for subjects with exposures up to 6 -8 months.

Table 3.1.5 Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints: Overall Olanzapine Exposure Combined Database

**Table APP.2.7.4.7.4.24. Mean Prolactin Values at Various Time Points Overall Olanzapine Exposure Combined Database**

| | | Summary | | | | |
|---|---|---|---|---|---|---|
| Database | Olz Exposure | N | Mean | Std | Median | Max |
| Bipolar | Baseline | 217 | 15.35 | 12.58 | 11.28 | 110.30 |
| | 1-6 weeks | 174 | 26.60 | 16.18 | 23.10 | 129.66 |
| | 7-18 weeks | 122 | 19.24 | 11.89 | 16.71 | 59.49 |
| | 19-32 weeks | 83 | 18.03 | 10.42 | 14.36 | 49.53 |
| Schizophrenia | Baseline | 214 | 18.84 | 19.97 | 11.87 | 131.57 |
| | 1-6 weeks | 190 | 31.82 | 20.75 | 26.48 | 110.84 |
| | 7-18 weeks | 88 | 22.75 | 16.24 | 18.62 | 112.00 |
| | 19-32 weeks | 93 | 19.01 | 15.60 | 14.81 | 109.97 |
| Overall | Baseline | 431 | 17.08 | 16.74 | 11.60 | 131.57 |
| | 1-6 weeks | 364 | 29.33 | 18.86 | 25.00 | 129.66 |
| | 7-18 weeks | 210 | 20.71 | 13.95 | 17.13 | 112.00 |
| | 19-32 weeks | 176 | 18.55 | 13.38 | 14.70 | 109.97 |

*Sponsor's Response*

Table 3.1.6. Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints: Overall Combined Database for Subjects Completing 19-32 weeks of Olanzapine Exposure

| | | Summary | | | | |
|---|---|---|---|---|---|---|
| Database | Olz Exposure | N | Mean | Std | Median | Max |
| Bipolar | Baseline | 83 | 12.91 | 8.04 | 10.36 | 37.41 |
| | 1-6 weeks | 49 | 27.21 | 11.65 | 25.86 | 60.72 |
| | 7-18 weeks | 83 | 18.88 | 10.78 | 17.11 | 59.49 |
| | 19-32 weeks | 83 | 18.03 | 10.42 | 14.36 | 49.53 |
| Schizophrenia | Baseline | 93 | 18.03 | 17.37 | 11.98 | 100.00 |
| | 1-6 weeks | 74 | 31.22 | 21.54 | 24.34 | 104.00 |
| | 7-18 weeks | 55 | 20.03 | 11.60 | 16.83 | 54.11 |
| | 19-32 weeks | 93 | 19.01 | 15.60 | 14.81 | 109.97 |
| Overall | Baseline | 176 | 15.62 | 13.98 | 11.17 | 100.00 |
| | 1-6 weeks | 123 | 29.62 | 18.30 | 24.68 | 104.00 |
| | 7-18 weeks | 138 | 19.34 | 11.09 | 16.87 | 59.49 |
| | 19-32 weeks | 176 | 18.55 | 13.38 | 14.70 | 109.97 |

*Reviewer Comments*
For this reanalysis (as in the original analysis), sample sizes vary by timepoint likely due to differences in the various protocols. Similar to the original analysis, the increase in mean prolactin values appears to occur early (1-6 weeks) and decreases at subsequent timepoints; though still elevated compared to baseline concentrations. This analysis was requested so that data could be evaluated over time in the same group of subjects – however, obviously, if subjects dropped out of the study due to prolactin elevations (or other reasons but also had elevated prolactin concentrations), this analysis would not include those subjects and may underestimate the effect. However, the prior analysis did include all subjects and results between the analyses were very similar.

*Proposed Language in Product Labeling re: Prolactin*
The Sponsor was asked to include the frequency of hyperprolactinemia in adolescents in this section and also included this data for the adult populations.

Section 5 – WARNINGS AND PRECAUTIONS; 5.16 Hyperprolactinemia
"In clinical studies, plasma prolactin concentrations were elevated in 34% of adults treated with olanzapine. These elevations were mild and transient (end-point mean not above upper limits of normal and not statistically significantly different from placebo). Associated clinical manifestations (e.g. gynecomastia, galactorrhea, and breast enlargement) were rare. In most patients, levels returned to normal ranges without cessation of treatment.
In placebo-controlled olanzapine monotherapy studies in adolescent patients with schizophrenia or bipolar disorder (manic or mixed episodes), elevated prolactin concentrations occurred in 47.4% of olanzapine-treated patients compared to 6.8% of patients in the placebo group."

This frequency data is also reflected in Section 6 ADVERSE REACTIONS, 6.2 Vital Signs and Laboratory Studies.
The frequency data do not indicate the magnitude of the elevations in prolactin, the adult data included in currently approved labeling also do not indicate the magnitude of prolactin elevation (only the frequency of occurrence). Unlike adverse events of weight gain or ALT increases, there is not a well recognized potentially clinically significant change in which to further categorize these increases. Therefore, it is reasonable to include only the frequencies of prolactin increases and then to note elsewhere in labeling adverse events that may be related to hyperprolactinemia.

Since the Sponsor has now included data about the frequency of potentially prolactin-related adverse events for adults, this data should also be included for adolescents – however, these effects are not rare in the latter population (refer to Sections 3.2 [Additional Narrative Summaries] and 4 [Safety Update] of review).
I would propose to add the following data which is from the original submission (Table 2.7.4.31 in summary-clin-safety document):
In 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).

These adverse events (gynecomastia and galactorrhea) should also be noted in the section of labeling: 6 ADVERSE REACTIONS, 6.1 Clinical Trials Experience, Other Adverse Events Observed During the Clinical Trial Evaluation of Oral Olanzapine. These events would be considered frequent (based on the 1/100 definition).

**3.2 Additional Narrative Summaries**
*Division Request #3*
Please provide narrative summaries for the following: 8 cases of gynecomastia, 2 cases with high prolactin concentrations (HGIN 005-503, HGIN 900-9009) and the case with a CPK of 7289 U/L.

The Sponsor supplied the requested narratives. This reviewer compiled a table (Table 3.2.1) summarizing some of the relevant information for the cases of gynecomastia (7 cases, one subject experienced the adverse event twice).

Prolactin reference ranges for adolescents (13 – 17 years) in study HGIN and HGIU: males = 2.8 – 11 ng/ml; females = 3.2 – 20 ng/ml

Prolactin reference ranges for adolescents in study LOAY:
Males $\geq$ 12 but $\leq$ 13 years = 2.8 – 24 ng/ml; $\geq$ 14 but $\leq$ 16 years = 2.8 – 16.1 ng/ml; > 16 but $\leq$ 19 years = 2.1 – 17.7 ng/ml
Females $\geq$ 12 but $\leq$ 13 years = 2.5 – 16.9 ng/ml; $\geq$ 14 but $\leq$ 16 years = 4.2 – 29 ng/ml; > 16 but $\leq$ 19 years = 2.8 – 29.2 ng/ml

Table 3.2.1. Summary Table for Gynecomastia Cases

| Patient ID | Demographics | Baseline Prolactin (mcg/L) | Prolactin During Study (mcg/L) *indicates prolactin at time of AE report | Clinical Description | Resolved? |
|---|---|---|---|---|---|
| HGIN-910-9103* | 15 YOM | 6.12 | 21.3 (~5 weeks)*<br>19.1 (3 months)<br>12.2 (7 months) | Left side gynecomastia (mild) | Ongoing at study completion |
| LOAY-400-4008 | 17 YOM | 10.50 | 23.0 (~2 weeks)*<br>16.8 (1 month)<br>16.8 (2 months)<br>7.4 (6 months) | Gynecomastia (mild) | Ongoing at study completion |
| LOAY-400-4009 | 14 YOM | 3.90 | 30 (2 weeks)<br>28 (3 weeks)<br>32 (5 weeks)<br>NA*<br>41 (2 months) | Gynecomastia (moderate) | Noted at baseline visit. Severity changed to severe at 2 months. Ongoing at time of discontinuation. |
| LOAY-406-4063 | 17 YOM | 5.50 | 25 (2 weeks)<br>36 (1 month)<br>34 (5 weeks)<br>30 (6 weeks)* | Gynecomastia (mild) | NA |
| LOAY-407-4074 | 17 YOM | 9.50 | 23 (2 weeks)<br>24 (1 month)<br>20 (5 weeks)<br>12.80 (6 months)* | Gynecomastia (mild) | AE noted at last study visit |
| LOAY-407-4077 | 16 YOM | 17.7 | 31 (2 weeks)<br>37 (1 month)<br>37 (6 weeks)<br>14.7 (7 months)* | Gynecomastia (mild) | AE noted at last study visit |
| LOAY-407-4201 | 16 YOM | 17.3 | 27 (2 weeks)<br>24 (1 month)*<br>20 (6 weeks)*<br>28 (2 months) | Gynecomastia (mild) | Ongoing at study discontinuation. |

* Sponsor indicates that 2 cases of gynecomastia occurred in this patient – the narrative indicates that the subject had these symptoms "periodically" since ~2 years prior to study participation. It is noteworthy that this subject had a prolactin concentration of 95.35 mcg/ml at Visit 1 (presumably screening visit).

*Reviewer Comments*

Seven subjects participating in the clinical trials for bipolar disorder and schizophrenia had an adverse event "gynecomastia". Interestingly, six of these subjects participated in the 24-week open label LOAY study conducted exclusively in Germany (these cases occurred at 3 different sites and 3 different investigators). These cases were associated with some elevations in prolactin concentration and most were considered by the investigators to be of mild severity. Though the narratives did not include vital sign data, this reviewer wanted to evaluate the weight gain in these subjects since fat deposition in the breast area, "pseudogynecomastia", might be mistaken as gynecomastia. Not surprisingly, these subjects gained a significant amount of weight over the course of these studies – from 9.1 to 24.6 kg over ~24 weeks (Table 3.2.2).

Table 3.2.2. Weight Changes in Subjects with the Adverse Event Gynecomastia

| | Baseline | | End of Study | | Change from Baseline to Endpoint | |
|---|---|---|---|---|---|---|
| | Weight | BMI | Weight | BMI | Weight | BMI |
| HGIN-910-9103 | 58 kg | 20.1 | 82 kg | 28.4 | 24 kg | 8.3 |
| LOAY-400-4008 | 83.5 kg | 24.7 | 108.1 kg | 31.9 | 24.6 kg | 7.2 |
| LOAY-400-4009 | 66.6 kg | 23.6 | 78.8 kg | 27.9 | 12.2 kg | 4.3 |
| LOAY-406-4063 | 62.7 kg | 20 | 71.8 kg | 22.9 | 9.1 kg | 2.9 |
| LOAY-407-4074 | 65.9 kg | 20.3 | 82.6 kg | 25.5 | 16.7 kg | 5.2 |
| LOAY-407-4077 | 63.3 kg | 19.8 | 82 kg | 25.6 | 18.7 kg | 5.8 |
| LOAY-407-4201 | 65.5 kg | 22.7 | 81.7 kg | 28.3 | 16.2 kg | 5.6 |

According to Harrison's medical textbook, gynecomastia is not uncommon in teenage boys with 65% of 14 year-old boys having gynecomastia that usually goes away on its own in 2 or 3 years (hormonally-related). However, the temporal association with olanzapine therapy may implicate the antipsychotic in this adverse event. These cases are not, however, associated with remarkably elevated prolactin concentrations (upper range of normal in males in this age range = 16 to 18 ng/ml for reference ranged used in LOAY) such that it is not clear that these were in fact cases of gynecomastia and may be cases of pseudogynecomastia secondary to significant weight gain. However, since the investigators used the term "gynecomastia" as an adverse event term for these cases, this reviewer will assume this to be correct (since it does not appear to have been queried by the Sponsor) and will recommend some labeling changes to reflect this information (see Section 3.1 [Prolactin] of review). It is not clear to this reviewer why the majority of these cases were from one clinical trial (LOAY).

Elevated Prolactin Cases

HGIN-005-0503 14 YOF. Baseline prolactin 17.2 mcg/L, increased to 90.68 mcg/L at ~6 weeks (no other labs available between these two values). Subsequent prolactin concentrations were 40.2 mcg/L at ~4.5 months and 45.5 mcg/L at ~7.5 months. The subject was receiving olanzapine 20 mg/day when the 90.68 and 45.5 mcg/L concentrations were obtained. No adverse events reported that were associated with elevated prolactin.

HGIN-900-9009 17 YOF. Baseline prolactin 17.5, elevation to 109.97 mcg/L noted at study completion (~8 months); prolactin concentration prior to this was 17.0 mcg/L at ~4 months. Subject was receiving olanzapine 10 mg/day when elevated concentration obtained. No adverse events associated with elevated prolactin were noted.

CPK Elevation Case

HGIN-004-0401 14 YOM. No baseline CPK available. Elevated CPK of 7289 U/L (reference range = 0 – 363 U/L noted one week after randomization – this was the highest CPK value obtained. CPKs were monitored weekly/monthly thereafter and ranged from 445 – 1766 U/L with no clear trend; last CPK noted as 781 U/L at ~8 months. CK-MB concentrations were obtained at some timepoints and most were elevated (5.2 – 10 ng/ml; reference range 0 – 4.9 ng/ml). Urine myoglobin obtained once (at ~2 months when CPK = 531 U/L) and was < 0.006.

Of note, the subject was receiving haloperidol decanoate prior to the study and, if narrative is correct, received his last dose approximately 9 days prior to randomization. No comments regarding extent of exercise or other potential contributing causes.

*Reviewer Comments*
This reviewer has recommended some labeling language to reflect the gynecomastia cases (see section 3.1 [Prolactin] of review).
The elevated prolactin cases appear to be related to olanzapine therapy and both occurred in female subjects who tend to have a more robust prolactin response to antipsychotics. These were the most significant elevations noted during the original review and appear to represent outliers. Per the Sponsor, there were no adverse events associated with the elevated prolactin, though it is not clear how this was determined (spontaneous reports vs. specific queries for prolactin-related adverse events).
The elevated CPK case was impressive and the highest value (7289 U/L0 was noted one week after randomization – it is possible that this could have been secondary to a haloperidol decanoate injection which appears to have been received 9 days prior to randomization (protocol violation). The CPK was consistently elevated over the course of the 8 month trial, though concentrations were quite variable.
No further labeling changes based on these additional cases (elevated prolactin and CPK) is recommended.

### 3.3 Hepatic Analytes

*Division Request #4*
The summary-clin-safe-app document includes comparisons of adult and adolescent data for metabolic parameters and prolactin but not for hepatic laboratory analytes. Please provide these comparisons for hepatic laboratory analytes. Although it is stated in the submission that the hepatic laboratory analyte comparisons were not provided due to differences in reference ranges for adults and adolescents, these comparisons were provided for the prolactin data despite differences in reference ranges for these populations.

*Sponsor's Response*
The Sponsor provided the following data for mean change from baseline to endpoint in hepatic analytes using normalized units for comparing the adolescent and adult populations. Statistically significant, though small, changes were noted for alkaline phosphatase (adolescents > adults) and total bilirubin (decreases noted in both populations).

Table 3.3.1. Sponsor's Table. Mean Change from Baseline to Endpoint in Hepatic Analytes (Normalized Units). Comparison of Adult Versus Adolescent Patients (Overall Exposure Database)

| Laboratory Evaluations | Unit | Population | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| AST/SGOT | %URL | Adolescent | 446 | 59.35 | 51.72 | 9.00 | 54.59 | 7.29 | -0.81 | .767 |
| | | Adult | 7074 | 63.19 | 36.97 | 7.99 | 59.21 | 8.10 | | |
| ALT/SGPT | %URL | Adolescent | 446 | 57.30 | 74.23 | 21.39 | 82.65 | 18.09 | 3.49 | .520 |
| | | Adult | 7084 | 66.00 | 57.78 | 14.39 | 115.43 | 14.60 | | |
| ALKALINE PHOSPHATASE | %URL | Adolescent | 446 | 65.27 | 30.13 | 4.38 | 18.19 | 4.33 | 1.96 | .019 |
| | | Adult | 7132 | 65.59 | 20.42 | 2.37 | 17.36 | 2.37 | | |
| GGT (GGPT/SGGT/YGGT) | %URL | Adolescent | 446 | 43.60 | 31.34 | 8.19 | 32.44 | 5.88 | 1.33 | .582 |
| | | Adult | 7051 | 54.40 | 52.99 | 4.40 | 51.93 | 4.54 | | |
| BILIRUBIN, TOTAL | umol/L | Adolescent | 446 | 8.56 | 5.96 | -1.12 | 4.60 | -1.19 | -0.94 | <.001 |
| | | Adult | 7182 | 8.71 | 5.22 | -0.26 | 6.05 | -0.25 | | |

The Sponsor also provided an analysis for treatment-emergent abnormally high hepatic analyte values (> 1X ULN) at anytime for adolescent and adult populations – the Sponsor did not include these data for ALT $\geq$ 3x ULN. In general, a greater percentage of adolescent subjects had increases in AST, ALT and alkaline phosphatase compared to adult subjects.

Table 3.3.2. Sponsor's Table. Treatment-Emergent Abnormally High Hepatic Analyte Values (> 1X ULN) at Anytime, Adult versus Adolescents (Overall Exposure Database)

| Laboratory Analyte | Direction | Population | N | n | (%) | *P-Value |
|---|---|---|---|---|---|---|
| AST/SGOT | High | Adolescent | 418 | 127 | 30.4% | <.001 |
| | | Adult | 6338 | 1459 | 23.0% | |
| ALT/SGPT | High | Adolescent | 396 | 169 | 42.7% | <.001 |
| | | Adult | 5891 | 1791 | 30.4% | |
| ALKALINE PHOSPHATASE | High | Adolescent | 387 | 52 | 13.4% | <.001 |
| | | Adult | 6655 | 469 | 7.0% | |
| GGT (GGPT/SGGT/YGGT) | High | Adolescent | 432 | 34 | 7.9% | .136 |
| | | Adult | 6292 | 642 | 10.2% | |
| BILIRUBIN, TOTAL | High | Adolescent | 423 | 9 | 2.1% | .054 |
| | | Adult | 7080 | 75 | 1.1% | |

*Reviewer Comments*
The mean change from baseline to endpoint in hepatic analytes for adult versus adolescents (including the open-label trials) did not indicate significant differences between these populations. In contrast, the percentage of subjects experiencing an abnormally high hepatic analyte concentration was generally higher for adolescents compared to adults; especially for AST, ALT and alkaline phosphatase.

*Proposed Language in Product Labeling re: Hepatic Analytes*

The proposed labeling includes data from the placebo-controlled trials and indicates the increased incidence of elevations in ALT (≥ 3x ULN) in adolescents compared to adults. This reviewer has no additional recommendations for further labeling based on these additional analyses.

In Section 5 Warnings and Precautions (5.12 Transaminase Elevations)
"In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from < 3 times the upper limit of normal at baseline to > 3 times the upper limit of the normal range) were observed in 12% (21/174) of patients exposed to olanzapine compared to 2% (2/87) of the placebo-treated patients. Discontinuation due to transaminase increases occurred in 3.4% (6/179) of patients exposed to olanzapine".

In Section 6.2 Vital Signs and Laboratory Studies
"In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT (> 3x ULN in patients with ALT at baseline < 3 X ULN) (12.1% vs. 2.3%); elevated AST (27.6% vs 3.8%); low total bilirubin (22.1% vs 6.7%); elevated GGT (10.1% vs 1.2%)..."

**3.4 Fatalities**
*Division Request #5*
Please review the MedWatch reports for fatalities and submit updates where possible for incomplete data. It was noted that these MedWatch reports had "DRAFT" at the top of the page and the date of the report was 7/27/06. Have all of these reports been previously filed with the Agency?

*Sponsor's Response*
The Sponsor indicated that because these MedWatch forms were generated for the purposes of a submission dossier, they all showed the date that they were generated (7/27/06) and were marked "draft". The Sponsor also stated that all of the MedWatch forms for fatalities had been previously filed to NDA 20-592 (submission dates 12/16/97 to 5/19/06).

*Reviewer Comments*
No further information is requested.

*Division Request #6*

For MedWatch fatality case US_010158510, the narrative states "this is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in (b) (4). The reported stated he has also notified the FDA...". The only MedWatch report included in this submission

is for US_010158510. Please provide the MedWatch reports for the additional 4 deaths indicated in this narrative.

*Sponsor's Response*
The Sponsor stated that all these cases had been previously filed to NDA 20-592. The Sponsor included brief narrative summaries for these cases. This reviewer compiled a table summarizing data from these cases (Table 3.4.1). As with most MedWatch cases, these patients were taking numerous concomitant medications.

Table 3.4.1. Summary of Additional Requested Fatality Narratives

| | Demographics | Olanzapine dose/duration | Diagnosis | Date of Death | Cause of Death |
|---|---|---|---|---|---|
| US_010158520 | 52 YOWF | 20 mg ~1 year | MDD with psychotic features | (b) (6) | Unknown, found dead in home. No autopsy |
| US_010158524 | 29 YOWF | 30 mg ~9 months | MDD with psychotic features | (b) (6) | Diabetic ketoacisosis |
| US_010158498 | 19 YOWM | 5 mg ~7 weeks | Intermittent explosive disorder, antisocial PD | (b) (6) | Unknown |
| US_010158510 | 17 YOWM | 2.5 mg not provided | Dysthymic disorder, schizophreniform disorder | (b) (6) | Accidental overdose vs. suicide |
| US_010158537 | 34 YOWF | 30 mg ~9 months | Psychotic disorder | (b) (6) | Unknown, found dead in home. No autopsy. Coroner comments indicate possible narcotic overdose. |

*Reviewer Comments*
It is difficult to interpret the relatedness of these fatalities to olanzapine therapy especially in light of the usual confounds inherent in MedWatch spontaneous reports. It is of interest that these cases were clustered in one geographic area with the majority occurring in 2000, but this could reflect reporting bias to some extent. It is troubling that there is very little data available for 3 of these cases – the narratives indicate that the Sponsor did attempt to obtain further information but was unable to do so.

## 3.5 AIMS Analysis

*Division Request #7*
Please provide an analysis of AIMS individual items and total score (change from baseline to endpoint) for the completers in the overall combined database.

This item was requested to evaluate potential emergent tardive dyskinesia for subjects who completed the long-term extension phases of the acute studies – since duration of antipsychotic use is a risk factor for development of this adverse event.

*Sponsor's Response*

Table 3.5.1. Sponsor's Table. Mean Change from Baseline to Endpoint in AIMS Scores. All Patients who Completed the Study – Overall Exposure Database.

| | | | Baseline | | Change to Endpoint | | |
|---|---|---|---|---|---|---|---|
| EPS Variables | Database | N | Mean | Std | Mean | Std | *P-value |
| AIMS Non-Global Total(1-7) | Bipolar | 129 | 0.06 | 0.35 | -0.04 | 0.29 | .132 |
| | Schizophrenia | 85 | 0.29 | 0.88 | -0.22 | 0.88 | .021 |
| | Overall | 214 | 0.15 | 0.63 | -0.11 | 0.60 | .007 |
| AIMS Total(1-10) | Bipolar | 129 | 0.10 | 0.50 | -0.05 | 0.54 | .332 |
| | Schizophrenia | 85 | 0.59 | 1.77 | -0.51 | 1.76 | .010 |
| | Overall | 214 | 0.29 | 1.20 | -0.23 | 1.21 | .006 |
| AIMS Item 1 - Muscles of Facial Expression | Bipolar | 129 | 0.00 | 0.00 | 0.01 | 0.09 | .319 |
| | Schizophrenia | 85 | 0.11 | 0.44 | -0.07 | 0.51 | .203 |
| | Overall | 214 | 0.04 | 0.28 | -0.02 | 0.33 | .298 |
| AIMS Item 2 - Lips and Perioral Area | Bipolar | 129 | 0.00 | 0.00 | 0.00 | 0.00 | |
| | Schizophrenia | 85 | 0.04 | 0.19 | -0.04 | 0.19 | .083 |
| | Overall | 214 | 0.01 | 0.12 | -0.01 | 0.12 | .083 |
| AIMS Item 3 - Jaw | Bipolar | 129 | 0.01 | 0.09 | -0.01 | 0.09 | .319 |
| | Schizophrenia | 85 | 0.00 | 0.00 | 0.00 | 0.00 | |
| | Overall | 214 | 0.00 | 0.07 | -0.00 | 0.07 | .318 |
| AIMS Item 4 - Tongue | Bipolar | 129 | 0.02 | 0.12 | -0.02 | 0.12 | .158 |
| | Schizophrenia | 85 | 0.04 | 0.33 | -0.04 | 0.33 | .320 |
| | Overall | 214 | 0.02 | 0.23 | -0.02 | 0.23 | .132 |
| AIMS Item 5 - Upper Extremity | Bipolar | 129 | 0.01 | 0.09 | 0.00 | 0.12 | 1.00 |

| | | | Baseline | | Change to Endpoint | | |
|---|---|---|---|---|---|---|---|
| EPS Variables | Database | N | Mean | Std | Mean | Std | *P-value |
| AIMS Item 5 - Upper Extremity | Schizophrenia | 85 | 0.06 | 0.28 | -0.05 | 0.30 | .159 |
| | Overall | 214 | 0.03 | 0.19 | -0.02 | 0.22 | .207 |
| AIMS Item 6 - Lower Extremity | Bipolar | 129 | 0.02 | 0.12 | -0.01 | 0.09 | .319 |
| | Schizophrenia | 85 | 0.05 | 0.34 | -0.04 | 0.36 | .369 |
| | Overall | 214 | 0.03 | 0.24 | -0.02 | 0.24 | .249 |
| AIMS Item 7 - Neck, Shoulders, Hips | Bipolar | 129 | 0.02 | 0.12 | -0.02 | 0.12 | .158 |
| | Schizophrenia | 85 | 0.01 | 0.11 | 0.00 | 0.15 | 1.00 |
| | Overall | 214 | 0.01 | 0.12 | -0.01 | 0.14 | .318 |
| AIMS Item 8 - Global Severity | Bipolar | 129 | 0.00 | 0.00 | 0.01 | 0.09 | .319 |
| | Schizophrenia | 85 | 0.13 | 0.48 | -0.12 | 0.47 | .024 |
| | Overall | 214 | 0.05 | 0.31 | -0.04 | 0.31 | .049 |
| AIMS Item 9 - Global Incapacitation | Bipolar | 129 | 0.00 | 0.00 | 0.00 | 0.00 | |
| | Schizophrenia | 85 | 0.05 | 0.21 | -0.05 | 0.21 | .045 |
| | Overall | 214 | 0.02 | 0.14 | -0.02 | 0.14 | .045 |
| AIMS Item 10 - Patient's Awareness | Bipolar | 129 | 0.04 | 0.19 | -0.02 | 0.28 | .529 |
| | Schizophrenia | 85 | 0.12 | 0.45 | -0.12 | 0.45 | .018 |
| | Overall | 214 | 0.07 | 0.32 | -0.06 | 0.36 | .023 |

*Reviewer Comments*

For the AIMS non-global (items 1-7), AIMS total (items 1-10) and most individual AIMS items, there was a decrease in score rating at endpoint compared to baseline for the bipolar, schizophrenia and overall (bipolar + schizophrenia) treatment groups. Based on this mean change analysis, there is no signal for increased risk of tardive dyskinesia in this dataset.

### 3.6 Disparity in Efficacy Results US vs. Russian Sites in HGIN

*Division Request #8*

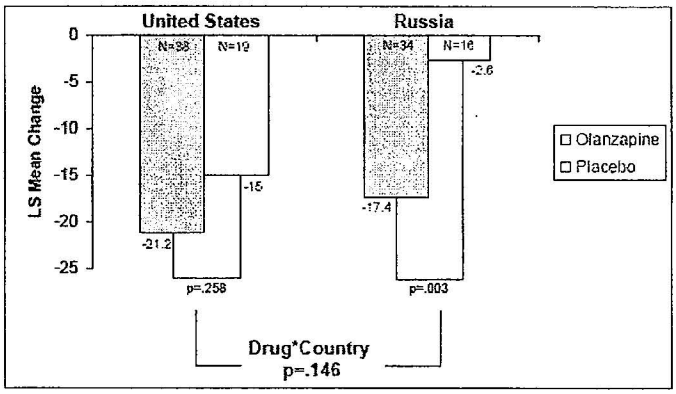
One concern we have for study HGIN is a finding that the positive results for this trial appeared to come predominantly from the Russian sites. For this study, the total sample was roughly split between these 2 regions. Although olanzapine was favored over placebo numerically in both regions, the data from the Russian sites appeared to be driving the overall result. For the US patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -21 and -15 respectively ($p = 0.258$). For the Russian patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -17 and -3, respectively ($p = 0.003$). So, the treatment effect in olanzapine patients was roughly the same in both regions, however, the placebo response was much larger in the US sites compared to the Russian sites. Please address this geographic discrepancy in the efficacy results.

*Sponsor's Response*

The Sponsor provided details for further exploratory analyses including:

1. Between-country comparisons, comparison of baseline characteristics, and inclusion of significant baseline characteristics into the ANCOVA model
2. Analyses by country for disposition, effect size, response rate, modal dose, concomitant medication use, and weight gain
3. Visit-wise LOCF and observed case (OC) mean change for BPRS-C total score by country
4. Analysis of treatment-by-country interaction and within-country effect for secondary efficacy measures
5. Evaluation of data from placebo-treated patients with therapeutic improvements similar to the olanzapine treatment magnitude

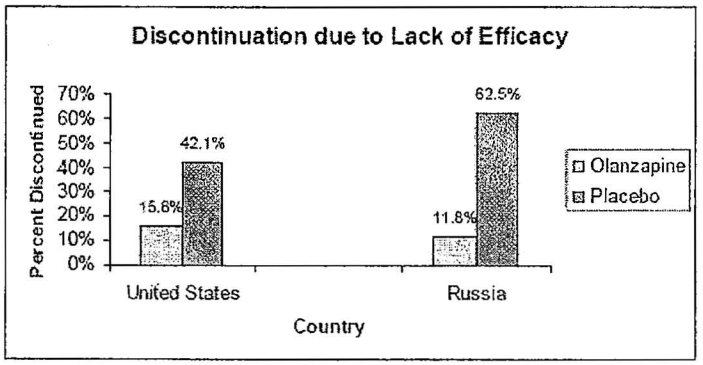
The Sponsor also reiterated in this response that the treatment-by-country interaction was not significant ($p = 0.146$):




Abbreviation: LS = least-squares.
Source: CLOBPRA1, CLOBPRA4.

**Figure APP.4.1. Brief Psychiatric Rating Scale for Children Total score mean change by country.**

The Sponsor reiterated that discontinuation due to lack of efficacy was significantly greater among placebo-treated patients compared with olanzapine-treated patients in both the US ($p = 0.049$) and Russia ($p < 0.001$). "This result is supportive of the efficacy demonstrated with olanzapine treatment compared with placebo treatment in both countries."




Source: INACMGA1.

**Figure APP.4.2. Percentage of patients discontinuing due to lack of efficacy in the United States and Russia.**

- The effect sizes were .63 for all patients, .32 for the US patients, and .96 for Russian patients.
- Protocol-defined response rate was not statistically different between the two treatment groups in either the United States (39.5% for olanzapine; 31.6% for placebo; p=.772) or in Russia (35.3% for olanzapine; 18.8% for placebo; p=.328).
- Use of concomitant benzodiazepine medication was not statistically significantly different in the United States (26.3% for olanzapine; 42.1% for placebo; p=.244) or in Russia (32.4% for olanzapine; 62.5 % for placebo; p=.066).
- The mean modal doses were calculated for patients in both countries. The mean modal doses were 13.2 mg for the United States and 11.8 for Russia.

Overall conclusion by Sponsor:

Despite numerous statistical and clinical evaluations, an explanation for the difference in placebo response between the United States and Russia remains unclear. It is possible that factors such as population heterogeneity or cultural availability of adjunct therapy may have influenced the placebo response, but this cannot be proven with the available data. Lilly believes that the lack of a clear explanation for the difference in placebo response in the two countries should be considered in light of the fact that a similar magnitude of efficacy response was observed for the olanzapine treatment group in both countries, and that the treatment-by-country interaction was not significant. Furthermore, the overall results of the trial are positive, and are consistent with the abundance of positive efficacy data for the use of olanzapine for the treatment of schizophrenia in adults.

*Reviewer Comments*
During the review of the original submission, this reviewer had asked the Sponsor for additional analyses (e.g. baseline illness characteristics) to evaluate potential differences between subjects enrolled in the US and Russian sites. No significant differences that might account for the low placebo response rate at the Russian sites was identified during review of these additional analyses.

Discontinuations Due to Lack of Efficacy
The Sponsor commented that the discontinuations due to lack of efficacy were significantly greater among placebo-treated patients compared with olanzapine-treated patients in both the US ($p = 0.049$) and Russia ($p < 0.001$) and that this result is supportive of the efficacy demonstrated with olanzapine treatment compared with placebo treatment in both countries. While this statement is true, the p-value for the US sites is marginally significant and could change depending on how you might categorize "lost to follow up" (1.4% in olanzapine group vs. 0% in placebo) and "patient decision" (5.6% in olanzapine group vs. 2.9% in placebo group). It bears mentioning that lack of efficacy, though different between the olanzapine and placebo groups, is the main reason for study discontinuation in both groups.

This reviewer also referred to the recent NDA submissions for the aripiprazole (NDA 21436 SE5-021) and risperidone (NDA 20272 SE5-046) adolescent schizophrenia programs (both recently granted approval actions). Though there are obvious limitations in comparing study HGIN to the pivotal trials for these other antipsychotics, there are certainly noteworthy differences with respect to several issues including discontinuations due to lack of efficacy:

Table 3.6.1. Subject Disposition: Adolescent Schizophrenia Pivotal Trials for Olanzapine, Aripiprazole, and Risperidone

| | Sample Size | Discontinuation Rates | DC due to Lack of Efficacy | DC due to AE | Withdrew Consent/Patient Decision | Lost to Follow-up |
|---|---|---|---|---|---|---|
| Olanzapine | 72 | 32% | 13.9% | 6.9% | 5.6% | 1.4% |
| Placebo | 35 | 57% | 51.4% | 0 | 2.9% | 0 |
| Aripiprazole 10 mg | 99 | 16% | 5% | 7% | 4% | 0 |
| Aripiprazole 30 mg | 97 | 18% | 1% | 3.9% | 11.8% | 0 |
| Placebo | 98 | 10% | 1% | 2% | 5% | 1% |
| Risperidone 1-3 mg | 54 | 18% | 5% | 5% | 5% | NA |
| Risperidone 4-6 mg | 50 | 14% | 2% | 8% | 2% | NA |
| Placebo | 54 | 33% | 24% | 4% | 4% | NA |

Comparing across these trials, the overall discontinuation rates for the olanzapine study (HGIN) are much higher compared to the aripiprazole and risperidone pivotal trials. This disparity is also reflected in the discontinuations due to lack of efficacy across these trials including what appear to be significant differences between the olanzapine-treated subjects compared to aripiprazole or risperidone-treated subjects. However, the discontinuations due to lack of efficacy in the aripiprazole 30 mg group may be more similar to the olanzapine group depending on the definition of "withdrew consent".

Evaluating the Low Placebo Response in Russian Sites Compared to US Sites.

Table HGIN.14.21. BPRS-C Total Score
Mean Change from Baseline to Endpoint (LOCF) by Country
Double-Blind Period

| Efficacy Variable | Country | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Diff. | *P-value | **P-value (Therapy by Country ) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BPRS-C Total Score | America | Olanzapine | 38 | 52.18 | 10.10 | -21.21 | 16.90 | -20.69 | -5.26 | .258 | .146 |
| | | Placebo | 19 | 51.42 | 8.64 | -15.00 | 18.28 | -15.64 | | | |
| | Russia | Olanzapine | 34 | 47.00 | 8.88 | -17.41 | 14.55 | -17.44 | -14.95 | .003 | |
| | | Placebo | 16 | 48.50 | 8.52 | -2.56 | 17.38 | -2.49 | | | |

Source: Original NDA submission

This reviewer again referred to the recent NDA submissions for the aripiprazole and risperidone adolescent schizophrenia programs to compare placebo response between the Russian sites in HGIN compared to the aripiprazole and risperidone pivotal schizophrenia trials. For these latter pivotal trials, the primary efficacy variable was the PANSS total score.

Approximately 32 % (93/294) of subjects in the aripiprazole pivotal trial were from US sites and 22% (64/294) from Russian sites (the remaining from Argentina, Bulgaria, Croatia, India, Jamaica, Mexico, Romania, Serbia, South Africa, south Korea and Ukraine). In the statistical analysis for this NDA, a separate subgroup analysis for the Russian sites was not performed by

the statistician. However, upon request from this reviewer, the statistician (Yeh Fong, Ph.D.) did provide an analysis of change from baseline for the Russian sites (Table 3.6.2). Contrary to the olanzapine pivotal trial (HGIN), the placebo response in the Russian sites was similar to the US sites (-17.8 vs. -23.7).

Table 3.6.2. Region Subgroup Analysis: Adolescent Schizophrenia Pivotal Trials for **Aripiprazole**

Table 7 Sponsor's Region Subgroup Analysis Results for Change from Baseline to End Visit of PANSS Total Score (by LOCF Data) for Study 31-03-239

| Treatment | Visit | Mean (SD) | Change from Baseline to Last Visit Mean (SD) |
|---|---|---|---|
| US | | | |
| Arip-10 mg (N=31) | Baseline | 97.2 (16.5) | -31.4 (22.5) |
| | Last Visit (Week 6) | 65.8 (21.8) | |
| Arip-30 mg (N=31) | Baseline | 101.3 (15.1) | -30.7 (21.4) |
| | Last Visit (Week 6) | 70.5 (24.1) | |
| Placebo (N=31) | Baseline | 98.6 (17.0) | -23.7 (20.9) |
| | Last Visit (Week 6) | 74.9 (26.8) | |

| Treatment | Visit | Mean (SD) | Change from Baseline to Last Visit Mean (SD) |
|---|---|---|---|
| **Russia** | | | |
| Arip-10 mg (N=21) | Baseline | 91.14 (15.56) | -19.57 (21.70) |
| | Last Visit (Week 6) | 71.57 (21.43) | |
| Arip-30 mg (N=25) | Baseline | 88.28 (12.31) | -19.76 (16.77) |
| | Last Visit (Week 6) | 68.52 (17.59) | |
| Placebo (N = 18) | Baseline | 95.72 (13.46) | -17.83 (14.33) |
| | Last Visit (Week 6) | 77.89 (11.67) | |

Approximately 21 % (33/160) of subjects in the risperidone pivotal trial were from US sites and 23% (37/160) from Russian sites (the remaining from India and Ukraine). In the risperidone pivotal trial, the placebo response in the Russian sites is consistent with the olanzapine HGIN pivotal trial (Table 3.6.3). Interestingly, the risperidone change from baseline is also much lower in the Russian sites compared to the US sites.

Table 3.6.3. Region Subgroup Analysis: Adolescent Schizophrenia Pivotal Trials for **Risperidone**

| Treatment | Change from Baseline to Endpoint LS Mean Change | P-value |
|---|---|---|
| **Russia** | | |
| Risperidone 1-3 mg (N=12) | -9.29 | 0.23 |
| Risperidone 4-6 mg (N=13) | -11.6 | 0.09 |
| Placebo (N = 12) | -0.44 | |

| Treatment | Change from Baseline to Endpoint LS Mean Change | P-value |
|---|---|---|
| **United States** | | |
| Risperidone 1-3 mg (N= 12) | -29.2 | 0.030 |
| Risperidone 4-6 mg (N= 11) | -27.7 | 0.046 |
| Placebo (N = 10) | -11.1 | |

Overall, though the placebo response is quite low in the Russian sites in the olanzapine pivotal trial HGIN, a similarly low placebo response in Russian sites has been noted in similar studies in similar populations (risperidone) though not all (aripiprazole). This reviewer did not look at individual investigators or individual sites within Russia for any further comparisons.

Evaluating the Change from Baseline to Endpoint in Olanzapine Groups (US vs. Russia)
The Sponsor states that although the olanzapine vs. placebo comparisons were statistically significant for the Russian sites and not the US sites (primarily due to the low placebo response rate in the Russian sites), the change from baseline to endpoint in the olanzapine groups are similar between the these geographic sites. This reviewer agrees that the overall decrease from baseline to endpoint between the olanzapine groups in the US and Russian sites is similar. Again the overall statistically significant finding is largely driven by the low placebo response in the Russian sites and not due to disparities between the olanzapine groups. It is also entirely likely that, when the US sites are evaluated separately, there is insufficient power to detect a statistical difference. In efforts to further evaluate efficacy signals, this reviewer also looked at the adolescent schizophrenia pivotal trials for aripiprazole and risperidone. It should be noted that the primary efficacy variable in the pivotal trials for aripiprazole and risperidone was the PANSS total score. MMRM analyses were not available for the aripiprazole and risperidone pivotal trials.

In general, when comparing the change from baseline to endpoint in the olanzapine group in the US sites (-21.2), it is of a similar magnitude to changes from baseline in other antipsychotic clinical trials in similar populations (most of these clinical trials enrolled ~20% of subjects from

US sites). Since study HGIN used the BPRS as the primary endpoint whereas the aripiprazole and risperidone pivotal trials used the PANSS, a decrease of this magnitude in HGIN (-21.2) may be more significant given the higher baseline scores in the latter trials due to the differences in the BPRS and PANSS instruments.

It is noteworthy that, largely due to differences in subject discontinuation rates (see Table 3.6.1), the OC analyses for the aripiprazole and risperidone pivotal trials were statistically significant whereas the OC analysis for the olanzapine HGIN trial was not (Table 3.6.4). Due to the 2:1 randomization scheme in HGIN, only 35 subjects received placebo and 57% of subjects in the placebo group discontinued the study leaving 15 subjects for the OC analysis.

Table HGIN.14.21. BPRS-C Total Score
Mean Change from Baseline to Endpoint (LOCF) by Country
Double-Blind Period

| Efficacy Variable | Country | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Diff. | *P-value | **P-value (Therapy by Country) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BPRS-C Total Score | America | Olanzapine | 38 | 53.16 | 10.10 | -31.31 | 16.30 | -20.89 | -5.26 | .258 | .146 |
| | | Placebo | 19 | 51.42 | 8.64 | -15.00 | 18.28 | -15.64 | | | |
| | Russia | Olanzapine | 34 | 47.00 | 8.88 | -17.41 | 14.55 | -17.44 | -14.95 | .003 | |
| | | Placebo | 16 | 48.50 | 8.52 | -2.56 | 17.38 | -2.49 | | | |

Table 3.6.4. LOCF and OC Analyses: Adolescent Schizophrenia Pivotal Trials for Olanzapine (US + Russian sites), Aripiprazole, and Risperidone

| | | | Change from Baseline to Endpoint or LS Mean Change | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Primary Endpoint | Baseline | LOCF analysis | | | OC analysis | | |
| | | | Change | P-value | Sample Size | Change | P-value | Sample Size |
| Olanzapine | BPRS | 50.3 | -19.3 | p = 0.003 | 72 | -24.5 | p = 0.947 | 50 |
| Placebo | | 50.1 | -9.1 | | 35 | -23.7 | | 15 |
| Aripiprazole 10 mg | PANSS | 93.7 | -26.7 | p = 0.04 | 99 | -30.6 | p = 0.001 | 84 |
| Aripiprazole 30 mg | | 94.9 | -28.6 | p = 0.006 | 97 | -31.9 | p = 0.0002 | 84 |
| Placebo | | 95.0 | -21.2 | | 98 | -22.3 | | 90 |
| Risperidone 1-3 mg | PANSS | 95.4 | -21.3 | p < 0.001 | 54 | -24.6 | p < 0.001 | 44 |
| Risperidone 4-6 mg | | 93 | -21.2 | p < 0.001 | 50 | -24.5 | p < 0.001 | 43 |
| Placebo | | 93.2 | -8.9 | | 54 | -13.6 | | 35 |

Discrepancies in MMRM analyses depending on model chosen

The primary efficacy endpoint for study HGIN was change from baseline in the BPRS-C total score by LOCF analysis with OC and MMRM as supportive analyses. The LOCF analysis was statistically significant favoring olanzapine (LS mean difference = -10.12; p = 0.003) as was the MMRM analysis (LS mean difference = -8.90; p = 0.015). The OC analysis was not statistically significant (LS mean difference = -0.26; p = 0.947).

In his original review, the statistician had indicated that the MMRM analysis was not statistically significant based on his analysis (not the Sponsor's). In an addendum to his review, he indicated that he had used a different model for the MMRM analysis (default variance-covariance structure model) than the Sponsor had used (unstructured model); however, he indicated that the unstructured model was the most appropriate to use based on the fit of the data.
However, it should be noted that, based on the MMRM model, the p-values are very different:

| Variance-covariance Structure | Placebo | Olanzapine | AIC |
|---|---|---|---|
| **Variance Components** | | | |
| LS Mean change from baseline (SE) | -24.1 (3.13) | -24.5 (1.73) | |
| Difference between LS Means and C.I. | -0.43 (-6.6,7.5) | | |
| P-value | 0.90 | | 4691 |
| **Unstructured** | | | |
| LS Mean change from baseline (SE) | -12.6 (2.99) | -21.5 (1.97) | |
| Difference between LS Means and C.I. | -8.9 (-16.0, -1.9) | | |
| P-value | 0.015 | | 4055.2 |
| **Compound Symmetry** | | | |
| LS Mean change from baseline (SE) | -17.8 (2.61) | -22.9 (1.60) | |
| Difference between LS Means and C.I. | -5.1 (-11.1, 0.9) | | |
| P-value | 0.10 | | 4353.0 |
| **Toeplitz** | | | |
| LS Mean change from baseline (SE) | -14.3 (2.68) | -21.9 (1.65) | |
| Difference between LS Means and C.I. | -7.67 (-13.8, -1.5) | | |
| P-value | 0.015 | | 4129.0 |
| **Toeplitz with Two Bands** | | | |
| LS Mean change from baseline (SE) | -21.7 (2.70) | -24.4 (1.53) | |
| Difference between LS Means and C.I. | -2.68 (-8.8, 3.4) | | |
| P-value | 0.39 | | 4356.0 |
| **First Order Auto-regression** | | | |
| LS Mean change from baseline (SE) | -15.4 (2.71) | -22.3 (1.64) | |
| Difference between LS Means and C.I. | -7.0 (-13.8, -0.8) | | |
| P-value | 0.029 | | 4129.0 |

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

Source: Statistician's review – addendum to review

Evaluating the different MMRM models for the data for study HGIU (bipolar study) yields very consistent results with p-values ranging from < 0.0001 to 0.0004 (see Appendix). It appears that the MMRM analyses are very unstable for the schizophrenia data (HGIN) and are quite dependent on the specific MMRM model used in contrast to the very stable results for the bipolar data (HGIU). It should also be noted that the drop-out rates in the two studies were different with more subjects remaining in study HGIU – how this impacts the various MMRM models is beyond the expertise of this clinical reviewer. The OC analysis for study HGIU was statistically significant.

Since the Sponsor prespecified the LOCF as the primary analysis and the statistician agrees that the unstructured MMRM model is the most appropriate, it would appear that the Sponsor's data support efficacy of olanzapine versus placebo in study HGIN.

DSI inspections for Russian sites

Fifty subjects were enrolled in Russian sites – 10 subjects in each of 5 sites in Moscow. Upon query, the Sponsor indicated that the maximum number of subjects any one site could enroll was 10. 20 US sites enrolled 57 subjects (only one US site enrolled 10 subjects).

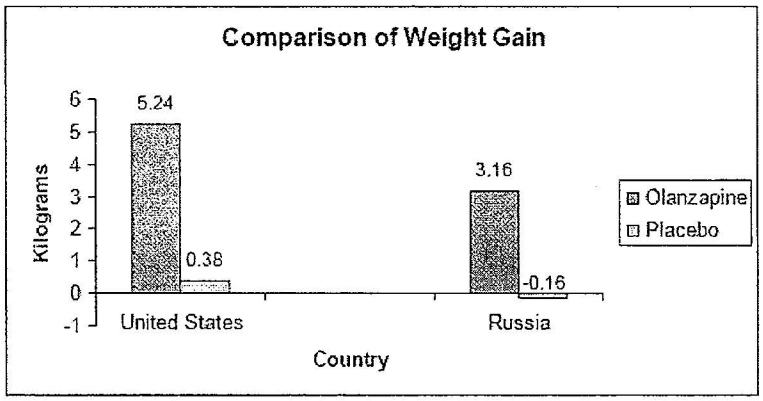
Because of the discrepancy in efficacy findings between the US and Russian sites, the Division requested that The Division of Scientific Investigations (DSI) inspect 2 Russian sites. The Moscow Research Institute of Psychiatry, Moscow, Russia; Valery Kransov, M.D. (principle investigator) was inspected between February 26 – March 2, 2007. The Moscow Medical University, Moscow, Russia; Leonid Bardenstein, M.D. (principle investigator) was inspected between February 19 – 22, 2007.

An audit of all subjects' records at these two sites was conducted and revealed few protocol violations. The overall conclusions of the DSI medical officer was that the study appeared to have been conducted adequately and the data generated by these sites may be used.

### 3.7 Other Issues

In this complete response document, the Sponsor included data comparing weight gain between the US and Russian sites:

- Comparison of weight gain in the 2 countries is illustrated in Figure APP.4.3. The significant differences between countries in weight do not explain the placebo effect difference seen within countries, but do suggest potential cultural differences in the two countries that may impact weight gain.




Source: INACMGA6.

**Figure APP.4.3. Comparison of weight gain in the United States and Russia.**

For the HGIN study (US + Russian sites), the increase in weight was 4.26 kg in the olanzapine group and 0.13 kg in the placebo group. The Sponsor did not include additional weight analyses between these geographic sites such as % of subjects having ≥ 7% weight gain. However, these

data do indicate a difference in the magnitude of weight gain in the US and Russian populations. The currently proposed labeling with regard to weight gain does not differentiate between these populations and the Sponsor was not asked to perform separate analyses for differences in geographic sites for the adult data either. However, the important issue of weight gain is being evaluated by another clinical reviewer and significant changes to proposed labeling are being made to further highlight this issue for both the adult and adolescent populations - though these data may underestimate the weight gain in the US population.

## 4. SAFETY UPDATE

The Sponsor provided an analysis of their database (Lilly Safety System) for spontaneously reported adverse events occurring from the time of product launch to May 31, 2007. The purpose of the review was to identify differences in the safety information between adolescent and adult patients treated with olanzapine.

As in the original submission, a proportional reporting ratio (PRR) and Chi-square value were calculated to compare the frequency of adverse event reports between the adolescent and adult populations. The Sponsor indicated the following general guidelines that may indicate an adverse event signal: at least 3 reports, a PRR > 2 and a Chi-square > 4.

The following table includes adverse events that indicate an increased frequency in the adolescent compared to the adult populations, again, based on spontaneous reports. It is noteworthy that galactorrhea occurs more frequently in the adolescent population and is further evidence that this adverse event should be included in product labeling (as recommended in section 3.1 of review).
The Sponsor commented that when evaluated the cases of aggression, some reported a history of the event, some reported use of concomitant medications, some of the events were considered to be disease-related, and some cases lacked sufficient information for an evaluation.

**Table 6. Adverse Events Reported with a PRR ≥2 in Olanzapine-Treated Patients Aged 13-17 Years Compared with Events Reported in Patients Aged 18-64 Years, with a Proportion of the Event of Interest ≥1.0% of All Events Reported in Patients Aged 13-17 Years, and with a Chi-Square Value ≥4**

| MedDRA Preferred Term (# of events in patients 13-17 years) | Proportion of Event in Patients 13-17 years (%) (N=3,754 events) | Proportion of Event in Patients 18-64 years (%) (N=85,420 events) | PRR[a] | Chi-Square Value |
|---|---|---|---|---|
| Somnolence (118) | 3.14 | 1.40 | 2.24 | 73.69 |
| Aggression (47) | 1.25 | 0.29 | 4.38 | 102.90 |
| Galactorrhoea (43) | 1.15 | 0.31 | 3.72 | 73.51 |
| Sedation (40) | 1. 07 | 0.41 | 2.62 | 35.80 |

[a] Ratio of event proportion in patients aged 13-17 years to event proportion in patients aged 18-64 years.

Based on this safety update, no new safety signals emerged that would require additional changes to product labeling.

# 5. LITERATURE UPDATE

A worldwide literature search was conducted for the time period August 25, 2006 through May 31, 2007 using Ovid Embase and Ovid Medline. Per the Sponsor, all resulting articles were reviewed by a Lilly clinical research physician. The Sponsor indicated that the adverse events and changes in laboratory parameters described in the citations are consistent with the types of adverse events reported for adult patients receiving olanzapine.

# 6. FOREIGN REGULATORY UPDATE

As of August 21, 2007, olanzapine has not been approved for pediatric use in any country.

# 7. STUDIES TO BE CONDUCTED IN ADOLESCENTS

In the Risk Management Plan document, the Sponsor indicated that they would be conducting a 52-week open-label safety study (Study F1D-MC-HGMX) in adolescent subjects.

The Sponsor provided a very brief synopsis of this safety study. The primary objective of this study is to evaluate the long-term safety of oral olanzapine in these adolescent populations. The study will enroll (b) (4) patients recruited at sites in the US and possibly other countries. Measurements to be included in the protocol are assessment of body weight, reported adverse events, vital signs, ECG parameters, and clinical laboratory tests including hepatic enzymes, insulin, fasting glucose, fasting lipids (total cholesterol, LDL and HDL cholesterol, triglycerides), and prolactin. The secondary objectives are to evaluate efficacy of olanzapine in these adolescent populations as well as the effect of an intervention program on weight gain.

The protocol for this study has not yet been submitted to the Division for review.

# 8. OVERALL ASSESSMENT

## 8.1 Recommendation on Regulatory Action

This is a review of the complete response to the approvable action taken on 4/30/07 for NDAs 20-592 SE5-040 "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents" and SE5-041 "treatment of schizophrenia in adolescents". It is recommended that the Division take an approvable action on these supplements and that olanzapine be considered as second line treatment for bipolar disorder and schizophrenia in the adolescent population.

The Sponsor responded to all additional requests for information pertaining to pivotal trials HGIU (bipolar disorder) and HGIN (schizophrenia) outlined in the 4/30/2007 approvable letter (other requests for additional safety data in adults and adolescents were also submitted and

reviewed by another clinical reviewer). A review of these data did not reveal new safety risks or significant changes to already known safety risks that warranted significant changes to proposed product labeling beyond the changes suggested in the approvable letter. However, it is recommended that gynecomastia and galactorrhea be included as adverse events in product labeling as they appear to occur more frequently in the adolescent population compared to adults. The Sponsor also adequately addressed the disparity in the efficacy signal primarily driven by the differential placebo response between the United States and Russian sites in study HGIN (schizophrenia).

The recommendation for an approvable action (rather than an approval action) is based on the need for the development of a medication guide discussing significant adverse events in adolescents (b) (4) . Though these adverse events are well known for olanzapine, they occur much more frequently in the adolescent population. Weight gain, hyperglycemia, and hyperlipidemia are significant risk factors for cardiovascular morbidity, especially in disease states such as schizophrenia or bipolar disorder in which it is likely that patients will be taking these medications chronically.

Given these safety concerns, it is recommended that olanzapine be considered as second line therapy for the treatment of bipolar disorder and schizophrenia in the adolescent population. Recently two other antipsychotics, risperidone and aripiprazole, received approval for treatment of bipolar disorder and schizophrenia in adolescents. In comparison to olanzapine, these antipsychotics are not associated with the same magnitude of risk with regard to weight gain, hyperglycemia and hyperlipidemia.

## 8.2 Recommendation on Postmarketing Actions

### 8.2.1 Risk Management Activity

The Sponsor submitted a "risk management plan" document, however, it was not a typical risk management plan. The Sponsor has proposed education, labeling changes and some further clinical trials to address the safety risks of olanzapine in both adults and adolescents.

### 8.2.2 Required Phase 4 Commitments

The Sponsor is planning to conduct a 52-week open-label safety study (Study F1D-MC-HGMX) in adolescent subjects with bipolar disorder or schizophrenia (see Section 7 of review - Studies to be Conducted In Adolescents ). This study is being considered as a Phase 4 commitment. As of this time, the protocols for this study has not been submitted.
No additional Phase 4 commitments are recommended.

# 9 APPENDICES

## 9.1 MMRM Analyses for HGIU (Bipolar Study)

**Table 1 MMRM Analysis Results Using Different Variance-Covariance Structure in Study HGIU (Without Country in Model)**

| Variance-covariance Structure | Placebo | Olanzapine | AIC |
|---|---|---|---|
| **Sample Size** | 54 | 105 | |
| **Variance Components (Default)** | | | |
| LS Mean change from baseline (SE) | -11.3 (1.33) | -16.9 (0.86) | |
| Difference between LS Means and C.I. | -5.6 (-8.7,-2.5) | | |
| P-value | 0.0004 | | 4171.5 |
| **Unstructured** | | | |
| LS Mean change from baseline (SE) | -9.4 (1.37) | -16.4 (0.92) | |
| Difference between LS Means and C.I. | -6.9 (-10.2, -3.7) | | |
| P-value | <0.0001 | | 3994.6 |
| **Compound Symmetry** | | | |
| LS Mean change from baseline (SE) | -10.3 (1.26) | -16.8 (0.84) | |
| Difference between LS Means and C.I. | -6.4 (-9.4, -3.5) | | |
| P-value | <0.0001 | | 4038.2 |
| **Toeplitz** | | | |
| LS Mean change from baseline (SE) | -9.6 (1.26) | -16.4 (0.84) | |
| Difference between LS Means and C.I. | -6.8 (-9.8, -3.8) | | |
| P-value | <0.0001 | | 4005.7 |
| **Toeplitz with Two Bands** | | | |
| LS Mean change from baseline (SE) | -9.9 (1.25) | -16.6 (0.82) | |
| Difference between LS Means and C.I. | -6.7 (-9.6, -3.7) | | |
| P-value | <0.0001 | | 4043.2 |
| **First Order Auto-regression** | | | |
| LS Mean change from baseline (SE) | -9.6 (1.26) | -16.4 (0.84) | |
| Difference between LS Means and C.I. | -6.8 (-9.8, -3.9) | | |
| P-value | <0.0001 | | 4003.4 |

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

Source: Statistician, upon request

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

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/s/
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Cara Alfaro
7/14/2008 12:33:38 PM
PHARMACIST

Ni Aye Khin
7/18/2008 09:57:26 AM
MEDICAL OFFICER
I concur with Dr. Alfaro's recommendations; see memo to file for additional comments.

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<br>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 evaluation 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 ($P < 0001$). 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 3.5weeks) 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 $\geq$ 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 $\geq$ 40 mg/dL compared to 4.5% of placebo controlled subjects ($p=0.036$); 37% of olanzapine treated subjects had a of $\geq$ 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 $\geq$ 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. The sponsor states in the proposed label (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 (b) (4)

(b) (4)

. 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-naive 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 (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) 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

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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Sally Yasuda
7/17/2008 03:19:57 PM
BIOPHARMACEUTICS

Review and Evaluation of Clinical Data - **Addendum**

Application Type: NDA 20-592
Submission Number: S-041 SE5
Established Name: Olanzapine (Zyprexa)
Therapeutic Class: Antipsychotic
Indication: Treatment of schizophrenia in adolescent patients
Letter Date: 10/30/06
Stamp Date: 10/31/06
Priority Designation: P
PDUFA Goal Date: 4/30/07
Reviewer: Cara Alfaro, Pharm.D.
Date: 5/19/07

**Background**

This is an addendum to the Clinical Review of NDA 20-592 S-041 SE5 that was completed (signed off) on 4/18/07. Prior to the action date of this NDA, a conference call was held to discuss issues related to this NDA. During this discussion, it was mentioned that the MMRM analysis conducted by the statistical reviewer was not statistically significant ($p = 0.72$) while the MMRM analysis conducted by the Sponsor was statistically significant ($p = 0.015$). The statistical reviewer was not able to explain the discrepancy and was going to recheck his analysis.

This addendum describes the results of the statistician's reanalysis as well as an additional analysis requested by this reviewer. It is noteworthy that this new information did not alter the final recommendation of this reviewer for a not approvable action (though the Division did take a different action).

**MMRM Analysis**

The primary analysis for this submission was the LOCF analysis for the BPRS-C total score mean change from baseline at endpoint. The Sponsor included OC and MMRM as secondary analyses for this primary endpoint.

The results from the Sponsor's analyses are in the table below:

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | LS Mean Change | LS Mean Difference | P-value |
| LOCF | Olanzapine | 72 | 50.3 | 10.0 | -19.4 | 15.5 | -19.3 | | |
| | Placebo | 35 | 50.1 | 8.6 | -9.3 | 18.7 | -9.1 | -10.1 | 0.003 |
| OC | Olanzapine | 50 | 50.6 | 10.6 | -24.5 | 13.5 | -24.4 | | |
| | Placebo | 15 | 49.0 | 8.5 | -23.7 | 14.6 | -24.1 | -0.26 | 0.947 |
| MMRM | Olanzapine | 50 | 50.6 | 10.6 | -24.5 | 13.5 | -21.3 | | |
| | Placebo | 15 | 49.0 | 8.5 | -23.7 | 14.6 | -12.4 | -8.90 | 0.015 |

The results from the MMRM analysis conducted by the statistician (Fanhui Kong) are as follows*:

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | LS Mean Change | LS Mean Difference | P-value |
| MMRM | Olanzapine | 50 | 50.6 | 10.6 | -24.5 | 13.5 | -24.7 | | |
| | Placebo | 15 | 49.0 | 8.5 | -23.7 | 14.6 | -23.5 | -1.25 | 0.72 |

*In the addendum to Dr. Kong's review, a recalculation of this MMRM analysis provided a p-value of 0.90

In the addendum to Dr. Kong's review, he stated that the reason for the discrepancy between MMRM analyses was due to the different models/assumptions used for these calculations. In his investigation of the different models, Dr. Kong did indicate that the best fit for the data was the unstructured variance-covariance model which the Sponsor used and that yielded significant results. However, it is also noteworthy that the results of the various MMRM analyses are quite variable and not consistent yielding p-values from 0.015 to 0.90 and LS mean differences ranging from -0.43 to -8.9 (table from Dr. Kong's addendum):

**Table 2.1 MMRM Analysis Results Using Different Variance-Covariance Structure in Study HGIN**

| Variance-covariance Structure | Placebo | Olanzapine | AIC |
|---|---|---|---|
| **Variance Components** | | | |
| LS Mean change from baseline (SE) | -24.1 (3.13) | -24.5 (1.73) | |
| Difference between LS Means and C.I. | -0.43 (-6.6,7.5) | | |
| P-value | 0.90 | | 4691 |
| **Unstructured** | | | |
| LS Mean change from baseline (SE) | -12.6 (2.99) | -21.5 (1.97) | |
| Difference between LS Means and C.I. | -8.9 (-16.0, -1.9) | | |
| P-value | 0.015 | | 4055.2 |
| **Compound Symmetry** | | | |
| LS Mean change from baseline (SE) | -17.8 (2.61) | -22.9 (1.60) | |
| Difference between LS Means and C.I. | -5.1 (-11.1, 0.9) | | |
| P-value | 0.10 | | 4353.0 |
| **Toeplitz** | | | |
| LS Mean change from baseline (SE) | -14.3 (2.68) | -21.9 (1.65) | |
| Difference between LS Means and C.I. | -7.67 (-13.8, -1.5) | | |
| P-value | 0.015 | | 4129.0 |
| **Toeplitz with Two Bands** | | | |
| LS Mean change from baseline (SE) | -21.7 (2.70) | -24.4 (1.53) | |
| Difference between LS Means and C.I. | -2.68 (-8.8, 3.4) | | |
| P-value | 0.39 | | 4356.0 |
| **First Order Auto-regression** | | | |
| LS Mean change from baseline (SE) | -15.4 (2.71) | -22.3 (1.64) | |
| Difference between LS Means and C.I. | -7.0 (-13.8, -0.8) | | |
| P-value | 0.029 | | 4129.0 |

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

One of the reasons that this reviewer recommended a not approvable action was the disparity between results from the U.S. and Russia sites. The Sponsor included the LOCF analysis for evaluation of the primary endpoint between the two geographic regions, but did not include companion OC or MMRM analyses. This reviewer asked Dr. Kong to perform an MMRM analysis between the U.S. and Russia sites (table from Dr. Kong's addendum):

**Table 2.2 Treatment Effect by Country by MMRM Analysis**

| Country | Placebo | Olanzapine |
|---|---|---|
| **Russia** | | |
| **N (Number of patients)** | 16 | 34 |
| LS Mean change from baseline (SE) | -5.3 (4.46) | -19.0 (2.73) |
| Difference between LS Means and C.I. | -13.7 (-23.9,3.3) | |
| P-value | 0.012 | |
| **US** | | |
| **N (Number of patients)** | 19 | 35 |
| LS Mean change from baseline (SE) | -18.7 (4.13) | -23.5 (2.89) |
| Difference between LS Means and C.I. | -4.8 (-14.7, -5.1) | |
| P-value | 0.35 | |

While exploratory in nature, this analysis is consistent with the LOCF analysis – robust findings in the Russia sites and not the U.S. sites.

Due to the inconsistent findings in the various MMRM analyses performed by Dr. Kong for study HGIN, this reviewer asked him to perform similar MMRM analyses for the HGIU study (SE5-040, bipolar disorder in adolescent patients) since the LOCF, OC and MMRM analyses performed by the Sponsor were consistent and statistically significant. Dr. Kong provided the summary table below (this table is not included in Dr. Kong's addendum). It is noteworthy that the different MMRM analyses for HGIU were consistent and robustly positive – in contrast to the inconsistent findings for these same analyses for study HGIN.

**Table 1 MMRM Analysis Results Using Different Variance-Covariance Structure in Study HGIU (Without Country in Model)**

| Variance-covariance Structure | Placebo | Olanzapine | AIC |
|---|---|---|---|
| **Sample Size** | 54 | 105 | |
| **Variance Components (Default)** | | | |
| LS Mean change from baseline (SE) | -11.3 (1.33) | -16.9 (0.86) | |
| Difference between LS Means and C.I. | -5.6 (-8.7,-2.5) | | |
| P-value | 0.0004 | | 4171.5 |
| **Unstructured** | | | |
| LS Mean change from baseline (SE) | -9.4 (1.37) | -16.4 (0.92) | |
| Difference between LS Means and C.I. | -6.9 (-10.2, -3.7) | | |
| P-value | <0.0001 | | 3994.6 |
| **Compound Symmetry** | | | |
| LS Mean change from baseline (SE) | -10.3 (1.26) | -16.8 (0.84) | |
| Difference between LS Means and C.I. | -6.4 (-9.4, -3.5) | | |
| P-value | <0.0001 | | 4038.2 |
| **Toeplitz** | | | |
| LS Mean change from baseline (SE) | -9.6 (1.26) | -16.4 (0.84) | |
| Difference between LS Means and C.I. | -6.8 (-9.8, -3.8) | | |
| P-value | <0.0001 | | 4005.7 |
| **Toeplitz with Two Bands** | | | |
| LS Mean change from baseline (SE) | -9.9 (1.25) | -16.6 (0.82) | |
| Difference between LS Means and C.I. | -6.7 (-9.6, -3.7) | | |
| P-value | <0.0001 | | 4043.2 |
| **First Order Auto-regression** | | | |
| LS Mean change from baseline (SE) | -9.6 (1.26) | -16.4 (0.84) | |
| Difference between LS Means and C.I. | -6.8 (-9.8, -3.9) | | |
| P-value | <0.0001 | | 4003.4 |

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

**Conclusions**

This reviewer continues to be troubled by the disparity in the results of the statistical analyses between the U.S. and Russia sites. While the overall LOCF and MMRM were positive, these results are largely driven by the Russia sites. It is noteworthy that of the various MMRM analyses that were performed by the statistician, results range from a p-value of 0.015 to 0.90 and LS mean differences ranging from -0.43 to -8.9. However, when the statistician performed this same set of MMRM analyses on the data from HGIU (a study in which the LOCF, OC and MMRM analyses were significant), the results were consistent and robust.

It is unclear why there is such a disparity in the efficacy results between the U.S. and Russia sites. While the Sponsor did include the LOCF analysis evaluating the efficacy endpoint between the U.S. and Russia sites, there is no further discussion on the disparate findings. The Sponsor has been asked to address this issue in the action letter.

Cara Alfaro, Pharm.D.
Clinical Reviewer
May 19, 2007

Cc: Khin/Bates/Laughren/Alfaro

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Cara Alfaro
5/19/2007 04:02:20 PM
PHARMACIST

Ni Aye Khin
5/21/2007 07:37:22 PM
MEDICAL OFFICER

# CLINICAL EXECUTIVE SUMMARY

| | |
|---|---|
| Application Type | NDA 20-592 |
| Submission Number | S-041 |
| Submission Code | SE5 |
| Letter Date | 10/30/06 |
| Stamp Date | 10/31/06 |
| PDUFA Goal Date | 04/30/07 |
| Reviewer Name | Cara Alfaro, Pharm.D. |
| Established Name | Olanzapine |
| Trade Name | Zyprexa |
| Therapeutic Class | Antipsychotic |
| Applicant | Eli Lilly |
| Priority Designation | P |
| Formulation | Oral tablets |
| Dosing Regimen | 2.5 – 5 mg starting, maximum dose 20 mg/day |
| Indication | Treatment of Schizophrenia |
| Intended Population | Adolescents (13 – 17 years) |

# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

I recommend that the Division take a not approvable action on NDA 20-592 SE5-041 that was filed to support the indication "treatment of schizophrenia in adolescents".

Fifty-three percent of randomized patients in pivotal trial HGIN were from sites in the United States and 47% of randomized patients were from sites in Russia. The primary endpoint, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia ($p = 0.003$) but not the sites in the United States ($p = 0.258$). The sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia.

Though the LOCF analysis was the primary analysis, it is also concerning that the OC and MMRM analyses (the latter by recalculation by the reviewing statistician in the Division) are substantially different from the LOCF analysis and not statistically significant.

I recommend that the Sponsor conduct another clinical trial in this population if they wish to pursue this indication. The majority of patients in this clinical trial should be from sites in the United States and efficacy will need to be established in these patients. It is also strongly recommended that this clinical trial be a fixed dose design since dose-response data for efficacy or safety cannot be evaluated in a flexible dose design.

A number of additional requests for safety information and analysis regarding this submission are included in the clinical review. If acceptable, these requests could be included in the action letter.

## 1.2 Recommendation on Postmarketing Actions

Since a not approvable action is recommended, there are no recommendations for postmarketing actions.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Study HGIN was the pivotal trial for establishing efficacy and safety for the indication "treatment of schizophrenia in adolescent patients". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with schizophrenia. The study consisted of a 6-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day ($n = 72$), or placebo ($n = 35$).

Additional open-label studies were also submitted by the Sponsor primarily in support of safety. The primary supportive studies were LOAY (n = 89 adolescents) and HGMF (n = 107), the latter study was the primary pharmacokinetic study in this population.

### 1.3.2 Efficacy

The mean modal daily dose of olanzapine was 12.5 mg and the mean daily dose was 11.1 mg. Seventy-five percent of patients in the olanzapine group and 56% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIN was change from baseline in the BPRS-C Total Score. The overall study results were statistically significant for olanzapine versus placebo in the primary LOCF analysis but not the supporting OC and MMRM (recalculated by statistician reviewer) analyses (see Table).

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | LS Mean Change | LS Mean Difference | P-value |
| LOCF | Olanzapine | 72 | 50.3 | 10.0 | -19.4 | 15.5 | -19.3 | | |
| | Placebo | 35 | 50.1 | 8.6 | -9.3 | 18.7 | -9.1 | -10.1 | 0.003 |
| OC | Olanzapine | 50 | 50.6 | 10.6 | -24.5 | 13.5 | -24.4 | | |
| | Placebo | 15 | 49.0 | 8.5 | -23.7 | 14.6 | -24.1 | -0.26 | 0.947 |
| MMRM | Olanzapine | 50 | 50.6 | 10.6 | -24.5 | 13.5 | -24.7 | | |
| | Placebo | 15 | 49.0 | 8.5 | -23.7 | 14.6 | -23.5 | -1.25 | 0.72 |

When evaluating the efficacy signal for the sites in the United States and the sites in Russia, only the latter were statistically significant in favor of olanzapine. The low placebo response in the sites in Russia appears to be driving these results.

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | LS Mean Change | LS Mean Difference | P-value |
| U.S. | Olanzapine | 38 | 53.2 | 10.1 | -21.1 | 16.3 | -20.9 | | |
| | Placebo | 19 | 51.4 | 8.6 | -15.0 | 18.3 | -15.6 | -5.3 | 0.258 |
| Russia | Olanzapine | 34 | 47.0 | 8.9 | -17.4 | 14.5 | -17.4 | | |
| | Placebo | 16 | 48.5 | 8.5 | -2.6 | 17.4 | -2.5 | -14.9 | 0.003 |

Since efficacy could not be demonstrated in patients in sites from the United States, this reviewer recommended a not approvable action.

### 1.3.3 Safety

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIU is the pivotal trial for bipolar disorder) and the Overall Combined Database that included studies HGIN, HGIU,

LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events ($\geq$ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30% vs. 6%), somnolence (25% vs. 3%), increased appetite (24% vs. 6%), sedation (19% vs. 6%), headache (17% vs. 12%), fatigue (10% vs. 5%), dizziness (7% vs. 2%), dry mouth (6% vs. 0%) and pain in extremity (5% vs. 1%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain
The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with $\geq$ 7% increase in body weight.

| | Olanzapine | Placebo | LS Mean Diff | P-value |
|---|---|---|---|---|
| *HGIN + HGIU Acute Database* | | | | |
| Weight (kg)<br>Mean Change to Endpoint (LOCF) | 3.90 (n = 177) | 0.24 (n = 88) | 3.66 | < 0.001 |
| Weight (kg)<br>Mean Change to Endpoint (OC) | 3.6 (n = 154) | 0.08 (n = 67) | 3.57 | < 0.001 |
| BMI<br>Mean Change to Endpoint (LOCF) | 1.22 | 0.05 | 1.17 | < 0.001 |
| $\geq$ 7% increase in body weight (%) | 43.5% | 6.8% | - | < 0.001 |
| Overall Combined Database | | | | |
| Weight (kg)<br>Mean Change to Endpoint (LOCF) | 7.35 | - | - | < 0.001<br>(compared to baseline) |
| Weight (kg)<br>Mean Change to Endpoint | 10.8 | - | - | < 0.001<br>(compared to baseline) |

| | | | | |
|---|---|---|---|---|
| (OC) | | | | |
| BMI<br>Mean Change to Endpoint (LOCF) | 2.31 | - | - | < 0.001<br>(compared to baseline) |
| ≥ 7% increase in body weight (%) | 65% | - | - | - |

In the Acute Database, weight gain (mean change from baseline to endpoint) was similar for the groups with baseline BMI < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

Weight changes were evaluated for the subgroups gender and age (< 15, ≥ 15 years). At the time this review was finalized, mean change in weight for the age subgroup analysis was only available for study HGIN (not HGIU or the Acute Database). Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine. A treatment-by-gender interaction was noted in the Acute Database, but was likely due to differences in the placebo groups since mean change in weight was similar in the olanzapine groups for males and females.

Liver Function Abnormalities
Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline ≤ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009).
No patients met criteria for Hy's rule (ALT ≥ 3x ULN and TBili ≥ 1.5 x ULN).

Hyperprolactinemia
The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, p < 0.001). The washout period prior to baseline could be as short as 2 days and it was noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to perform further analyses in the subgroup of patients with baseline prolactin within normal limits.
In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).
For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females

(15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN + HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$).

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

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

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were also similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality
Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in patients with bipolar disorder. Suicidal behaviors or ideation is not uncommon in these disorders and, in the absence of a placebo comparator, it is difficult to interpret causality to olanzapine therapy.

1.3.4 Dosing Regimen and Administration

This section not completed since a not approvable action was recommended.

1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies were done as part of this clinical development program and none are needed.

1.3.6 Special Populations

These studies were conducted in accordance with a pediatric Written Request and the Agency has granted the Sponsor's request for pediatric exclusivity.

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Ni Aye Khin
4/12/2007 12:52:53 PM

# CLINICAL EXECUTIVE SUMMARY

| | |
|---|---|
| Application Type | NDA 20-592 |
| Submission Number | S-040 |
| Submission Code | SE5 |
| Letter Date | 10/30/06 |
| Stamp Date | 10/31/06 |
| PDUFA Goal Date | 04/30/07 |
| Reviewer Name | Cara Alfaro, Pharm.D. |
| Established Name | Olanzapine |
| Trade Name | Zyprexa |
| Therapeutic Class | Antipsychotic |
| Applicant | Eli Lilly |
| Priority Designation | P |
| Formulation | Oral tablets |
| Dosing Regimen | 2.5 – 5 mg starting, maximum dose 20 mg/day |
| Indication | Treatment of Bipolar I Disorder |
| Intended Population | Adolescents (13 – 17 years) |

# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

I recommend that the Division take an approvable action on NDA 20-592 SE5-040 that was filed to support the indication "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents".

A number of additional requests for safety information and analysis regarding this submission are included in the clinical review. If acceptable, these requests could be included in the action letter.

## 1.2 Recommendation on Postmarketing Actions

### 1.2.1 Risk Management Activity

The Sponsor included a document discussing risk management in the submission. The actions proposed for risk minimization included product labeling and prescriber education though details for the latter were not included. These actions are the minimum steps that could be taken to manage risk associated with olanzapine therapy in this patient population. Distribution of a medication education guide could reinforce risk information to patients and their families.

### 1.2.2 Required Phase 4 Commitments

Pivotal trial HGIU (as well as HGIN – schizophrenia; SE5-041) included a flexible-dose paradigm for olanzapine. As such, a dose-response relationship for efficacy and safety cannot be determined since the important parameters of dose and time on drug can only be adequately addressed in a fixed dose trial. To minimize risk, it would be important to use the minimum effective dose to the extent that risk may be dose-related – however, in a flexible-dose design one cannot determine the dose-response for efficacy. I recommend that the Sponsor perform a fixed dose study in adolescent patients with bipolar disorder to better characterize the relationship of dose to efficacy and adverse events so that risk may be reduced.

Since bipolar disorder is a chronic illness, patients will likely require medication for a prolonged period. Some of the adverse events occurring in this adolescent patient population are significant (see Summary of Clinical Findings). It is important not only to identify these risks but to study the effect of interventions on these adverse events. The long-term cardiovascular risk of significant weight gain, hypertriglyceridemia and hypercholesterolemia is significant and efforts to minimize these adverse events is important. I recommend that the Sponsor perform a clinical study to evaluate interventions (e.g. dietary modification, exercise) on these adverse events.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Study HGIU was the pivotal trial for establishing efficacy and safety for the indication "treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with schizophrenia. The study consisted of a 3-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 107), or placebo (n = 54).

Additional open-label studies were also submitted by the Sponsor primarily in support of safety. The primary supportive studies were LOAY (n = 89 adolescents) and HGMF (n = 107), the latter study was the primary pharmacokinetic study in this population.

### 1.3.2 Efficacy

The mean modal daily dose of olanzapine was 10.7 mg and the mean daily dose was 8.9 mg. Seventy-nine percent of patients in the olanzapine group and 65% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIU was change from baseline in the Adolescent-Structured YMRS Total Score. The overall study results were statistically significant for olanzapine versus placebo in the primary LOCF analysis as well as the supporting OC and MMRM analyses (see Table). The LOCF analysis for the secondary endpoint CGI-Severity Mania and CGI-Severity Overall were statistically significant favoring olanzapine.

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | LS Mean Change | LS Mean Difference | P-value |
| LOCF | Olanzapine | 105 | 33.1 | 6.5 | -15.9 | 10.0 | -17.6 | | |
| | Placebo | 54 | 32.0 | 6.2 | -7.7 | 9.4 | -10.0 | -7.7 | < 0.001 |
| OC | Olanzapine | 88 | 33.2 | 6.5 | -17.2 | 9.7 | -19.1 | | |
| | Placebo | 37 | 32.4 | 6.2 | -11.1 | 9.0 | -13.4 | -5.7 | 0.001 |
| MMRM | Olanzapine | 88 | 33.2 | 6.5 | -17.2 | 9.7 | -15.8 | | |
| | Placebo | 37 | 32.4 | 6.2 | -11.1 | 9.0 | -8.8 | -6.9 | < 0.001 |

Subgroup analyses included gender, age ($< 15, \geq 15$), Caucasian vs. nonCaucasian, manic vs. mixed, psychotic vs. without psychotic features and rapid vs. nonrapid cycling. Statistically significant differences favoring olanzapine were found for all subgroups except < 15 year olds ($p = 0.094$), patients with psychotic features ($p = 0.111$) and rapid cyclers ($p = 0.271$) – the latter two groups had few patients in those subgroups. A significant treatment-by-age interaction was found (see Table). The Sponsor conducted

three additional posthoc analyses, two of these did not indicate a treatment-by-age interaction.

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | LS Mean Change | LS Mean Difference | P-value |
| < 15 years | Olanzapine | 49 | 32.8 | 7.0 | -14.6 | 10.2 | -16.6 | | |
| | Placebo | 20 | 32.4 | 5.7 | -9.4 | 11.0 | -12.1 | -4.5 | 0.094 |
| ≥ 15 years | Olanzapine | 56 | 33.3 | 6.2 | -17.0 | 9.9 | -18.9 | | |
| | Placebo | 34 | 31.8 | 6.6 | -6.7 | 8.4 | -9.0 | -9.9 | < 0.001 |

Since HGIU was a flexible-dose study, it is not possible to evaluate the dose-response with regard to efficacy. Proposed labeling states the range that was included in the clinical trial, but no data is available to determine whether higher doses confer greater efficacy and it is likely that higher doses confer greater risk from an adverse event perspective.

### 1.3.3 Safety

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIN is the pivotal trial for schizophrenia) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events (≥ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30% vs. 6%), somnolence (25% vs. 3%), increased appetite (24% vs. 6%), sedation (19% vs. 6%), headache (17% vs. 12%), fatigue (10% vs. 5%), dizziness (7% vs. 2%), dry mouth (6% vs. 0%) and pain in extremity (5% vs. 1%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain

The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with ≥ 7% increase in body weight.

| | Olanzapine | Placebo | LS Mean Diff | P-value |
|---|---|---|---|---|
| *HGIN + HGIU Acute Database* | | | | |
| Weight (kg) Mean Change to Endpoint (LOCF) | 3.90 (n = 177) | 0.24 (n = 88) | 3.66 | < 0.001 |
| Weight (kg) Mean Change to Endpoint (OC) | 3.6 (n = 154) | 0.08 (n = 67) | 3.57 | < 0.001 |
| BMI Mean Change to Endpoint (LOCF) | 1.22 | 0.05 | 1.17 | < 0.001 |
| ≥ 7% increase in body weight (%) | 43.5% | 6.8% | - | < 0.001 |
| Overall Combined Database | | | | |
| Weight (kg) Mean Change to Endpoint (LOCF) | 7.35 | - | - | < 0.001 (compared to baseline) |
| Weight (kg) Mean Change to Endpoint (OC) | 10.8 | - | - | < 0.001 (compared to baseline) |
| BMI Mean Change to Endpoint (LOCF) | 2.31 | - | - | < 0.001 (compared to baseline) |
| ≥ 7% increase in body weight (%) | 65% | - | - | - |

In the Acute Database, weight gain (mean change from baseline to endpoint) was similar for the groups with baseline BMI < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

Weight changes were evaluated for the subgroups gender and age (< 15, ≥ 15 years). At the time this review was finalized, mean change in weight for the age subgroup analysis was only available for study HGIN (not HGIU or the Acute Database). Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine. A treatment-by-gender interaction was noted in the Acute Database, but was likely due to differences in the placebo groups since mean change in weight was similar in the olanzapine groups for males and females.

Liver Function Abnormalities
Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline $\leq$ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group ($p = 0.009$).
No patients met criteria for Hy's rule (ALT $\geq$ 3x ULN and TBili $\geq$ 1.5 x ULN).

Hyperprolactinemia
The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, $p < 0.001$). The washout period prior to baseline could be as short as 2 days and it was noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to perform further analyses in the subgroup of patients with baseline prolactin within normal limits.

In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU and HGIN.

For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females (15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN + HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$).

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

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

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality
Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in patients with bipolar disorder. Suicidal behaviors or ideation are not uncommon in these disorders and, in the absence of a placebo comparator, it is difficult to interpret causality to olanzapine therapy.

Although there are significant risks outlined in this review, there is also significant morbidity and mortality associated with untreated bipolar I disorder.

## 1.3.4 Dosing Regimen and Administration

Proposed labeling

(b) (4)

(b) (4)

This dosing regimen is (b) (4)

1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies were done as part of this clinical development program and none are needed.

1.3.6 Special Populations

These studies were conducted in accordance with a pediatric Written Request and the Agency has granted the Sponsor's request for pediatric exclusivity.

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Ni Aye Khin
4/12/2007 11:33:33 AM

# CLINICAL EXECUTIVE SUMMARY

| | |
|---|---|
| Application Type | NDA 20-592 |
| Submission Number | S-040 |
| Submission Code | SE5 |
| Letter Date | 10/30/06 |
| Stamp Date | 10/31/06 |
| PDUFA Goal Date | 04/30/07 |
| Reviewer Name | Cara Alfaro, Pharm.D. |
| Established Name | Olanzapine |
| Trade Name | Zyprexa |
| Therapeutic Class | Antipsychotic |
| Applicant | Eli Lilly |
| Priority Designation | P |
| Formulation | Oral tablets |
| Dosing Regimen | 2.5 – 5 mg starting, maximum dose 20 mg/day |
| Indication | Treatment of Bipolar I Disorder |
| Intended Population | Adolescents (13 – 17 years) |

# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

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## 1.2 Recommendation on Postmarketing Actions

### 1.2.1 Risk Management Activity

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## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

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Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

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| ≥ 7% increase in body weight (%) | 65% | - | - | - |

In the Acute Database, weight gain (mean change from baseline to endpoint) was similar for the groups with baseline BMI < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

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No patients met criteria for Hy's rule (ALT $\geq$ 3x ULN and TBili $\geq$ 1.5 x ULN).

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The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, $p < 0.001$). The washout period prior to baseline could be as short as 2 days and it was noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to perform further analyses in the subgroup of patients with baseline prolactin within normal limits.

In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU and HGIN.

For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females (15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN + HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$).

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

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

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality
Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in patients with bipolar disorder. Suicidal behaviors or ideation are not uncommon in these disorders and, in the absence of a placebo comparator, it is difficult to interpret causality to olanzapine therapy.

Although there are significant risks outlined in this review, there is also significant morbidity and mortality associated with untreated bipolar I disorder.

### 1.3.4 Dosing Regimen and Administration

Proposed labeling

(b) (4)

(b) (4)

This dosing regimen is (b) (4)

1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies were done as part of this clinical development program and none are needed.

1.3.6 Special Populations

These studies were conducted in accordance with a pediatric Written Request and the Agency has granted the Sponsor's request for pediatric exclusivity.

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/s/
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Ni Aye Khin
4/12/2007 04:48:56 PM
This is the revised version.

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA 20-592 |
| Submission Number | S-040 |
| Submission Code | SE5 |
| Letter Date | 10/30/06 |
| Stamp Date | 10/31/06 |
| PDUFA Goal Date | 04/30/07 |
| Reviewer Name | Cara Alfaro, Pharm.D. |
| Review Completion Date | 04/06/07 |
| Established Name | Olanzapine |
| Trade Name | Zyprexa |
| Therapeutic Class | Antipsychotic |
| Applicant | Eli Lilly |
| Priority Designation | P |
| Formulation | Oral tablets |
| Dosing Regimen | 2.5 – 5 mg starting, maximum dose 20 mg/day |
| Indication | Treatment of Bipolar I Disorder |
| Intended Population | Adolescents |

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# 1 EXECUTIVE SUMMARY

## Recommendation on Regulatory Action

I recommend that the Division take an approvable action on NDA 20-592 SE5-040 that was filed to support the indication "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents".

A number of additional requests for safety information and analysis regarding this submission are included at the end of this review. If acceptable, these requests could be included in the action letter.

## Recommendation on Postmarketing Actions

### 1.1.1 Risk Management Activity

The Sponsor included a document discussing risk management in the submission. The actions proposed for risk minimization included product labeling and prescriber education though details for the latter were not included. These actions are the minimum steps that could be taken to manage risk associated with olanzapine therapy in this patient population. Distribution of a medication education guide could reinforce risk information to patients and their families.

### 1.1.2 Required Phase 4 Commitments

Pivotal trial HGIU (as well as HGIN – schizophrenia; SE5-041) included a flexible-dose paradigm for olanzapine. As such, a dose-response relationship for efficacy and safety cannot be determined since the important parameters of dose and time on drug can only be adequately addressed in a fixed dose trial. To minimize risk, it would be important to use the minimum effective dose to the extent that risk may be dose-related – however, in a flexible-dose design one cannot determine the dose-response for efficacy. I recommend that the Sponsor perform a fixed dose study in adolescent patients with bipolar disorder to better characterize the relationship of dose to efficacy and adverse events so that risk may be reduced.

Since bipolar disorder is a chronic illness, patients will likely require medication for a prolonged period. Some of the adverse events occurring in this adolescent patient population are significant (see Summary of Clinical Findings). It is important not only to identify these risks but to study the effect of interventions on these adverse events. The long-term cardiovascular risk of significant weight gain, hypertriglyceridemia and hypercholesterolemia is significant and efforts to minimize these adverse events is important. I recommend that the Sponsor perform a clinical study to evaluate interventions (e.g. dietary modification, exercise) on these adverse events.

## Summary of Clinical Findings

### 1.1.3 Brief Overview of Clinical Program

Study HGIU was the pivotal trial for establishing efficacy and safety for the indication "treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with bipolar I disorder. The study consisted of a 3-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 107), or placebo (n = 54).

Additional open-label studies were also submitted by the Sponsor primarily in support of safety. The primary supportive studies were LOAY (n = 89 adolescents) and HGMF (n = 107), the latter study was the primary pharmacokinetic study in this population.

### 1.1.4 Efficacy

The mean modal daily dose of olanzapine was 10.7 mg and the mean daily dose was 8.9 mg. Seventy-nine percent of patients in the olanzapine group and 65% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIU was change from baseline in the Adolescent-Structured YMRS Total Score (LOCF analysis). The overall study results were statistically significant for olanzapine versus placebo (LS Mean Diff = -7.66, p < 0.001).

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy Variable | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Difference | *P-value |
| YMRSTOT.Total(1-11) | Olanzapine | 105 | 33.08 | 6.55 | -15.90 | 10.03 | -17.65 | -7.66 | <.001 |
| | Placebo | 54 | 32.04 | 6.23 | -7.72 | 9.42 | -9.99 | | |

The supportive OC analysis was similar to the LOCF analysis (LS Mean Diff = -5.74, p = 0.001). The supportive MMRM analysis was similar to the LOCF analysis (LS Mean Diff = -6.95, p < 0.001). The LOCF analysis for the secondary endpoint CGI-Severity Mania and CGI-Severity Overall were statistically significant favoring olanzapine.

Subgroup analyses included gender, age (< 15, ≥ 15), Caucasian vs. nonCaucasian, manic vs. mixed, psychotic vs. without psychotic features and rapid vs. nonrapid cycling. Statistically significant differences favoring olanzapine were found for all subgroups except < 15 year olds (p = 0.094), patients with psychotic features (p = 0.111) and rapid cyclers (p = 0.271) – the latter two groups had few patients in those subgroups. A significant treatment-by-age interaction was found.

Since HGIU was a flexible-dose study, it is not possible to evaluate the dose-response with regard to efficacy. Proposed labeling states the range that was included in the clinical trial, but no data is available to determine whether higher doses confer greater efficacy and it is likely that higher doses confer greater risk from an adverse event perspective.

### 1.1.5 Safety

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIN is the pivotal trial for schizophrenia) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events ($\geq$ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain
The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with $\geq$ 7% increase in body weight.

| | Olanzapine | Placebo | LS Mean Diff | P-value |
|---|---|---|---|---|
| *HGIN + HGIU Acute Database* | | | | |
| Weight (kg) Mean Change to Endpoint (LOCF) | 3.90 (n = 177) | 0.24 (n = 88) | 3.66 | < 0.001 |
| Weight (kg) Mean Change to Endpoint (OC) | 3.6 (n = 154) | 0.08 (n = 67) | 3.57 | < 0.001 |
| BMI | 1.22 | 0.05 | 1.17 | < 0.001 |

| | | | | |
|---|---|---|---|---|
| Mean Change to Endpoint (LOCF) | | | | |
| ≥ 7% increase in body weight (%) | 43.5% | 6.8% | - | < 0.001 |
| Overall Combined Database | | | | |
| Weight (kg) Mean Change to Endpoint (LOCF) | 7.35 | - | - | < 0.001 (compared to baseline) |
| Weight (kg) Mean Change to Endpoint (OC) | 10.8 | - | - | < 0.001 (compared to baseline) |
| BMI Mean Change to Endpoint (LOCF) | 2.31 | - | - | < 0.001 (compared to baseline) |
| ≥ 7% increase in body weight (%) | 65% | - | - | - |

In the Acute Database, weight gain (mean change from baseline to endpoint) was similar for the groups with baseline BMI < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

Weight changes were evaluated for the subgroups gender and age (< 15, ≥ 15 years). At the time this review was finalized, mean change in weight for the age subgroup analysis was only available for study HGIN (not HGIU or the Acute Database). Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine. A treatment-by-gender interaction was noted in the Acute Database, but was likely due to differences in the placebo groups since mean change in weight was similar in the olanzapine groups for males and females.

Liver Function Abnormalities
Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline ≤ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009).
No patients met criteria for Hy's rule (ALT ≥ 3x ULN and TBili ≥ 1.5 x ULN).

Hyperprolactinemia
The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, p < 0.001). The washout period prior to baseline could be as short as 2 days and it was noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to perform further analyses in the subgroup of patients with baseline prolactin within normal limits.

In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).

For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females (15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN + HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$).

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

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

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these

types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality
Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in patients with bipolar disorder. Suicidal behaviors or ideation is not uncommon in these disorders and, in the absence of a placebo comparator, it is difficult to interpret causality to olanzapine therapy.

Although there are significant risks outlined in this review, there is also significant morbidity and mortality associated with untreated bipolar I disorder.

### 1.1.6 Dosing Regimen and Administration

Proposed labeling

(b) (4)

This dosing regimen is (b) (4)

# 2 INTRODUCTION AND BACKGROUND

## Product Information

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

Olanzapine is not currently indicated for use in child/adolescent populations.

## Currently Available Treatment for Indications

Other currently available atypical antipsychotics include clozapine (Clozaril), risperidone (Risperdal), aripiprazole (Abilify), quetiapine (Seroquel), ziprasidone (Geodon). Many of these atypical antipsychotics are approved for the indication treatment of acute mixed or manic episodes associated with bipolar I disorder, but none are approved for use in children/adolescents.

Risperidone (Risperdal) was recently approved for the indication "treatment of irritability associated with autistic disorder in children and adolescents" (5 to 16 years of age).

Lithium (various salts) and divalproex sodium are indicated in the treatment of manic episodes of bipolar I disorder in adults.

## Important Issues With Pharmacologically Related Products

Although the atypical antipsychotics have less extrapyramidal side effects compared to typical antipsychotics, the adverse event profile is notable for weight gain, hyperglycemia, and diabetes mellitus in adults. Little data is available with regard to the adverse event profile in other populations including children and adolescents.

## Presubmission Regulatory Activity

This summary was taken from the note to reviewer document contained in the Sponsor's submission.

On June 11, 1999, Eli Lilly and Company (Lilly) submitted a Proposed Pediatric Study Request to FDA related to the conduct of pediatric studies of Zyprexa.

In response to Lilly's proposed pediatric study request, the FDA issued to Lilly a Written Request for Pediatric Studies dated November 30, 2001 (reissued under the Best Pharmaceuticals for Children Act (BPCA) on July 3, 2002) and amended on April 9, 2002, May 7, 2004, and June 29, 2005. FDA's Written Request (WR) as amended, included a request for clinical data on the use of Zyprexa to treat adolescents with schizophrenia and adolescents with acute bipolar mania in order to make Zyprexa eligible for the pediatric exclusivity extension under Section 505A of the Federal Food, Drug, and Cosmetic Act. More details regarding FDA's WR, and Lilly's response, are provided in Item 20 of this submission.

FDA granted an indication for olanzapine for the treatment of bipolar mania in adults (NDA 20-592/S006) on March 17, 2000. As part of the approval, the FDA requested a study in pediatric patients with bipolar mania as a post-marketing commitment. Study F1D-MC-HGIU is included in this submission to fulfill this post-marketing commitment.

On January15, 2004, the FDA met with Lilly to discuss the PK package proposed by Lilly to fulfill FDA's Written Request for Pediatric Studies. At this meeting, Lilly provided an overview of the available PK data. FDA requested additional justification of

the utility of the data from Study LOAY in order to make a final decision on whether or not the data is acceptable to sufficiently meet the PK aspects of the Written Request.

On March 22, 2004 Lilly submitted to IND 28,705 additional information regarding study LOAY and requested a meeting to further discuss fulfillment of the PK aspects of the WR. In response to questions from FDA sent to Lilly on July 7, 2004, Lilly submitted additional information to IND 28,705 on July 13, 2004.

Lilly met with FDA on July 21, 2004 to again discuss the PK information needed to fulfill the WR. At that meeting, FDA agreed with Lilly's proposal to provide PK data in adolescents from Studies HGCS, HGCR, HGGC, and LOAY to address the PK requirements outlined in the Written Request.

In discussions with FDA, it was noted that information about the exact sampling time relative to the dose were not collected as part of the protocol in Study LOAY; however, extensive simulations showed that lack of data regarding timing of samples in Study LOAY should not adversely affect the ability to perform a meaningful population analysis. Nonetheless, to assure the robustness of the PK data, Lilly collected additional population PK data in adolescent patients with schizophrenia or bipolar disorder by conducting Study HGMF. Inclusion of data from Study HGMF in this submission was discussed at a pre-NDA meeting on March 17, 2006. At that meeting, FDA requested that Lilly conduct the population PK analysis both with and without the data from Study LOAY. Both analyses were conducted by Lilly and are included with this submission. The population PK analysis also includes a comparison of pediatric olanzapine PK data with the adult olanzapine PK data from Study HGAJ.

The format and content of the submission were also discussed and agreed to at the March 17, 2006 pre-sNDA meeting. The FDA indicated that, based on the pre-sNDA package and discussions, the proposed submission content appeared to be adequate to respond to FDA's Written Request and that Study HGIU appeared to be adequate to fulfill the post-marketing commitment which was part of the bipolar mania in adults approval.

In the 11/30/01 written request, the Division stated "We strongly recommend that the trial be a fixed dose study including at least two fixed doses of the study drug". The Division also recommended that a relapse prevention trial should follow the acute treatment trial. The Sponsor did not follow either recommendation and neither was required in order to fulfill the pediatric written request.

## Other Relevant Background Information

The Pediatric Exclusivity Board met on January 10, 2007 to determine whether the Sponsor had fulfilled the requirements in the written request. It was determined that the requirements had been met and exclusivity was granted.

# 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

## Statistics

The statistician (Fanhui Kong) reviewed the efficacy data from the pivotal trial, HGIU. In general, the data submitted by the Sponsor provide evidence for efficacy per his review (see Statistical review).

# 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

## Tables of Clinical Studies

The Sponsor included study reports for 9 pediatric studies in this submission. HGIN is the pivotal study for adolescent schizophrenia and HGIU is the pivotal study for adolescent bipolar I disorder. HGMF is the primary study for determining pharmacokinetic parameters in the adolescent population. The other studies are supportive and provide safety and pharmacokinetic data.

Table 4.1.1 Summary of Clinical Studies

| Study | Description | Length | Age Range (years) | Number of Patients |
|---|---|---|---|---|
| HGIN | MC, DB, PC study in adolescent patients with schizophrenia.<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S. and Russia sites | 6 weeks DB<br>26 weeks OL extension | 13 to 17 | 107<br>(n = 72 olanzapine, n = 35 placebo) |
| HGIU | MC, DB, PC study in adolescent patients with mixed/manic episode of bipolar I disorder.<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S., Puerto Rico | 3 weeks DB<br>26 weeks OL extension | 13 – 17 | 161<br>(n = 107 olanzapine, n = 54 placebo) |
| LOAY | OL study in patients with schizophrenia, schizoaffective, and schizophreniform disorders<br>Flexible dose olanzapine (5 – 20 mg)<br>German sites | 24 weeks | 12 – 21 | 96<br>(n = 89, 13-17 years) |
| HGMF | OL study in adolescent patients with schizophrenia or bipolar I disorder<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S., Puerto Rico, Russia | 4.5 weeks | 13 – 17 | 107<br>(n = 37 schizophrenia, n = 70 bipolar) |

| | | | | |
|---|---|---|---|---|
| HGCS | OL study in adolescent patients with schizophrenia<br>Dosing: 2.5 to 20 mg/day<br>Single site | 8 weeks | 10 – 18 | 8 |
| HGCR | DB study in adolescent patients with schizophrenia, haloperidol as active comparator<br>Dosing: 2.5 qod – 20 mg/day<br>Single site | 8 weeks | 12 – 16 | 2 |
| HGGC | OL study in children and adolescents with bipolar disorder<br>Dosing: 2.5 to 20 mg/day<br>Single site (U.S.) | 8 weeks | 5 – 14 | 23 |

Modified from Sponsor Table 2.5.1.1 clinical-overview.
MC = multicenter, DB = double-blind, PC = placebo-controlled, OL = open-label

## Data Quality and Integrity

The Division of Scientific Investigations was asked to inspect a number of sites for studies HGIN and HGIU – some sites enrolled patients for both studies. DSI was asked to audit one site in Georgia (n = 7 HGIU, n = 5 HGIN) and one site in Ohio (n = 15 HGIU, n = 6 HGIN). The final DSI report was not available at the time this review was completed, but preliminary comments from the investigator did not indicate any major issues thought to effect efficacy.

## Compliance with Good Clinical Practices

Per protocols, the studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Of note, one clinical trial site was omitted from the primary efficacy analyses due to significant GCP issues. This site enrolled patients in both HGIU (site 028) and HGIN (site 021). Details regarding the GCP issues are in Section 6.1.3 (Efficacy Findings) of this review.

## Financial Disclosures

Financial disclosure information was provided for the study (b) (6). Two investigators received ~$40,000 in honoraria or other grant monies (sites (b) (6)), a (b) (6) number of patients were randomized from these sites (n = (b) (6)).

# 5 CLINICAL PHARMACOLOGY

## Pharmacokinetics

The pharmacokinetics of oral olanzapine were evaluated primarily in study HGMF (see Table 4.1.1 in Section 4.1 Tables of Clinical Studies) via population pharmacokinetic analyses. These data have been extensively reviewed by the biopharmaceutical reviewer (see Biopharm review).

# 6 INTEGRATED REVIEW OF EFFICACY

One pivotal trial, F1D-MC-HGIU, was submitted to support the efficacy of olanzapine in the treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents.

## Indication

The Sponsor proposes the following indication "indicated for the treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents".

### 6.1.1 General Discussion of Endpoints

The primary efficacy endpoint for the clinical trial was the change from baseline to endpoint on the YMRS-adolescent structured rating scale total score. The YMRS is a standard rating scale used to evaluate efficacy in adult bipolar populations and is appropriate for evaluating efficacy in this clinical trial.
The Sponsor also included the Clinical Global Impression-Severity rating scale to rate severity of mania, depression and overall severity of bipolar disorder. The Children's Rating Scale for Depression was also included to assess depressive symptoms. Due to the presence of mania and depression in bipolar illness, inclusion of these endpoints was appropriate.

### 6.1.2 Study Design

Protocol F1D-MC-HGIU is the pivotal study submitted to support the indication "for the treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents". The other studies submitted as supportive studies in this population are open-label trials and are supportive primarily from a safety and not efficacy perspective. Therefore, only study HGIU is reviewed here.

**Protocol HGIN**
**"Olanzapine versus placebo in the treatment of mania in adolescents with bipolar I disorder"**
First patient enrolled 11/18/02, last patient completed 5/9/05.

*Investigators and sites*
This study enrolled patients at 23 sites in the United States and 2 sites in Puerto Rico. Investigator and site information (including numbers of patients randomized and completing the trial) are included in Appendix 10.1.

*Study Objectives*
Primary objective: To assess the efficacy of a flexible dose of olanzapine (2.5 to 20 mg/day) compared to placebo in the treatment of mania in bipolar I disorder (manic or mixed episode associated with bipolar I disorder, with or without psychotic features) in adolescents (ages 13 – 17) as measured by the difference between treatment groups in mean change from baseline to endpoint in the Adolescent Structured Young-Mania Rating Scale (YMRS) total score.

Secondary objectives:
To assess secondary efficacy measures 1) YMRS individual items; 2) Clinical Global Impression Scale – Bipolar Version Severity of Illness (Severity of Mania, Severity of Depression, Severity Overall); 3) Children's Depression Rating Scale-Revised; 4) Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version (investigator administered and scored) and 5) Overt Aggression Scale.

To assess the safety of olanzapine compared with placebo for up to 3 weeks of double-blind treatment and for up to an additional 26 weeks of open-label olanzapine treatment.

To assess the health-related quality of life associated with olanzapine compared with placebo for up to 3 weeks of double-blind treatment and for up to an additional 26 weeks of open-label olanzapine treatment.

Compare the frequency of response during the double-blind treatment period (up to 3 weeks), as defined by a $\geq$ 50% reduction in YMRS total score from baseline to endpoint and a CGI-BP Severity of Mania score of $\leq$ 3 at endpoint for olanzapine vs. placebo treatment.

*Study Population*
The study population consisted of generally healthy adolescents, ages 13 to 17 inclusive, with a DSM-IV-TR diagnosis of bipolar I disorder and currently displaying an acute manic or mixed episode (with or without psychotic features). The diagnosis was confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime (K-SADS-PL). The inclusion and exclusion criteria are listed in Appendix 10.2. Patients must have obtained an YMRS total score $\geq$ 20 at Visit 1 and 2. The patient's parent/authorized legal representative must sign an informed consent document and the patient must sign an informed consent document/assent document as required by local regulations. Exclusion criteria included patients who have been judged clinically to be at serious suicidal risk; patients who have previously not responded to an adequate dose and/or duration of olanzapine treatment; patients currently meeting DSM-IV-TR criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.

*Design*
This was a multicenter, randomized, double-blind, parallel, placebo-controlled trial consisting of three periods: screening/washout, 3-week double-blind trial, 26-week open-label olanzapine treatment. The screening/washout period was 2-14 days. Patients were then randomized to olanzapine flexible dose (2.5 to 20 mg/day) or placebo treatment (2:1 randomization) for the 3-week acute double-blind trial. Olanzapine was initiated at 2.5 or 5 mg/day and the dose could be increased by 2.5 or 5 mg/day dose increments at the investigator's discretion. If no tolerability or safety issues were apparent, the dose had to be titrated to at least 10 mg/day by Visit 4 (end of week 1). The investigator could continue to increase the dose by 2.5 or 5 mg/day to the maximum tolerable dose not to exceed 20 mg/day. The investigator could decrease the dose at any time and in any number of dose decrements if patients experienced an adverse event. The minimum allowable olanzapine dose was 2.5 mg/day. During this 3-week acute trial, 3 study visits occurred during the first week and then weekly thereafter.

Patients who did not respond after at least 10 days during the 3-week double-blind trial could participate in the optional 26-week open-label extension study and receive open-label olanzapine therapy (2.5 to 20 mg/day). Response was defined as having a $\geq$ 20% decrease in the YMRS total score compared to baseline and a CGI-BP Severity of Mania score $\leq$ 3. Study visits occurred weekly x 2 visits, biweekly x 4 visits and then monthly until the end of the 26-week study.

*Assessments* (The Schedule of Events is in Appendix 10.3)
Rating scales – efficacy:
Primary efficacy endpoint: Adolescent Structured Young-Mania Rating Scale (YMRS)
Secondary efficacy endpoints: Clinical Global Impression – Severity of Mania, Severity of Depression, Severity Overall; Children's Depression Rating Scale-Revised; Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version; Overt Aggression Scale (OAS); Child Health Questionnaire (CHQ)

Safety assessments:
Vital signs (blood pressure, pulse, weight, height, temperature) – including orthostatic assessments, ECG, Labs (hematology, clinical chemistry, urinalysis, lipid panel, hepatitis screen and panel, serum pregnancy test, prolactin, thyroid stimulating hormone, HgbA1c, urine drug screen.
Fasting glucose at baseline, end of 3-week study and end of 26-week open-label study.
HbA1c was only obtained for patients with diabetes.

Rating scales: Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BAS), Abnormal Involuntary Movement Scale (AIMS)
Spontaneous reporting of adverse events.

### 6.1.3 Efficacy Findings

One hundred sixty one patients were randomized, 107 to the olanzapine group and 54 to the placebo group. In the olanzapine group, 22 patients discontinued with lack of efficacy as the primary reason for discontinuation for 54.5% of drop-outs. In the placebo group, 19 patients discontinued with lack of efficacy as the primary reason for discontinuation for 84.2% of drop-outs. Drop-outs due to adverse events were the primary reason for discontinuation for 3 patients in the olanzapine group and 1 patient in the placebo group.

Table 6.1.3.1 Patient Disposition

| | Olanzapine N = 107 | Placebo N = 54 | P-value |
|---|---|---|---|
| Completers | 85 (79.4%) | 35 (64.8%) | 0.056 |
| Drop Outs | 22 (20.6%) | 19 (35.2%) | |
| Adverse Event | 3 (2.8%) | 1 (1.9%) | 1.00 |
| Lack of Efficacy | 12 (11.2%) | 16 (29.6%) | 0.007 |
| Lost to Follow-up | 0 | 0 | - |
| Patient Decision | 4 (3.7%) | 1 (1.9%) | 0.665 |
| Criteria Not Met/Compliance | 0 | 1 (1.9%) | 0.335 |
| Sponsor Decision | 0 | 0 | - |
| Physician Decision | 1 (0.9%) | 0 | 1.00 |
| Other | 2 (1.9%) | 0 | 0.551 |

Modified from Sponsor table HGIU.10.1 in study report

*Demographics and Baseline Disease Severity*

There were no statistically significant differences between the olanzapine and placebo groups with regard to baseline demographics.

Statistically significant differences indicating a potential imbalance in severity of illness were found for several categories – most indicated that more ill patients were randomized into the olanzapine treatment group (although the YMRS baseline scores, the primary efficacy measure, were not statistically different between the groups). Statistical differences were found for the mean number of previous mania episodes (olanzapine = 2.07, placebo = 4.43), mean number of previous depressive episodes (olanzapine = 1.6, placebo = 3.98), mean number of previous mixed episodes (olanzapine = 1.19, placebo = 3.85), psychiatric hospitalization within the past year (olanzapine = 32.1%, placebo = 16.7%). Scores on most rating scales at baseline did not differ between the two treatment groups with the exception of the CGI-Severity Depression (olanzapine = 3.1, placebo = 2.6).

The groups did not differ with regard to the number of patients with psychotic features (olanzapine = 21%, placebo = 13%) or current episode, manic (olanzapine = 41%, placebo = 54%). The groups did differ with regard to the number of rapid cyclers (olanzapine = 23%, placebo = 9%).

Table 6.1.3.2 Baseline Demographics and Severity of Disease

| | | Olanzapine N = 107 | Placebo N = 54 | P-value |
|---|---|---|---|---|
| Gender | Male | 61 (57.0%) | 24 (44.4%) | 0.137 |
| | Female | 46 (43%) | 30 (55.6%) | |
| Age (years) | Mean | 15.14 | 15.38 | 0.250 |
| | Median | 15.12 | 15.41 | |
| | St. Dev | 1.28 | 1.20 | |
| | Minimum | 13.02 | 13.07 | |
| | Maximum | 17.89 | 17.68 | |
| Origin | African descent | 13 (12.1%) | 2 (3.7%) | 0.247 |
| | Caucasian | 71 (66.4%) | 41 (75.9%) | |
| | East/Southeast Asian | 0 | 1 (1.8%) | |
| | Hispanic | 18 (16.8%) | 8 (14.8%) | |
| | Other | 5 (4.7%) | 2 (3.7%) | |
| Country | America | 95 (88.8%) | 48 (88.9%) | 1.00 |
| | Puerto Rico | 12 (11.2%) | 6 (11.1%) | |
| Age of onset of illness (years) | Mean | 10.93 | 11.46 | 0.331 |
| | Median | 12.00 | 12.00 | |
| | St. Dev. | 3.32 | 3.13 | |
| | Minimum | 1.00* | 4.00 | |
| | Maximum | 17.00 | 17.00 | |
| No. of Prev. Mania episodes | Mean | 2.07 | 4.43 | 0.048 |
| | Median | 1.00 | 1.00 | |
| | St. Dev. | 4.97 | 8.95 | |
| | Minimum | 0.00 | 0.00 | |
| | Maximum | 35.00 | 42.00 | |
| No. of Prev. Depressive episodes | Mean | 1.60 | 3.98 | 0.014 |
| | Median | 1.00 | 1.50 | |
| | St. Dev. | 2.84 | 8.26 | |
| | Minimum | 0.00 | 0.00 | |
| | Maximum | 20.00 | 50.00 | |
| No. of Prev. mixed episodes | Mean | 1.19 | 3.85 | 0.027 |
| | Median | 0.00 | 0.00 | |
| | St. Dev. | 3.65 | 9.40 | |
| | Minimum | 0.00 | 0.00 | |
| | Maximum | 25.00 | 42.00 | |
| Total hospitalization for the past year (months) | Mean | 0.85 | 1.43 | 0.327 |
| | Median | 0.50 | 0.50 | |
| | St. Dev. | 1.23 | 2.53 | |
| | Minimum | 0.13 | 0.10 | |
| | Maximum | 6.00 | 8.00 | |
| Length of current episode (days) | Mean | 309.8 | 237.2 | 0.521 |
| | Median | 45.50 | 50.50 | |
| | St. Dev. | 749.1 | 542.20 | |
| | Minimum | 2.00 | 4.00 | |
| | Maximum | 4441 | 2902 | |
| Days since last hospitalization | Mean | 145.4 | 361.0 | 0.072 |
| | Median | 8.00 | 33.00 | |
| | St. Dev. | 310.3 | 540.9 | |
| | Minimum | 0.00 | 0.00 | |
| | Maximum | 1688 | 1651 | |
| Psychiatric | Yes | 34 (32.08%) | 9 (16.67%) | 0.040 |

| | | | | |
|---|---|---|---|---|
| hospitalization within the past year | No | 72 (67.92%) | 45 (83.33%) | |
| Current episode has concurrent psychotic features | Yes<br>No | 22 (20.75%)<br>84 (79.25%) | 7 (12.96%)<br>47 (87.04%) | 0.281 |
| Current episode, manic | Yes<br>No | 44 (41.1%)<br>63 (58.9%) | 29 (53.7%)<br>25 (46.3%) | 0.136 |
| Rapid Cyclers | Yes<br>No<br>Unknown | 25 (23.4%)<br>71 (66.4%)<br>11 (10.3%) | 5 (9.3%)<br>43 (79.6%)<br>6 (11.1%) | 0.031 |
| CDRS Raw Total Score | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 40.2<br>39<br>15.3<br>17<br>82 | 36.2<br>33.5<br>15.5<br>17<br>101 | 0.096 |
| CGI-Severity of depression | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 3.14<br>4.00<br>1.57<br>1.00<br>6.00 | 2.65<br>2.00<br>1.60<br>1.00<br>6.00 | 0.043 |
| CGI-Severity of mania | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 4.79<br>5.00<br>0.70<br>4.00<br>6.00 | 4.81<br>5.00<br>0.75<br>3.00<br>6.00 | 0.852 |
| CGI-Severity overall | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 4.79<br>5.00<br>0.71<br>4.00<br>6.00 | 4.83<br>5.00<br>0.75<br>3.00<br>6.00 | 0.727 |
| YMRS Total score | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 33.05<br>33.00<br>6.53<br>20.00<br>48.00 | 32.04<br>32.00<br>6.23<br>21.00<br>43.00 | 0.347 |

Modified from Sponsor table HGIU.11.1, HGIU.11.2, HGIU.11.3, HGIU.11.4, HGIU.11.6 in study report
*An age of onset of 1 year old is highly suspect.

No statistically significant differences were noted between groups in baseline OAS verbal aggression total, OAS physical aggression toward self total, OAS physical aggression toward objects, OAS total, ADHD total, ADHD inattention subtotal. Baseline ADHD hyperactivity-impulsivity subtotal bordered on significance (olanzapine 13.68 vs. placebo 11.67; p = 0.051).

A diagnosis of comorbid ADHD was present in more patients in the olanzapine group compared to the placebo group (42% vs. 24%, p = 0.024). Though not common, a diagnosis of comorbid conduct disorder was present in more patients in the olanzapine group compared to the placebo group (n = 14, n = 1, p = 0.021).

## *Efficacy Analyses*

*Site Issues*

In the efficacy analysis, the sponsor included analyses with and without site 028. Per the sponsor, site 028 had significant GCP issues and patients from this site were dropped from the primary analyses (efficacy analyses were similar with and without this site). The study report did not specify what the GCP issues were with this site. The sponsor was asked to provide details and indicated the following:

> Lilly discontinued site 021 (Dr. Robb) from study HGIN, and also discontinued Dr Robb's site (site 028) from study HGIU. Lilly informed FDA of the discontinuation of Dr Robb's site from these studies in a submission to IND 28,705; serial number 953, dated May 21, 2004. In a letter dated May 2, 2004 sent to Dr Robb, Lilly listed the following GCP issues that occurred at this site related to studies HGIN and HGIU:
>
> - Not following the randomization procedures outlined in the protocol
> - Not submitting protocol amendment A, approved by Lilly on October 17, 2002, to the Institutional Review Board (IRB) for approval before use
> - Not submitting revised informed consent documents to IRB
> - Not communicating to patients about safety issues in risk profile of study drug. The risk profile was updated by Lilly on December 4, 2003 and faxed to the site on January 6, 2004 and a reminder fax was sent on January 28, 2004.
> - Significant problems with drug accountability
> - Not being able to reconstruct the regulatory document in the Clinical Trial Record Binder
> - Violation of inter-active voice response system (IVRS) security personal identification number process.

*Concomitant Medications*

Interestingly, 39.3% (42/107) of patients in the olanzapine group and 46.3% (25/54) of patients in the placebo group had no previous medications for bipolar I disorder. It is not known whether these patients participated in nonpharmacological treatment of their disorder.

The most commonly used concomitant medications (> 5% of patients) included benzodiazepines (see next paragraph) and mixed amphetamine salts in 7.5% (8/107) of patients in the olanzapine group and 5.6% (3/54) patients in the placebo group.

There were no statistically significant differences in the frequency of concomitant benzodiazepine use between the olanzapine and placebo groups. Concomitant lorazepam use occurred in 9.3% (10/107) patients in the olanzapine group and 7.4% (4/54) patients in the placebo group. Concomitant temazepam use occurred in 3.7% (4/107) patients in the olanzapine

group and 1.9% (1/54) patients in the placebo group. A few patients in both groups had concomitant clonazepam, alprazolam and diazepam use. There was a statistically significant difference in the mean number of days of benzodiazepine use between the treatment groups: 2.8 ± 3.5 days in the olanzapine group and 10 ± 7.0 days in the placebo group ($p = 0.019$). The mean dose of benzodiazepines (using equivalent doses) did not differ between the treatment groups: 1.4 ± 0.5 mg in the olanzapine group and 2.0 ± 1.7 mg in the placebo group.

There were no statistically significant differences in the frequency of concomitant anticholinergic medication use between the olanzapine and placebo groups. However, only 5 patients in the study had concomitant use of anticholinergic medications and all 5 were in the olanzapine group: benztropine mesylate (n = 3), amantadine (n = 1), and diphenhydramine (n = 1). The mean number of days on anticholinergic medication was 3 ± 2.6 days. The mean dose of anticholinergic medication was 1.4 ± 0.5 mg.

*Primary Endpoint*
*Primary Analysis - LOCF*
The mean modal daily dose of olanzapine was 10.7 mg and the mean daily dose was 8.9 mg.

The primary efficacy analysis is in Table 6.1.3.3 below. The analysis including site 028 was similar, least square mean difference was 7.88 favoring the olanzapine group ($p < 0.001$).

Table 6.1.3.3 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint – *LOCF.* (Excluding site 028)

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy Variable | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Difference | *P-value |
| YMRSTOT.Total(1-11) | olanzapine | 105 | 33.08 | 6.55 | -15.90 | 10.03 | -17.65 | -7.66 | <.001 |
| | Placebo | 54 | 32.04 | 6.23 | -7.72 | 9.42 | -9.99 | | |

*Supportive Analyses – OC and MMRM*
The findings for the OC analysis (Table 6.1.3.4) and MMRM analysis (Table 6.1.3.5) were similar to the LOCF analysis.

Table 6.1.3.4 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint by Visit– *OC*.

| Efficacy Variable | Visit | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| YMRSTOT:Total(1-11) | 3 | Olanzapine | 105 | 33.08 | 6.55 | -7.98 | 7.26 | -6.37 | -2.24 | .048 |
| | | Placebo | 54 | 32.04 | 6.23 | -5.37 | 6.83 | -4.13 | | |
| | 4 | Olanzapine | 104 | 33.11 | 6.57 | -12.62 | 9.01 | -11.46 | -3.97 | .002 |
| | | Placebo | 53 | 32.17 | 6.21 | -8.06 | 7.38 | -7.49 | | |
| | 5 | Olanzapine | 103 | 33.03 | 6.56 | -15.46 | 9.47 | -16.16 | -7.40 | <.001 |
| | | Placebo | 53 | 32.17 | 6.21 | -7.49 | 10.56 | -8.77 | | |
| | 6 | Olanzapine | 88 | 33.23 | 6.48 | -17.17 | 9.71 | -19.14 | -5.74 | .001 |
| | | Placebo | 37 | 32.41 | 6.19 | -11.11 | 9.05 | -13.40 | | |

Sponsor's Table HGIU.14.21

Table 6.1.3.5 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint by Visit– *MMRM*

| Efficacy Variable | Visit (Week) | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean StdErr | LSMean Difference | Diff StdErr | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| YMRSTOT:Total(1-11) | Combined | Olanzapine | | | | | | -12.41 | 0.85 | -5.19 | 1.08 | <.001 |
| | | Placebo | | | | | | -7.23 | 1.05 | | | |
| | 3 (0.5) | Olanzapine | 105 | 33.08 | 6.55 | -7.98 | 7.26 | -7.27 | 0.88 | -2.14 | 1.14 | .062 |
| | | Placebo | 54 | 32.04 | 6.23 | -5.37 | 6.83 | -5.13 | 1.09 | | | |
| | 4 (1) | Olanzapine | 104 | 33.11 | 6.57 | -12.62 | 9.01 | -11.84 | 0.94 | -4.08 | 1.28 | .002 |
| | | Placebo | 53 | 32.17 | 6.21 | -8.06 | 7.38 | -7.76 | 1.19 | | | |
| | 5 (2) | Olanzapine | 103 | 33.03 | 6.56 | -15.46 | 9.47 | -14.77 | 1.06 | -7.58 | 1.53 | <.001 |
| | | Placebo | 53 | 32.17 | 6.21 | -7.49 | 10.56 | -7.19 | 1.37 | | | |
| | 6 (3) | Olanzapine | 88 | 33.23 | 6.48 | -17.17 | 9.71 | -15.78 | 1.10 | -6.95 | 1.68 | <.001 |
| | | Placebo | 37 | 32.41 | 6.19 | -11.11 | 9.05 | -8.83 | 1.50 | | | |

Sponsor's Table HGIU.14.27

*U.S. vs. Puerto Rico Sites*

The Sponsor did perform an analysis comparing the efficacy between U.S. and Puerto Rico sites. There were, however, very few subjects from the latter sites.

Table 6.1.3.6 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint by Country– U.S. vs. Puerto Rico sites.

| Efficacy Variable | Country | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Diff. | *P-value | **P-value (Therapy*Country) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| YMRSTOT:Total(1-11) | America | Olanzapine | 93 | 32.80 | 6.65 | -15.28 | 9.99 | -15.09 | -7.87 | <.001 | .668 |
| | | Placebo | 48 | 31.71 | 6.38 | -6.85 | 8.63 | -7.22 | | | |
| | Puerto Rico | Olanzapine | 12 | 35.25 | 5.45 | -20.75 | 9.38 | -20.71 | -5.97 | .297 | |
| | | Placebo | 6 | 34.67 | 4.37 | -14.67 | 13.23 | -14.74 | | | |

*Secondary Analyses*
Efficacy results from select secondary analyses were reviewed.

YMRS Individual Item Analyses
Mean change from baseline to endpoint (LOCF) for the individual items of the YMRS were analyzed. Statistically significant differences favoring olanzapine were evident for all YMRS items except sexual interest and insight (see Appendix 10.4).

CGI-BP (Severity)
Mean change from baseline to endpoint (LOCF) for CGI-BP Severity of Mania, Depression and Overall were analyzed. Statistically significant differences favoring olanzapine were found for CGI-BP Severity – Mania and CGI-BP Severity-Overall, but not for CGI-BP Severity-Depression (see Table 6.1.3.7). Patients enrolled in this clinical trial were exhibiting acute manic or mixed bipolar symptoms. In the olanzapine group, 42% (44/105) exhibited manic symptoms and 58% (61/105) exhibited mixed symptoms at baseline. In the placebo group, 54% (29/54) exhibited manic symptoms and 46% (25/54) exhibited mixed symptoms at baseline. The CGI-BP Depression mean scores at baseline indicated mildly ill severity while the CGI-BP Mania and Overall mean scores at baseline indicated moderate-markedly ill severity.

Table 6.1.3.7 Sponsor's Table. CGI-BP Severity for Mania, Depression and Overall

**Table HGIU.11.23. CGI-BP Severity (Mania, Depression, Overall)**
**Mean Change from Baseline to Endpoint (LOCF)**
**Double-Blind Period**

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy Variable | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Difference | *P-value |
| CGI Severity Depression | Olanzapine | 105 | 3.12 | 1.59 | -0.86 | 1.21 | -0.89 | -0.10 | .533 |
| | Placebo | 54 | 2.65 | 1.60 | -0.54 | 1.04 | -0.80 | | |
| CGI Severity Mania | Olanzapine | 105 | 4.81 | 0.69 | -1.70 | 1.29 | -1.73 | -0.67 | <.001 |
| | Placebo | 54 | 4.81 | 0.75 | -1.04 | 1.12 | -1.05 | | |
| CGI Severity Overall | Olanzapine | 105 | 4.81 | 0.71 | -1.60 | 1.30 | -1.63 | -0.64 | <.001 |
| | Placebo | 54 | 4.83 | 0.75 | -0.98 | 1.17 | -0.99 | | |

Children's Depression Rating Scale - Revised
No statistically significant differences were found between olanzapine and placebo for mean change from baseline to endpoint for CDRS-R Total Score (The CDRS-R contains 17 anchored items, most are rated from 1 to 7 for severity; maximum score = 113). Some statistical differences were found for individual items – one favored olanzapine (sleep disturbance) and three items favored placebo (appetite disturbance, excessive fatigue, and depressed facial affect) [See Appendix 10.5]. Most of these statistical differences on individual items could have been related more to the side effect profile of olanzapine. Of note, the baseline mean score for suicidal ideation[1] was 1.77 in the olanzapine group and 1.42 in the placebo group, mean change

1 CDRS-R Suicidal ideation item scoring: 1 = understands the word "suicide" but does not apply the term to

to endpoint was -0.47 and -0.23 respectively (p = NS) [one of the exclusion criterion was "patients who have been judged clinically to be at serious suicidal risk"]. A further analysis and discussion of the suicidal ideation item is in Section 7.1.5 (Less Common Adverse Events).

Table 6.1.3.8 Sponsor's Table. CDRS-R Total Score

**Table HGIU.11.24. CDRS-R Total Score**
**Mean Change from Baseline to Endpoint (LOCF)**
**Double-Blind Period**

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy Variable | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Difference | *P-value |
| CDRS Raw Total Score | Olanzapine | 100 | 40.43 | 15.60 | -7.18 | 12.09 | -8.37 | 1.14 | .508 |
| | Placebo | 53 | 35.77 | 15.35 | -5.85 | 13.27 | -9.50 | | |

Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version (ADHDRS) and Overt Aggression Scale (OAS)
Statistically significant differences favoring olanzapine were found for the mean change from baseline to endpoint in the ADHDRS hyperactivity-impulsivity subtotal (-4.96 vs. -1.62, p = 0.008) and the ADHDRS total score (-9.47 vs. -3.97, p = 0.048) [See Appendix 10.6]. It should be noted that at baseline, there were more patients with comorbid ADHD in the olanzapine group compared to the placebo group (42% vs. 24%, p = 0.024). The Sponsor did not provide changes in the ADHDRS separately for patients with and without comorbid ADHD.
Statistically significant differences favoring olanzapine were found for the mean change from baseline to endpoint for all subscales (except physical aggression towards self) and total score for the OAS. Comorbid conduct disorder was present in a small number of patients (olanzapine n = 14, placebo n = 1). See Appendix 10.6.

*Subgroup Analyses*
The Sponsor evaluated the following subgroups: gender, age (< 15, ≥ 15), Caucasian vs. nonCaucasian, manic vs. mixed, psychotic vs. without psychotic features, rapid vs. nonrapid cycling.
Statistically significant differences favoring olanzapine were found for all subgroups except < 15 year olds (p = 0.094), patients with psychotic features (p = 0.111) and rapid cyclers (p = 0.271). The mean change to endpoint was similar in both the patients with and without psychotic features; failure to show efficacy in patients with psychotic features may have been due to the small sample size (n = 20 olanzapine, n = 7 placebo). The mean change to endpoint was also similar in both rapid and nonrapid cyclers – again, the small sample size in the rapid cycler

himself/herself, 2 = sharp denial of suicidal thoughts, 3 = has thoughts about suicide, or of hurting himself/herself (if he/she does ont understand the concept of suicide), usually when angry; 4 = intermediate rating, not anchored; 5 = has recurrent thoughts of suicide; 6 = intermediate rating, not anchored; 7 = has made a suicide attempt within the last month or is actively suicidal

subgroup may have contributed to the negative findings. A significant treatment-by-age interaction was found.

Table 6.1.3.9 Sponsor's Table. YMRS Total Score - Subgroup Analyses

| Efficacy Variable | Subgroup | Strata | N | Therapy | Baseline n | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Diff. | *P-value | **P-value (Therapy*Subgroup) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| YMRSTOT:Total(1-11) | Gender | Female | 75 | Olanzapine | 45 | 32.69 | 6.41 | -14.73 | 10.06 | -20.07 | -5.98 | .005 | .213 |
| | | | | Placebo | 30 | 33.17 | 6.38 | -9.27 | 9.33 | -14.10 | | | |
| | | Male | 84 | Olanzapine | 60 | 33.37 | 6.69 | -16.78 | 10.01 | -17.47 | -9.87 | <.001 | |
| | | | | Placebo | 24 | 30.63 | 5.85 | -5.79 | 9.35 | -7.60 | | | |
| | Age | < 15 | 69 | Olanzapine | 49 | 32.78 | 6.96 | -14.63 | 10.17 | -16.61 | -4.49 | .094 | .089 |
| | | | | Placebo | 20 | 32.40 | 5.70 | -9.45 | 10.96 | -12.12 | | | |
| | | >=15 | 90 | Olanzapine | 56 | 33.34 | 6.21 | -17.02 | 9.87 | -18.90 | -9.86 | <.001 | |
| | | | | Placebo | 34 | 31.82 | 6.59 | -6.71 | 8.39 | -9.03 | | | |

| Efficacy Variable | Subgroup | Strata | N | Therapy | Baseline n | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Diff. | *P-value | **P-value (Therapy*Subgroup) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| YMRSTOT:Total(1-11) | Origin | Caucasian | 111 | Olanzapine | 70 | 32.84 | 6.90 | -14.17 | 9.58 | -13.90 | -6.95 | <.001 | .570 |
| | | | | Placebo | 41 | 31.05 | 6.40 | -6.49 | 8.85 | -6.95 | | | |
| | | Non-Caucasian | 48 | Olanzapine | 35 | 33.54 | 5.85 | -19.37 | 10.16 | -20.80 | -9.19 | .005 | |
| | | | | Placebo | 13 | 35.15 | 4.58 | -11.62 | 10.44 | -10.82 | | | |
| | Mania Type | Manic | 73 | Olanzapine | 44 | 34.50 | 5.63 | -16.43 | 10.67 | -17.44 | -5.59 | .019 | .160 |
| | | | | Placebo | 29 | 33.10 | 5.20 | -10.07 | 9.15 | -11.85 | | | |
| | | Mixed | 86 | Olanzapine | 61 | 32.05 | 7.00 | -15.52 | 9.62 | -19.66 | -9.70 | <.001 | |
| | | | | Placebo | 25 | 30.80 | 7.15 | -5.00 | 9.16 | -9.96 | | | |
| | Psychotic features | N | 132 | Olanzapine | 85 | 32.53 | 6.49 | -15.94 | 9.82 | -18.07 | -7.92 | <.001 | .739 |
| | | | | Placebo | 47 | 31.72 | 6.09 | -7.62 | 9.58 | -10.15 | | | |
| | | Y | 27 | Olanzapine | 20 | 35.40 | 6.45 | -15.75 | 11.17 | -7.71 | -7.24 | .111 | |
| | | | | Placebo | 7 | 34.14 | 7.24 | -8.43 | 8.89 | -0.46 | | | |

| Subgroup | Strata | N | Therapy | Baseline n | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Diff. | *P-value | **P-value (Therapy*Subgroup) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rapid Cycling | N | 114 | Olanzapine | 71 | 32.97 | 6.48 | -15.63 | 9.17 | -18.75 | -7.64 | <.001 | .885 |
| | | | Placebo | 43 | 32.51 | 6.56 | -7.72 | 9.55 | -11.11 | | | |
| | Y | 29 | Olanzapine | 24 | 33.50 | 7.07 | -16.79 | 12.70 | -13.67 | -6.35 | .271 | |
| | | | Placebo | 5 | 30.60 | 4.22 | -7.40 | 10.57 | -7.32 | | | |

The Sponsor further evaluated the age subgroup in post hoc analyses since the findings suggested a differential effect. Three additional analyses were performed: age as a continuous variable, age subgroups defined as < 16 and ≥ 16 years of age and age subgroups defined by age at last birthday. The treatment-by-age interaction was not significant in the first two analyses, but the last analysis did not show a similar treatment effect (i.e. change to endpoint) for the 14 year olds compared to the 13, 15, 16 and 17 year olds. In this last analysis, neither the 14 year old subgroup nor the 17 year old subgroup showed a statistically significant treatment effect, the

smaller sample size in the 17 year old group could have contributed to those findings. See Appendix 10.7 for these additional analyses.

The Sponsor also evaluated the subgroups with or without past or current ADHD or ODD diagnoses. Statistically significant differences favoring olanzapine occurred within each subgroup with no differences between patients with and without a past or current ADHD diagnosis or between patients with and without a past or current ODD diagnosis (data not shown).

### 6.1.4 Efficacy Conclusions

The mean modal daily dose of olanzapine was 10.7 mg and the mean daily dose was 8.9 mg. Seventy-nine percent of patients in the olanzapine group and 65% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIU was change from baseline in the Adolescent-Structured YMRS Total Score (LOCF analysis). The overall study results were statistically significant for olanzapine versus placebo (LS Mean Diff = -7.66, $p < 0.001$).

The supportive OC analysis was similar to the LOCF analysis (LS Mean Diff = -5.74, $p = 0.001$). The supportive MMRM analysis was similar to the LOCF analysis (LS Mean Diff = -6.95, $p < 0.001$). The LOCF analysis for the secondary endpoint CGI-Severity Mania and CGI-Severity Overall were statistically significant favoring olanzapine.

Subgroup analyses included gender, age ($< 15$, $\geq 15$), Caucasian vs. nonCaucasian, manic vs. mixed, psychotic vs. without psychotic features and rapid vs. nonrapid cycling. Statistically significant differences favoring olanzapine were found for all subgroups except < 15 year olds ($p = 0.094$), patients with psychotic features ($p = 0.111$) and rapid cyclers ($p = 0.271$) – the latter two groups had few patients in those subgroups. A significant treatment-by-age interaction was found.

Since HGIU was a flexible-dose study, it is not possible to evaluate the dose-response with regard to efficacy. Proposed labeling states the range that was included in the clinical trial, but no data is available to determine whether higher doses confer greater efficacy and it is likely that higher doses confer greater risk from an adverse event perspective.

## 7 INTEGRATED REVIEW OF SAFETY

The Sponsor used the following databases for assessment of safety (see Table 4.1.1 in Section 4.1 – Tables of Clinical Studies for more information on individual studies). For studies HGCS (n = 8), HGCR (n = 2), and HGGC (n = 23), the Sponsor included only information regarding deaths, serious adverse events and discontinuations due to adverse events.

Sponsor's Table. Databases for Summary of Clinical Safety

**Table 2.7.4.1. Databases for Summary of Clinical Safety**

| Database | Indication | Studies Used | Number of Patients |
|---|---|---|---|
| Acute Placebo-Controlled Databases | Schizophrenia | HGIN | N=107 (Olz=72, Pla=35) |
| | Bipolar | HGIU | N=161 (Olz=107, Pla=54) |
| | Combined | HGIN, HGIU | N=268 (Olz=179, Pla=89) |
| Overall Olanzapine Exposure Databases | Schizophrenia | HGIN, LOAY, HGMF[a] | N=227 |
| | Bipolar | HGIU, HGMF[a] | N=227 |
| | Combined | HGIN, HGIU, LOAY, HGMF | N=454 |

a Because Study HGMF enrolled patients with schizophrenia or bipolar disorder, some patients from Study HGMF were included in the Overall Olanzapine Exposure Bipolar Database and some patients from Study HGMF were included in the Overall Olanzapine Exposure Schizophrenia Database.

The Sponsor also included information on serious adverse events and discontinuations due to adverse events for the 37 adolescent patients who participated in the olanzapine adult studies:

Study HGBG and HGCL were clinical trials for adult patients aged 18 or older – two adolescent patients were enrolled in those trials (17.9 and 17.8 years of age).
Study HGDH – acute and long-term efficacy of olanzapine in first-episode psychotic patients aged 16 – 40 years (n = 7 adolescents).
Study HGGF – delaying or preventing psychosis onset in persons aged 12 to 45 years prodromal to psychosis (n = 24 adolescents).
Study HGKL – clinical trial in patients aged 15 to 65 years with borderline personality disorder (n = 4 adolescents).

**"Acute Placebo Controlled Database" hereafter called HGIN + HGIU Acute Database**
A total of 268 patients were included in the HGIN + HGIU Acute Database. Eight (4.5%) patients discontinued due to adverse events in the olanzapine treatment group.

Patient Disposition (HGIN + HGIU)

| | Olanzapine N = 179 | Placebo N = 89 | P-value |
|---|---|---|---|
| Completers | 134 (74.9%) | 50 (56.2%) | 0.003 |
| Drop Outs | 45 (25%) | 39 (44%) | |
| Adverse Event | 8 (4.5%) | 1 (1.1%) | 0.279 |
| Lack of Efficacy | 22 (12.3%) | 34 (38.2%) | < 0.001 |
| Lost to Follow-up | 1 (0.6%) | 0 | 1.00 |
| Patient Decision | 8 (4.5%) | 2 (2.2%) | 0.504 |
| Criteria Not Met/Compliance | 2 (1.1%) | 2 (2.2%) | 0.602 |
| Sponsor Decision | 1 (0.6%) | 0 | 1.00 |
| Physician Decision | 1 (0.6%) | 0 | 1.00 |
| Other | 2 (1.1%) | 0 | 1.00 |

Modified from Sponsor table 2.7.4.20 in summary-clin-safety document

Patient demographics (HGIN + HGIU): The majority of patients were male (60%), Caucasian (70%) with a mean age of ~ 15.6 years (see Appendix 10.8). For study HGIN, the majority of patients were 16 and 17 years of age at baseline (61%); for study HGIU, the majority of patients were 14 and 15 (55%). This is expected and consistent with the psychiatric diagnoses in these two trials. A table of age distribution at baseline is in Appendix 10.8.

**"Overall Olanzapine Exposure Combined Database" hereafter called Overall Combined Database**

A total of 454 patients were included in the Overall Combined Database. The patient disposition by diagnoses (bipolar vs. schizophrenia) is given in Table 6.1.4.2. Twice as many patients with bipolar disorder discontinued due to an adverse event compared to patients with schizophrenia (14.5% vs. 7.9%). More than twice as many patients with schizophrenia discontinued due to lack of efficacy compared to patients with bipolar disorder (16.3% vs. 5.7%).

Sponsor's Table. Patient Disposition (Overall Combined Database)

**Table 2.7.4.23. Patient Disposition**
**All Patients with Olanzapine Exposure**
**Overall Olanzapine Exposure Combined Database**

| | Bipolar | | Schizophrenia | | Overall | |
|---|---|---|---|---|---|---|
| Patient Disposition | N | % | N | % | N | % |
| Reporting Interval Completed | 130 | 57.3% | 119 | 52.4% | 249 | 54.8% |
| Adverse Event | 33 | 14.5% | 18 | 7.9% | 51 | 11.2% |
| Lack of Efficacy | 13 | 5.7% | 37 | 16.3% | 50 | 11.0% |
| Lost To Follow-Up | 9 | 4.0% | 4 | 1.8% | 13 | 2.9% |
| Patient Decision | 24 | 10.6% | 10 | 4.4% | 34 | 7.5% |
| Criteria Not Met/Compliance/Protocol Violation | 2 | 0.9% | 28 | 12.3% | 30 | 6.6% |
| Sponsor Decision | 3 | 1.3% | 5 | 2.2% | 8 | 1.8% |
| Physician Decision | 10 | 4.4% | 4 | 1.8% | 14 | 3.1% |
| Other | 3 | 1.3% | 2 | 0.9% | 5 | 1.1% |
| Total | 227 | 100.0% | 227 | 100.0% | 454 | 100.0% |

The patient demographics in the Overall Combined Database were fairly consistent with the demographics of the HGIU + HGIN Acute Database with the exception of country – 89 additional patients with schizophrenia from study LOAY (German sites) were included in the Overall Combined Database. Patient demographics for the Overall Combined Database are included in Appendix 10.8.

## Methods and Findings

### 7.1.1 Deaths

No deaths occurred in the HGIU + HGIN Acute Database, Overall Combined Database, studies HGCS, HGCR, HGGC or in adolescent patients from the adult studies.

### 7.1.2 Other Serious Adverse Events

The following tables for serious adverse events were compiled from narratives provided by the Sponsor.

A total of 7 serious adverse events occurred in 6 patients in the olanzapine treatment arm in the HGIU + HGIN Acute Database (see Table 7.1.2.1).
One serious adverse event (schizophrenia) occurred in 1 patient in the placebo arm of study HGIN (no SAEs in the placebo group in study HGIU).

Table 7.1.2.1. Serious Adverse Events: HGIN + HGIU Acute Database

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Severity Outcome |
|---|---|---|---|---|---|
| HGIN 025-2504 | 15 YOWF | Olanzapine DB phase | Migraine | Migraine | Severe Worsened from baseline; failed to restart study med and discontinued from study |
| HGIN 930-9301 | 15 YOWM | Olanzapine DB phase | Closed fracture of right forearm | Forearm fracture | Severe Fracture from fall, treated in hospital |
| HGIN 026-2603 | 14 YOWF | Olanzapine DB phase | Weight gain | Weight increased | Mild/moderate Onset of AE in DB phase, patient discontinued OL phase due to weight gain of 18.3 kg over 4 months |
| HGIU 012-1211 | 14 YOWF | Olanzapine DB phase | Exacerbation of bipolar symptoms | Bipolar disorder | Severe Discontinued during OL phase |
| HGIU 035-3501 | 14 YOWF | Olanzapine DB phase | Relapse of bipolar disorder | Bipolar disorder | Moderate Hospitalized, Discontinued due to weight gain |
| HGIU 031-3103 | 14 YOWM | Olanzapine DB phase | Decreased WBC count and decreased neutrophils | WBC count decreased, neutrophil count decreased | Moderate WBC 4.04 to 2.52; ANC 1.63 to 0.83; Discontinued in OL phase due to persistently low counts |

A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database (see Table 7.1.2.2). The majority of these SAEs, 19/35 patients, were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

Table 7.1.2.2 Serious Adverse Events: Overall Combined Database

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Severity Outcome |
|---|---|---|---|---|---|
| HGIN 007-0704 | 15 YOBM | Olanzapine OL phase | Exacerbation of schizophrenia | Schizophrenia | Severe Hospitalization, discontinuation from study |
| HGIN 013-1302 | 17 YOM | Olanzapine OL phase | Wosening of schizophrenia symptoms | Schizophrenia | Moderate |
| HGIN 019-1901 | 15 YOWF | Olanzapine OL phase | Depressive with psychotic features, weight gain | Major depression, weight increased | Severe Hospitalization, discontinuation from study |
| HGIN 021-2101 | 14 YOBM | Olanzapine OL phase | Worsening of schizophrenia | Schizophrenia | Severe |
| HGIN 026-2603 | 14 YOWF | Olanzapine OL phase | Exacerbation of schizophrenia, suicidal ideation, weight gain | Schizophrenia, weight increased | Severe (schiz) Moderate (weight) Hospitalization, weight gain of 18.3 kg over 4 months |
| HGIN 030-3001 | 17 YOWM | Olanzapine OL phase, 1st visit | Exacerbation of psychosis | Psychotic disorder | Severe Hospitalized |
| HGIN 910-9101 | 16 YOWF | Olanzapine OL phase | Worsening of Schizophrenia | Schizophrenia | Moderate Hospitalized |
| HGIN 930-9301 | 15 YOWM | Olanzapine OL phase | Closed fracture of right forearm | Forearm fracture | Severe Fracture from fall, treated in hospital |
| HGIN 930-9307 | 15 YOWF | Olanzapine OL phase | Attempted suicide | Suicide attempt | Severe Attempted overdose with Phenobarbital, hospitalized, discontinued from study |
| HGIU 001-0103 | 13 YOWM | Olanzapine OL phase | Increased agitation | Agitation | Severe Hospitalized, completed study |
| HGIU 001-0107 | 13 YOWM | Olanzapine OL phase | Agitation, aggression | Agitation, aggression | Severe Hospitalized, completed study |
| HGIU 001-0108 | 14 YOWF | Olanzapine OL phase | Alcohol intoxication, suicidal ideation | Alcohol poisoning, suicidal ideation | Severe (alcohol) Moderate (SI) Discontinued from study |
| HGIU 012-1202 | 15 YOWF | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized, completed study |
| HGIU 012-1211 | 14 YOWF | Olanzapine OL phase | Exacerbation of bipolar | Bipolar disorder | Severe Discontinued study |

| | | | | | |
|---|---|---|---|---|---|
| | | | symptoms | | |
| HGIU 012-1212 | 14 YOBF | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized, discontinued "patient decision" |
| HGIU 020-2016 | 14 YOWF | Olanzapine OL phase | Attempted suicide | Suicide attempt | Mild Overdose of Benadryl and ibuprofen, recovered without treatment; completed study |
| HGIU 026-2604 | 16 YOHM** | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized, completed study |
| HGIU 026-2605 | 14 YOM | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized and discontinued study |
| HGIU 026-2608 | 13 YOWF | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized, discontinued study |
| HGIU 027-2705 | 15 YOBM | Olanzapine OL period | Worsening of bipolar disorder, self-inflicted superficial lacerations | Bipolar disorder, Intentional self-injury | Severe (BP) Moderate (SIB) Hospitalized, discontinued study (cut arms with fingernails) |
| HGIU 027-2707 | 14 YOBF | Olanzapine OL phase | Worsening of bipolar disorder | Bipolar disorder | Severe Hospitalized, completed study |
| HGIU 028-2804 | 15 YOWF | Olanzapine OL phase | Recurrence of bipolar symptoms | Bipolar disorder | Severe Hospitalized, discontinued study "sponsor's decision" – GCP issues at site |
| HGIU 028-2805 | 14 YOWF | Olanzapine OL phase | Suicidal ideation | Suicidal ideation | Severe Hospitalized, discontinued – GCP issues at site |
| HGIU 028-2806 | 15 YOBF | Olanzapine OL phase | Bipolar mania | Bipolar disorder | Severe Hospitalized, discontinued study |
| HGIU 031-3103 | 14 YOWM | Olanzapine OL phase | Decreased WBC count and decreased neutrophils | WBC count decreased, neutrophil count decreased | See Table 7.1.2.1. |
| HGIU 033-3304 | 15 YOWF | Olanzapine OL phase | Intensifying aggressiveness and irritability | Aggression, irritability | Severe Hospitalized, discontinued study |
| HGIU 035-3519 | 14 YOWM | Olanzapine OL phase | Violent behavior | Aggression | Severe Hospitalized, discontinued study |
| HGIU 730-7302 | 13 YOHM | Olanzapine OL phase | Oppositional defiant behavior | Oppositional defiant disorder | Severe Hospitalized, discontinued due to noncompliance |
| HGMF 003-0303 | 17 YOWF | Olanzapine OL | Acute appendicitis | Appendicitis | Severe Hospitalized, completed study |
| HGMF | 16 YOWF | Olanzapine | Exacerbation of | Bipolar disorder | Severe |

| | | | | | |
|---|---|---|---|---|---|
| 003-0304 | | OL | bipolar illness with positive suicidal ideation | | Hospitalized, discontinued study |
| LOAY 407-4078 | 17 YOWM | Olanzapine OL | Recurrence of acute psychotic symptoms | Psychotic disorder | Severe Hospitalized |
| LOAY 407-4207 | 14 YOWM | Olanzapine OL | Borrelia infection | Borrelia infection | Mild Discontinued study |
| LOAY 413-4145 | 16 YOWM | Olanzapine OL | Worsening of underlying disease schizophrenia | Schizophrenia | Severe Hospitalized Discontinued study |

Table 7.1.2.3 Serious Adverse Events: HGCR, HGCS, HGGC

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Severity Outcome |
|---|---|---|---|---|---|
| HGCR 001-2001 | 12 YOWM | Olanzapine OL | Headache lumbar puncture | Headache | Moderate Completed study |
| HGCS 001-1001 | 14 YOHF | Olanzapine OL | Mallory Weiss tear, vomiting blood | Esophageal hemorrhage, hematemesis | Severe Completed study |
| HGGC 001-2023 | 14 YOWF | Olanzapine | Suicidality | Depression | Hospitalized and discontinued from study |

The Sponsor was asked to provide narratives for the adolescent patients in the adult studies who experienced serious adverse events (Table 7.1.2.4).

Table 7.1.2.4 Serious Adverse Events: Adolescent Patients from Adult Studies (n = 37)

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Comments |
|---|---|---|---|---|---|
| HGDH 007-1607 | 17 YOWM | Olanzapine | Overdose | Overdose | Ingested 175 mg olanzapine, completed the study |
| HGGF 001-0102 | 15 YOWM | Olanzapine | Worsening depression with suicidal ideation | Depression, affective disorder, suicidal ideation | Gained significant amount of weight- 14 kg in 17 weeks; patient discontinued |
| HGGF 001-113 | 16 YOWF | Olanzapine | Dysphoria, Superficial self-mutilation | Dysphoria, self mutilation | Cuts on upper arm made with piece of glass, discontinued from study |
| HGGF 004-405 | 17 YOWF | Olanzapine | Auditory perceptual abnormalities, depersonalization, depressed mood, suicidal ideation, worsening psychosis | Auditory hallucination, depersonalization, depressed mood, illusion, suicidal ideation, psychotic disorder | |
| HGGF 004-406 | 17 YOWF | Olanzapine | Depressed mood, suicidal ideation | Depressed mood, suicidal ideation | Discontinued study |

Narratives were provided by Sponsor upon request

## 7.1.3 Dropouts and Other Significant Adverse Events

### 7.1.3.1 Adverse events associated with dropouts

Table 7.1.3.1.1 Discontinuations Due to Adverse Events: HGIN + HGIU Acute Database

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Comments |
|---|---|---|---|---|---|
| HGIN 007-703 | 13 YOBF | Olanzapine DB phase | Clinically significant increased ALT | ALT increased | ALT up to 231<br>(AST up to 142)<br>Returned to WNL after discontinuation from study |
| HGIN 010-1001 | 17 YOWM | Olanzapine DB phase | Elevated liver function | Liver function test abnormal | ALT = up to 597<br>AST = up to 410<br>GGT = up to 129<br>Noted at randomization visit (was taking olanzapine prior to study)<br>Discontinued study |
| HGIN 021-2103 | 17 YOBM | Olanzapine DB phase | Elevated transaminases | Transaminases increased | AST up to 136<br>ALT up to 396<br>Returned to WNL after discontinuation from study |
| HGIN 910-9110 | 17 YOWM | Olanzapine DB phase | AST increased | AST increased | AST up to 190<br>(ALT up to 321)<br>Returned to WNL after discontinuation from study |
| HGIN 920-9202 | 17 YOWM | Olanzapine DB phase | Rise ALT | ALT increased | ALT up to 393<br>(AST up to 179<br>GGT up to 82)<br>ALT and GGT returned to WNL after discontinuation from study (AST N/A) |
| HGIU 035-3503 | 16 YOBF | Olanzapine DB phase | Heart rate increased | Elevated pulse | Holter noted sinus tachycardia<br>Discontinued from study, pulse WNL at 4$^{th}$ follow-up visit |
| HGIU 012-1203 | 15 YOWF | Olanzapine DB phase | Hepatic enzyme increased | Elevated liver enzymes | AST up to 148<br>ALT up to 325<br>GGT up to 53<br>Returned to near WNL after discontinuation from study (ALT 48) |
| HGIU 035-3501 | 14 YOWF | Olanzapine DB phase | Weight increased | Weight gain | Weight increase of 4.5 kg in ~ 15 days |

Table 7.1.3.1.2 Discontinuations Due to Adverse Events: Overall Combined Database

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Comments |
|---|---|---|---|---|---|
| HGIN 003-0302 | 17 YOWM | Olanzapine OL | Weight increased | Weight gain | Gained 12.7 kg in 3 months |
| HGIN 019-1901 | 15 YOWF | Olanzapine OL | Weight increased | Weight gain | Gained 6.62 kg during DB phase,<br>Gained 15.88 kg over 5.7 months |
| HGIN 020-2002 | 15 YOBM | Olanzapine OL | Sedation | Sedation | |
| HGIN 025-2502 | 16 YOWM | Olanzapine OL | Weight increased | Weight gain | Gained 12.2 kg over 183 days |
| HGIN 027-2701 | 17 YOWM | Olanzapine OL | Weight increased | Weight gain | Gained 12 kg over 92 days |
| HGIN 027-2702 | 13 YOWF | Olanzapine OL | Weight increased | Weight gain | Gained 17.5 kg over 148 days |
| HGIN 030-3007 | 13 YOWF | Olanzapine OL | Increased appetite | Increased appetite | Gained 21.8 kg over 94 days |
| HGIN 900-9003 | 16 YOWM | Olanzapine OL | Weight increased | Weight gain | Gained 12.8 kg over 169 days |
| HGIN 930-9307 | 15 YOWF | Olanzapine OL | Suicide attempt | Suicide attempt | See Table 7.1.2.2 |
| HGIN 940-9403 | 16 YOWM | Olanzapine OL | Weight increased | Weight gain | Gained 13.4 kg over 152 days |
| HGIU 001-108 | 14 YOWF | Olanzapine OL | Alcohol intoxication | Alcohol poisoning | See Table 7.1.2.2. |
| HGIU 007-708 | 15 YOWM | Olanzapine OL | Drowsiness | Somnolence | |
| HGIU 009-902 | 15 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 14.2 kg over 78 days |
| HGIU 013-1303 | 17 YOWF | Olanzapine OL | Syncope | Syncope | 100/60 mm Hg, 88 bpm supine, 98/62 mmHg, 100 bpm standing |
| HGIU 013-1308 | 14 YOHF | Olanzapine OL | Weight gain | Weight increased | Gained 9.1 kg over 103 days |
| HGIU 013-1310 | 16 YOWF | Olanzapine OL | Increased appetite | Increased appetite | Gained 9.5 kg over ~ 56 days (at time of weight patient had been off drug for 11 days) |
| HGIU 013-1311 | 13 YOHM | Olanzapine OL | Worsened aggressive behavior | Aggression | |
| HGIU 019-1901 | 16 YOBF | Olanzapine OL | Pregnancy | Pregnancy | |
| HGIU 019-1907 | 15 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 17.7 kg over 170 days |
| HGIU 020-2007 | 14 YOWF | Olanzapine OL | Elevated liver function test | Liver function test abnormal | AST up to 204, ALT up to 330<br>Resolved after discontinuation from study |
| HGIU 020-2008 | 15 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 9.3 kg over 58 days |

| | | | | | |
|---|---|---|---|---|---|
| HGIU 020-2019 | 16 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 9.5 kg over 81 days |
| HGIU 024-2404 | 13 YOWF | Olanzapine OL | Fear of more weight gain | Fear of weight gain | Gained 5.9 kg over 34 days |
| HGIU 026-2608 | 13 YOWF | Olanzapine OL | Exacerbation of bipolar disorder | Bipolar disorder | |
| HGIU 027-2701 | 15 YOWF | Olanzapine OL | Sedation | Sedation | |
| HGIU 027-2704 | 15 YOBM | Olanzapine OL | Weight gain | Weight increased | Gained 18.6 kg over 119 days |
| HGIU 027-2705 | 15 YOBM | Olanzapine OL | Worsening of bipolar disorder | Bipolar disorder | |
| HGIU 028-2806 | 15 YOBF | Olanzapine OL | Bipolar mania | Bipolar disorder | |
| HGIU 031-3103 | 14 YOWM | Olanzapine OL | Decreased WBC | WBC count decreased | See Table 7.1.2.1. |
| HGIU 033-3304 | 15 YOWF | Olanzapine OL | Intensifying aggressiveness | Aggression | See Table 7.1.2.2 |
| HGIU 035-3510 | 15 YOWM | Olanzapine OL | Weight gain | Weight increased | Gained 5.4 kg over 89 days |
| HGIU 035-3517 | 13 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 5 kg over ~6 weeks |
| HGIU 720-7217 | 15 YOHM | Olanzapine OL | Hepatic enzymes increases | Hepatic enzyme increased | AST up to 103, ALT up to 125 (also had significant weight gain, 21 kg over ~ 5 months) |
| HGIU 720-7219 | 14 YOHF | Olanzapine OL | Pregnancy | Pregnancy | |
| HGMF 002-0211 | 17 YOWF | Olanzapine OL | Somnolence | Somnolence | |
| HGMF 003-0304 | 16 YOWF | Olanzapine OL | Exacerbation of bipolar illness with positive suicidal ideation | Bipolar disorder | See Table 7.1.2.2. |
| HGMF 008-0806 | 15 YOWM | Olanzapine OL | Increased depression | Depression | |
| HGMF 014-1400 | 17 YOBF | Olanzapine OL | Elevated CK level lab | Blood creatine phosphokinase | CK up to 690 U/L |
| HGMF 025-2501 | 15 YOWM | Olanzapine OL | Drowsiness | Somnolence | |
| HGMF 028-2801 | 18 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 8.9 kg over 27 days |
| LOAY 405-4057 | 13 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 10.1 kg over 42 days |
| LOAY 407-4207 | 14 YOWM | Olanzapine OL | Suspicion of neuroborreliosis | Neuroborreliosis | See Table 7.1.2.2. |
| LOAY 407-4218 | 15 YOWF | Olanzapine OL | Galactorrhea | Galactorrhea | Prolactin up to 35 mcg/L (ULN = 29) |

There were no discontinuations due to adverse events for studies HGCS, HGCR and HGGC.

The Sponsor was asked to provide narratives for the adolescent patients in the adult studies who discontinued due to adverse events (Table 7.1.3.1.3).

Table 7.1.3.1.3 Discontinuations Due to Adverse Events: Adolescent Patients from Adult Studies

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Comments |
|---|---|---|---|---|---|
| HGGF 001-127 | 13 YOWM | Olanzapine | Weight gain | Weight increased | Gained 23 kg in ~5 months (BMI from 32 to 39) |
| HGKL 014-1416 | 15 YOWM | Olanzapine | Weight gain | Weight increased | Gained 12.5 kg over 3 months; triglycerides also increased from 260 to 508 mg/dL |

## 7.1.4 Common Adverse Events

### 7.1.4.1 Eliciting adverse events data in the development program

Adverse events were obtained by spontaneous reports, patient observation and investigator query at every study visit. Rating scales were included for evaluation of extrapyramidal symptoms (SAS), akathisia (BAS) and dyskinesias (AIMS). Vital signs, ECGs and laboratory tests were obtained at intervals throughout the study.

### 7.1.4.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using the MedDRA version 8.0 coding dictionary. A sample of patient narratives was reviewed and the coding of verbatim terms to preferred terms was appropriate.

### 7.1.4.3 Common adverse event tables

Adverse events occurring in $\geq$ 2% of patients in the HGIU + HGIN Acute Database is in Table 7.1.4.3.1. The majority of adverse events in this table occurred more than twice as frequently in the olanzapine group compared to the placebo group, that adverse events that were statistically more frequent in the olanzapine group were weight increased (30% vs. 6%), somnolence (25% vs. 3%), increased appetite (24% vs. 6%) and sedation (24% vs. 6%).

Table 7.1.4.3.1 Sponsor's Table. Adverse Events Occurring in ≥ 2% of Patients: HGIN + HGIU Acute Database

| | Therapy | | | | | | |
|---|---|---|---|---|---|---|---|
| | Olanzapine | | | Placebo | | | |
| Event Classification | N | n | % | N | n | % | *P-value |
| Patients with >=1 TESS | 179 | 158 | 88.3% | 89 | 54 | 60.7% | <.001 |
| Weight increased | 179 | 53 | 29.6% | 89 | 5 | 5.6% | <.001 |
| Somnolence | 179 | 44 | 24.6% | 89 | 3 | 3.4% | <.001 |
| Increased appetite | 179 | 43 | 24.0% | 89 | 5 | 5.6% | <.001 |
| Sedation | 179 | 34 | 19.0% | 89 | 5 | 5.6% | .003 |
| Headache | 179 | 30 | 16.8% | 89 | 11 | 12.4% | .374 |
| Fatigue | 179 | 17 | 9.5% | 89 | 4 | 4.5% | .227 |
| Dizziness | 179 | 13 | 7.3% | 89 | 2 | 2.2% | .155 |
| Dry mouth | 179 | 11 | 6.1% | 89 | 0 | 0.0% | .018 |
| Dysmenorrhoea | 67 | 4 | 6.0% | 41 | 4 | 9.8% | .475 |
| Pain in extremity | 179 | 9 | 5.0% | 89 | 1 | 1.1% | .173 |
| Vomiting | 179 | 9 | 5.0% | 89 | 6 | 6.7% | .580 |
| Constipation | 179 | 8 | 4.5% | 89 | 0 | 0.0% | .055 |
| Nausea | 179 | 8 | 4.5% | 89 | 8 | 9.0% | .172 |
| Nasopharyngitis | 179 | 7 | 3.9% | 89 | 2 | 2.2% | .722 |
| Abdominal pain upper | 179 | 6 | 3.4% | 89 | 5 | 5.6% | .514 |
| Diarrhoea | 179 | 6 | 3.4% | 89 | 0 | 0.0% | .183 |
| Irritability | 179 | 6 | 3.4% | 89 | 4 | 4.5% | .735 |
| Pharyngolaryngeal pain | 179 | 6 | 3.4% | 89 | 3 | 3.4% | 1.00 |
| Restlessness | 179 | 6 | 3.4% | 89 | 2 | 2.2% | 1.00 |
| Alanine aminotransferase increased | 179 | 5 | 2.8% | 89 | 0 | 0.0% | .174 |
| Dyspepsia | 179 | 5 | 2.8% | 89 | 1 | 1.1% | .667 |
| Epistaxis | 179 | 5 | 2.8% | 89 | 0 | 0.0% | .174 |
| Hepatic enzyme increased | 179 | 5 | 2.8% | 89 | 0 | 0.0% | .174 |
| Insomnia | 179 | 5 | 2.8% | 89 | 10 | 11.2% | .009 |
| Sinusitis | 179 | 5 | 2.8% | 89 | 0 | 0.0% | .174 |

Sponsor's Table 2.7.4.27 from summary-clin-safety document

The common adverse events for the two trials are listed separately in Table 7.1.4.3.2 since the trials differed in duration (6 vs. 3 weeks) and study population. For study HGIN, the adverse events that were statistically different between olanzapine and placebo included weight increased ($p = 0.014$) and somnolence ($p = 0.0006$). For study HGIU, the adverse events that were statistically different between olanzapine and placebo included weight increased ($p < 0.001$), increased appetite ($p < 0.001$), somnolence ($p < 0.001$) and sedation ($p = 0.011$). The adverse events and frequencies occurring in the olanzapine group between the two clinical trials were fairly similar though more patients in HGIU exhibited somnolence (25% vs. 17%), increased appetite (29% vs. 17%), sedation (22% vs. 15%), dry mouth (8% vs. 4%) and fatigue (14% vs. 3%)

Table 7.1.4.3.2 Adverse Events Occurring in > 2% of Patients with Olanzapine > 2x Placebo: HGIU and HGIN Clinical Trials

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | 6 Week Trial % Schizophrenia Patients | | 3 Week Trial % Bipolar Patients | |
| Adverse Event | Olanzapine (N = 72) | Placebo (N = 35) | Olanzapine (N = 107) | Placebo (N = 54) |
| Weight increased | 31%* | 9% | 29%* | 4% |
| Somnolence | 17%* | 3% | 25%* | 4% |
| Headache | 17% | 6% | 17% | 17% |
| Increased appetite | 17% | 9% | 29%* | 4% |
| Sedation | 15% | 6% | 22%* | 6% |
| Dizziness | 8% | 3% | 7% | 2% |
| Pain in extremity | 6% | 3% | 5% | 0 |
| Abdominal pain | 4% | 0 | 5% | 7% |
| ALT increase | 4% | 0 | - | - |
| AST increase | 4% | 1% | 1% | 0 |
| Constipation | 4% | 0 | 5% | 0 |
| Dry mouth | 4% | 0 | 8% | 0 |
| Fatigue | 3% | 3% | 14% | 6% |
| Diarrhea | 1% | 0 | 5% | 0 |
| Dyspepsia | - | - | 5% | 0 |
| Hepatic enzyme increased | 1% | 0 | 4% | 0 |
| Sinusitis | 1% | 0 | 4% | 0 |

From Tables HGIN.12.4, HGIN.14.27 and HGIU.12.4 clinical study reports
*p < 0.05

7.1.4.4 Common adverse events – further analysis

**Weight Gain**

Weight gain was a significant adverse event occurring in these clinical trials and is further analyzed and discussed in this section along with the weight data.

*HGIU + HGIN Acute Database*

In the HGIU + HGIN Acute Database, patients in the olanzapine treatment group had significantly greater weight gain and increase in BMI compared to the placebo group (see Table 7.1.4.4.1).

Table 7.1.4.4.1 Weight and BMI Data (LOCF): HGIN + HGIU Database

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | LS Mean Change | LS Mean Difference | P-value |
| Weight (kg) | Olanzapine | 177 | 66.03 | 17.93 | 3.90 | 2.72 | 3.68 | | |
| | Placebo | 88 | 67.63 | 17.24 | 0.24 | 2.16 | 0.01 | 3.66 | < 0.001 |
| BMI | Olanzapine | 177 | 23.91 | 6.01 | 1.22 | 1.01 | 1.11 | | |
| | Placebo | 88 | 23.98 | 5.67 | 0.05 | 0.91 | -0.07 | 1.17 | < 0.001 |

From Table 2.7.4.43 in summary-clin-safety document

The visit wise weight change for observed cases was similar to the LOCF analysis. The mean change at visit 6 was + 3.63 kg for olanzapine (n = 154) and + 0.08 kg for placebo (n = 67) (LS Mean Diff = 3.57, $p < 0.001$).

A $\geq$ 7% increase in body weight from baseline was considered a potentially clinically significant change. Seventy-seven (43.5%) patients in the olanzapine group and 6 (6.8%) of patients in the placebo group had a $\geq$ 7% increase in body weight ($p < 0.001$). Only 2 patients, both randomized to placebo, had a $\geq$ 7% decrease in body weight.

Since studies HGIN and HGIU were different with respect to types of patients and duration of the double-blind period (HGIN 6 weeks, HGIU 3 weeks), the weight and BMI data were also evaluated separately:

Table 7.1.4.4.2. Weight and BMI Data: Study HGIU

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | LS Mean Change | LS Mean Difference | P-value |
| Weight (kg) | Olanzapine | 105 | 65.33 | 20.55 | 3.66 | 2.18 | 3.51 | | |
| | Placebo | 54 | 66.83 | 17.55 | 0.30 | 1.67 | 0.16 | 3.36 | < 0.001 |
| BMI | Olanzapine | 105 | 24.21 | 6.82 | 1.18 | 0.85 | 1.15 | | |
| | Placebo | 54 | 24.05 | 5.44 | 0.02 | 0.62 | 0.00 | 1.15 | < 0.001 |

From Table HGIU.12.44 in study report

A $\geq$ 7% increase in body weight from baseline was considered a potentially clinically significant change. Forty-four (41.9%) patients in the olanzapine group and 1 (1.9%) patient in the placebo group had a $\geq$ 7% increase in body weight ($p < 0.001$). No patients in the study had a $\geq$ 7% decrease in body weight.

Table 7.1.4.4.3. Weight and BMI Data: Study HGIN

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | LS Mean Change | LS Mean Difference | P-value |
| Weight (kg) | Olanzapine | 72 | 67.04 | 13.31 | 4.26 | 3.33 | 4.22 | | |
| | Placebo | 34 | 68.91 | 16.93 | 0.13 | 2.80 | 0.08 | 4.13 | < 0.001 |
| BMI | Olanzapine | 72 | 23.45 | 4.59 | 1.39 | 1.21 | 1.37 | | |
| | Placebo | 34 | 24.02 | 6.12 | -0.05 | 1.03 | -0.07 | 1.44 | < 0.001 |

From Table HGIN.12.42 in study report

The results for the OC analysis for change in weight and BMI were similar to the LOCF analysis. At end of study, patients in the olanzapine group (n = 50) gained 4.95 kg from baseline and patients in the placebo group (n = 15) gained 0.61 kg [LS mean diff = 4.65, $p < 0.001$]. BMI increased by 1.56 in the olanzapine group and decreased by 0.04 in the placebo group [LS mean diff = 1.62, $p < 0.001$].

A $\geq$ 7% increase in body weight from baseline was considered a potentially clinically significant change. Thirty-three (45%) patients in the olanzapine group and 5 (14.7%) of patients in the placebo group had a $\geq$ 7% increase in body weight ($p = 0.002$). Only 2 patients in the study, both randomized to placebo, had a $\geq$ 7% decrease in body weight.

Only 1 of the 8 discontinuations due to adverse events was due to weight gain in the HGIU + HGIN Acute Database (4.5 kg increase over ~15 days).
Unfortunately, insufficient data were collected during the follow-up visits to adequately address weight loss after patients completed the clinical trial (if they switched to a different antipsychotic). Though many of the investigators noted that the adverse event of "weight gain" had resolved at some of the follow-up visits, no actual weights were obtained for the majority of patients (or at least not recorded in the CRFs).

*Overall Combined Database*
Though no placebo comparison is available in this database, weight change over longer duration of time could be evaluated in general terms. Similar to the acute data, weight did appear to increase over time. This patient population (adolescents) are expected to increase in height and weight during this developmental period, however, the increases in weight are well above what would be considered expected (see Section 7.1.9 – Assessment of Effect on Growth).

Table 7.1.4.4.4. Weight and BMI Data (LOCF): Overall Combined Database

| | | | Baseline | | Change to Endpoint | | |
|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | P-value |
| Weight (kg) | Bipolar | 224 | 68.58 | 21.21 | 7.63 | 6.62 | < 0.001 |
| | Schizophrenia | 226 | 65.71 | 13.30 | 7.07 | 6.53 | < 0.001 |
| | Overall | 450 | 67.13 | 17.72 | 7.35 | 6.58 | < 0.001 |
| BMI | Bipolar | 216 | 24.92 | 7.34 | 2.37 | 2.39 | < 0.001 |
| | Schizophrenia | 223 | 22.40 | 4.17 | 2.24 | 2.25 | < 0.001 |
| | Overall | 439 | 23.64 | 6.07 | 2.31 | 2.31 | < 0.001 |

From Table 2.7.4.45 in summary-clin-safety document

Sixty-five percent of patients in the Overall Combined Database gained $\geq$ 7% body weight.

The Sponsor provided a summary of weight change by visit for observed cases for the Overall Combined Database (see Appendix 10.9). For the 131 patients who completed visits > 25 and $\leq$ 32 weeks, the mean increase in weight was 10.8 kg ($p < 0.001$ compared to baseline).

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months. The patient who gained 21.8 kg did so over a period of 3 months.

For those patients in the Overall Combined Database who participated in HGIU or HGIN, the weight gain for the acute phase of these trials was also evaluated to determine whether they

gained a greater amount of weight early in the trial. These data were readily available for only 10 patients (some of the patients had been randomized to placebo and are not included here). The mean weight gain at the end of the double-blind phase of the study (or early termination) was 4.8 ± 2.6 kg, similar to the overall mean weight gain of 3.9 ± 2.7 kg in the acute database (see Table 7.1.4.4.1).

*Weight – Subgroup Analyses*
Because of the different duration of dosing in the HGIN and HGIU acute phases, these data were reviewed separately for each study.
The Sponsor evaluated weight changes for the subgroups gender and age (< 15, ≥ 15 years) for the adverse event "weight increased". Approximately 30% of females and males had this adverse event in the olanzapine group in both HGIU and HGIN acute studies while this adverse event was ~4% for the placebo group (with the exception of females in HGIN). No significant differences were noted between the gender subgroups (see Appendix 10.9). For the age subgroups, 28-40% had the adverse event "weight increased" in the olanzapine group compared to 0 – 14% in the placebo group. No significant differences were noted between the age subgroups (see Appendix 10.9).

Mean change in weight (kg) was also evaluated between the subgroups gender and age. These data were not included in the study report for HGIU, the Sponsor has been asked to submit these data (per the study report, only those data where results were significant were included). Data from HGIN are included in Appendix 10.9. Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine.

The Sponsor also did not include mean change in weight for the age subgroup for the HGIN + HGIU Acute Database (per the study reports, only those data where results were significant were included). The Sponsor has been asked to provide these data. In the HGIN + HGIU Acute Database, significant treatment-by-gender differences were noted (see Table 7.1.4.4.5). However, these findings are likely due to the differences in the placebo group since the weight gain (mean change to endpoint) in the olanzapine group was similar between females and males.

Table 7.1.4.4.5 Sponsor's Table. Mean Change in Weight (kg) – Gender Subgroup Analysis: HGIU + HGIN Acute Database

By Subgroup: Gender

| | | | | Baseline | | Change to Endpoint | | | LSMean | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Vital Signs | Subgroup | N | Therapy | n | Mean | Std | Mean | Std | LSMean | Diff. | *P-value | **P-value |
| Weight in Kg | Female | 106 | Olz | 66 | 61.79 | 16.68 | 3.66 | 2.65 | 3.63 | 3.05 | <.001 | .083 |
| | | | Placebo | 40 | 62.83 | 13.65 | 0.55 | 2.27 | 0.59 | | | |
| | Male | 159 | Olz | 111 | 68.54 | 18.25 | 4.05 | 2.76 | 3.79 | 4.16 | <.001 | |
| | | | Placebo | 48 | 71.64 | 18.97 | -0.03 | 2.05 | -0.36 | | | |

Table 2.7.4.70 in Summary-clin-safety

The Sponsor was asked to evaluate the relationship of weight gain to baseline BMI. The Sponsor evaluated 4 BMI subgroups: $< 18$, $\geq 18$ and $< 25$, $\geq 25$ and $< 30$, $\geq 30$. There was a similar magnitude of weight gain by patients in each of these categories (Table 7.1.4.4.6). The percentage of patients who had a $\geq 7\%$ weight gain was greatest in the $< 18$ BMI group and least in the $\geq 30$ BMI group (Table 7.1.4.4.7).

Table 7.1.4.4.6 Sponsor's Table. Mean Change in Weight by Baseline BMI: HGIN + HGIU Acute Database

**Table 1.** **Mean Change in Weight (kg) from Baseline to Endpoint (LOCF) by Baseline BMI**
**Acute Placebo-Controlled Combined Database**

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| BMI (Baseline) | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Difference | *P-value |
| BMI<18 | Olz | 15 | 45.68 | 5.62 | 4.21 | 2.29 | 4.39 | 3.51 | .005 |
| | Placebo | 10 | 48.19 | 6.54 | 0.70 | 2.89 | 0.88 | | |
| 18<=BMI<25 | Olz | 107 | 58.84 | 9.37 | 3.52 | 2.53 | 3.24 | 3.12 | <.001 |
| | Placebo | 49 | 61.18 | 8.41 | 0.50 | 2.16 | 0.12 | | |
| 25<=BMI<30 | Olz | 30 | 76.31 | 10.29 | 4.44 | 3.61 | 4.25 | 3.93 | <.001 |
| | Placebo | 19 | 77.50 | 9.32 | -0.09 | 1.41 | 0.32 | | |
| BMI>=30 | Olz | 25 | 96.66 | 15.02 | 4.71 | 2.33 | 3.93 | 5.59 | <.001 |
| | Placebo | 10 | 99.93 | 16.42 | -0.90 | 2.37 | -1.66 | | |

Table 7.1.4.4.7 Sponsor's Table. PCS Weight Changes by Baseline BMI: HGIN + HGIU Acute Database

**Table 2.** **Potentially Clinically Significant Weight Changes (7% Weight Gain)**
**By Baseline BMI**
**Acute Placebo-Controlled Combined Database**

| Vital Signs | BMI (Baseline) | Direction | Therapy | N | n | % | *P-value |
|---|---|---|---|---|---|---|---|
| Weight in kg | BMI<18 | Gain | Olz | 15 | 12 | 80.0% | .005 |
| | | | Placebo | 10 | 2 | 20.0% | |
| | 18<=BMI<25 | Gain | Olz | 107 | 49 | 45.8% | <.001 |
| | | | Placebo | 49 | 4 | 8.2% | |
| | 25<=BMI<30 | Gain | Olz | 30 | 12 | 40.0% | .001 |
| | | | Placebo | 19 | 0 | 0.0% | |
| | BMI>=30 | Gain | Olz | 25 | 4 | 16.0% | .303 |
| | | | Placebo | 10 | 0 | 0.0% | |

The Sponsor was also asked to provide data regarding the numbers of patients at baseline and endpoint who were obese (BMI > 30) and whether there were differences between the treatment groups. At baseline, 14% (25/177) of patients in the olanzapine group and 11.4% (10/88) patients in the placebo group had BMI > 30. At endpoint, 18.6% of patients in the olanzapine group and 11.4% of patients in the placebo group had BMI > 30 ($p = 0.158$, NS).

The Sponsor was also asked to provide an analysis of laboratory parameters for patients who gained > 3.9 kg (mean weight gain). The major differences between olanzapine and placebo in this subgroup are noted in Table in Appendix 10.9. The LS mean change appears to be fairly similar between this subgroup and the entire study population except for a larger increase in CPK (LS mean diff 39 vs. 16 U/L) and triglycerides (LS mean diff 54 vs. 34 mg/dL) in the subgroup with > 3.9 kg weight gain. Of course, the entire population includes this subgroup – the Sponsor was not asked to provide laboratory data for patients with $\leq$ 3.9 kg weight gain.

### 7.1.5 Less Common Adverse Events

**Hyperprolactinemia**
The summary of the prolactin laboratory data is included in Sections 7.1.6 (Laboratory Findings) and 7.1.6.3 (Special Assessments). The adverse event tables were reviewed for any terms that might be related to hyperprolactinemia. In the HGIU + HGIN Acute Database, gynecomastia occurred in 1 (0.9%) patient in the olanzapine group and no patients in the placebo group and amenorrhea occurred in no patients in the olanzapine group and 1 (2.4%) patient in the placebo group.

The Overall Combined Database was evaluated since adverse events such as gynecomastia are not expected to occur with acute use but rather more long term use of antipsychotics. In the Overall Combined Database, gynecomastia occurred in 7 (4.3%) of patients (all from schizophrenia trials), galactorrhea occurred in 2 (3.1%) patients with schizophrenia and 1 (1%) patient with bipolar disorder and amenorrhea occurred in 1 (1.5%) patient with schizophrenia and 1 (1%) patient with bipolar disorder. The Sponsor has been asked to provide narrative summaries for all cases of gynecomastia – it is unknown whether this adverse event occurred in both male and female patients. If cases of gynecomastia occurred exclusively in female patients, it would be important to differentiate this adverse event from usual adolescent female physical development. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

**Extrapyramidal Symptoms**
Due to the difference in frequency of EPS occurring in patients with schizophrenia and bipolar disorder taking antipsychotics, these data are summarized separately for each diagnostic group from the individual study reports (HGIN and HGIU).

Data for EPS is from a number of sources including rating scales (primarily the BAS and SAS), use of anticholinergic medications (though benzodiazepines may be used to treat EPS, they are more commonly used for managing psychiatric symptoms) and adverse events.

HGIN
Mean change from baseline for the BAS, SAS and AIMS are in Table 7.1.5.1. There were no statistically significant differences between the olanzapine and placebo groups at baseline (data not shown). In both the olanzapine and placebo groups, the mean change to endpoint was a decrease in rating scale score. This is not necessarily surprising depending on which

antipsychotics patients may have been taking during screening and the length of the washout period prior to obtaining the baseline rating.

Table 7.1.5.1. Sponsor's Table. AIMS, BAS and SAS Rating Scale Scores: HGIN

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| EPS Variables | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Difference | *P-value |
| AIMS Non-Global Total(1-7) | Olanzapine | 72 | 0.38 | 0.94 | -0.18 | 0.84 | -0.18 | 0.02 | .897 |
| | Placebo | 35 | 0.54 | 1.50 | -0.20 | 0.72 | -0.21 | | |
| BRNS 4:Global Assessment of Akathisia | Olanzapine | 72 | 0.31 | 0.66 | -0.15 | 0.69 | -0.15 | 0.05 | .747 |
| | Placebo | 35 | 0.31 | 0.63 | -0.20 | 0.76 | -0.20 | | |
| Simpson-Angus Total(1-10) | Olanzapine | 72 | 0.81 | 1.87 | -0.22 | 1.51 | -0.24 | 0.33 | .260 |
| | Placebo | 35 | 0.97 | 2.41 | -0.54 | 1.34 | -0.57 | | |

The Sponsor provided a categorical analysis of the proportion of patients exhibiting treatment-emergent parkinsonism, akathisia or dyskinetic symptoms using these rating scales. Although no statistical differences were noted between the olanzapine and placebo groups, it is unclear how this treatment-emergent EPS was defined. The Sponsor has been asked to provide an analysis for the individual items of these scales.

Only 5 patients in study HGIN (acute phase) had concomitant anticholinergic medication use: 4.2% (3/72) in the olanzapine group and 5.7% (2/35) in the placebo group (p = 0.661).

The adverse event tables were reviewed for any terms that might be related to an extrapyramidal symptom adverse event. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Table 7.1.5.2. Adverse Events Potentially Related to EPS: HGIN

| | Olanzapine N = 72 | Placebo N = 35 |
|---|---|---|
| Akathisia | 2 (2.8%) | 2 (5.7%) |
| Drooling | 2 (2.8%) | 0 |
| Restlessness | 2 (2.8%) | 0 |
| Dyskinesia | 1 (1.4%) | 0 |
| Muscle twitching | 1 (1.4%) | 0 |
| Musculoskeletal stiffness | 1 (1.4%) | 0 |
| Cogwheel rigidity | 0 | 1 (2.9%) |
| Tremor | 0 | 1 (2.9%) |

From Sponsor Table HGINB.14.27 in study report

Open-Label Phase HGIN

Noteworthy EPS-related adverse events occurring in the open-label phase of HGIN included oculogyration (n = 1, 0.4%) and opisthotonus (n = 1, 0.4%). The Sponsor has been asked to provide narrative summaries for these events.

Since tardive dyskinesia is a risk with longer duration of antipsychotic use, the AIMS scores were evaluated from the open-label phase of HGIN. The mean change to endpoint on the AIMS was -0.12 ± 0.94. The incidence of "treatment emergent" dyskinesia was 2.6% - again, it is

unclear how this was defined. Because this analysis was LOCF, the Sponsor will be asked to perform a similar analysis (as well as analyses for individual items) for completers since time on therapy is a risk factor for tardive dyskinesia.

HGIU

Mean change from baseline for the BAS, SAS and AIMS are in Table 7.1.5.3. There were no statistically significant differences between the olanzapine and placebo groups at baseline (data not shown) – though the mean baseline scores were numerically higher in the olanzapine group.

Table 7.1.5.3 Sponsor's Table. AIMS, BAS and SAS Rating Scale Scores: HGIU

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| EPS Variables | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Difference | *P-value |
| AIMS Non-Global Total(1-7) | Olanzapine | 105 | 0.16 | 0.90 | -0.10 | 0.71 | -0.12 | -0.10 | .289 |
| | Placebo | 54 | 0.04 | 0.19 | 0.00 | 0.19 | -0.02 | | |
| BRNS 4:Global Assessment of Akathisia | Olanzapine | 105 | 0.20 | 0.49 | -0.04 | 0.44 | -0.06 | -0.09 | .264 |
| | Placebo | 54 | 0.09 | 0.35 | 0.06 | 0.60 | 0.03 | | |
| Simpson-Angus Total(1-10) | Olanzapine | 105 | 0.24 | 0.89 | 0.02 | 0.93 | 0.02 | 0.04 | .769 |
| | Placebo | 54 | 0.07 | 0.33 | -0.02 | 0.14 | -0.02 | | |

As with study HGIN, the Sponsor provided a categorical analysis of the proportion of patients exhibiting treatment-emergent parkinsonism, akathisia or dyskinetic symptoms using these rating scales. Although no statistical differences were noted between the olanzapine and placebo groups, it is unclear how this treatment-emergent EPS was defined.

Only 5 patients in study HGIU (acute phase) had concomitant anticholinergic medication use, all in the olanzapine group: 4.7% (5/107) in the olanzapine group and 0% (0/54) in the placebo group (p = 0.169).

The adverse event tables were reviewed for any terms that might be related to an extrapyramidal symptom adverse event. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Table 7.1.5.3. Adverse Events Potentially Related to EPS: HGIU

| | Olanzapine N = 107 | Placebo N = 54 |
|---|---|---|
| Restlessness | 4 (3.7%) | 2 (3.7%) |
| Musculoskeletal stiffness | 3 (2.8%) | 0 |
| Tremor | 2 (1.9%) | 0 |
| Akathisia | 1 (0.9%) | 0 |
| Drooling | 1 (0.9%) | 0 |
| Dysarthria | 1 (0.9%) | 0 |
| Dyskinesia | 1 (0.9%) | 0 |
| Muscle tightness | 1 (0.9%) | 0 |
| Muscle twitching | 1 (0.9%) | 0 |
| Salivary hypersecretion | 1 (0.9%) | 0 |

From Sponsor's table HGIU.14.30 in study report

Open-Label Phase HGIU
Noteworthy EPS-related adverse events occurring in the open-label phase of HGIU included oculogyration (n = 1, 0.4%). The Sponsor has been asked to provide narrative summaries for this event.

Since tardive dyskinesia is a risk with longer duration of antipsychotic use, the AIMS scores were evaluated from the open-label phase of HGIU. The mean change to endpoint on the AIMS was -0.03 ± 0.30. The incidence of "treatment emergent" dyskinesia was 0.7% - again, it is unclear how this was defined. Because this analysis was LOCF, the Sponsor will be asked to perform a similar analysis (as well as analyses for individual items) for completers since time on therapy is a risk factor for tardive dyskinesia.

**Suicidality**

The Sponsor included an analysis of suicide-related events, specifically the incidence of possible suicidal behavior or ideation, in the HGIN + HGIU Acute Database. These data were summarized for the Overall Combined Database. The following suicide-related categories were included: completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation, self-injurious behavior (intent unknown), not enough information (fatal), not enough information (non-fatal).

The analysis for events included categorizing suicidal behaviors as follows: suicidal behavior or ideation (includes completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation), suicidal behavior (includes completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior), suicidal ideation (includes suicidal ideation) and possible suicidal behavior or ideation (includes all categories). The searches included the subsequent visit (if available) after stopping treatment.

To identify cases, all preferred AE term, verbatim AE terms and comments of clinical trial data were searched for the following: accident, attempt, burn, cut, drown, gas, gun, hang, hung, immolat, injur, jump, monoxide, mutilat, overdos, self-damag, self-harm, self-inflict, self-damage, self harm, shoot, slash, suic, poison, asphyxiation, suffocation, firearm. All blinded patient listings were independently reviewed by two members of the Sponsor's medical staff "trained to evaluate suicide-related events". If a discrepancy arose, the case was discussed between them and, if necessary, a third reviewer was consulted to achieve consensus.

HGIN + HGIU Acute Database
Three possible suicidal behaviors or ideation events were identified, all three occurred in study HGIU. Two events occurred in patients treated with olanzapine (self-injurious behavior [intent unknown] in a 14.2 YOWF, suicidal ideation in a 14.6 YOWF) and one occurred in a patient receiving placebo (self-injurious behavior [intent unknown] in a 13.9 YOWM). The Sponsor's brief description of the event (from the case narratives) are provided in Appendix 10.10. No statistical differences were noted between treatment groups. The risk ratio was calculated as 1.01 (95% CI [0.09, 10.88], p = 1.000). Additional analyses (Mantel-Haenszel risk diff) also did not show statistical differences between the olanzapine and placebo groups (data not shown).

Overall Combined Database
Twenty-four cases of possible suicidal behaviors or ideation were identified – two of these events occurred in olanzapine-treated patients during the acute phase of study HGIU. The events were as follows: completed suicide (n = 0), suicide attempt (n = 2), preparatory acts toward imminent suicidal behavior (n = 2), suicidal ideation (n = 13), self-injurious behavior (intent unknown) (n = 6), not enough information (fatal) (n = 0), not enough information (non-fatal) (n = 1). The number of days to the event ranged from 4 to 214 (mean/SD = 73.5 ± 57.4 days, median = 57 days). The cases occurred in the following trials: HGIN (4), HGIU (13), HGMF (2), LOAY (5).

It is more difficult to ascertain whether a medication is associated with this adverse event in this database due to lack of a comparison group as well as the presence of a psychiatric disorder that can be associated with suicidal behaviors (esp. bipolar disorder). Of the 24 cases of suicide-related behaviors, 15 (62%) occurred in bipolar patients.

This reviewer also evaluated the individual item "suicidal ideation" in the Children's Depression Rating Scale-Revised. Though rating scales may not capture this specific adverse event, these data were reviewed to see if any trends in worsening occurred on the suicide-related item. For the CDRS[2], most patients scored a "1" at baseline. For patients who scored > 1, most showed improvement (decrease in score). Two patients in the placebo group had worsening on this item; one patient had an increase from a 1 to a 3 and another from a 2 to a 3 severity rating. Two patients in the olanzapine group had worsening on this item; one patient had an increase from a 2 to a 3 and another from a 2 to a 4 severity rating. Of note, 3 patients had a severity rating of 7 at baseline (all were randomized to olanzapine). The Sponsor will be asked to provide details regarding inclusion of these patients in the clinical trial.

**Hostility and Aggression Adverse Events**
Similar to the strategy used to identify possible suicide-related behaviors, the Sponsor identified patient cases for hostility and aggression. The following categories were used for these cases: aggressive behavior with physical harm directed toward another person, aggressive behavior with physical harm directed toward animals, aggressive behavior with physical harm directed toward objects, aggressive behavior with nonspecific information, aggressive behavior with indirect or no potential for direct physical harm, hostility without aggression, anger without hostility or aggressive behavior, violent ideation with no anger, hostility or aggressive behavior, and does not meet case definition.

In the HGIN + HGIU Acute Database, 7 cases were identified (1 case in HGIN, 6 cases in HGIU). Four cases occurred in patients in the olanzapine treatment groups. The olanzapine

2 CDRS-R Suicidal ideation item scoring: 1 = understands the word "suicide" but does not apply the term to himself/herself, 2 = sharp denial of suicidal thoughts, 3 = has thoughts about suicide, or of hurting himself/herself (if he/she does ont understand the concept of suicide), usually when angry; 4 = intermediate rating, not anchored; 5 = has recurrent thoughts of suicide; 6 = intermediate rating, not anchored; 7 = has made a suicide attempt within the last month or is actively suicidal

cases included aggressive behavior with physical harm directed toward another person, aggressive behavior with nonspecific information, hostility without aggression and anger without hostility or aggressive behavior. The placebo cases included aggressive behavior with physical harm directed toward another person, aggressive behavior with nonspecific information, and hostility without aggression. Given the patient population, it is surprising that not more cases of hostility or aggression were identified. However, overtly hostile patients or patients with a strong history of hostility or aggression would be less likely to be enrolled in a clinical trial. No statistical differences were noted between treatment groups (data not shown).

In the Overall Combined Database, 23 cases of possible hostility or aggression-related events were identified: HGIN (5), HGIU (13), HGMF (1), LOAY (4). It is not unexpected for hostility or aggressive behaviors to be exhibited by patients with inadequately controlled symptoms of schizophrenia or bipolar disorder.

### 7.1.6 Laboratory Findings

The data from the HGIN + HGIU Acute Database was the primary source of data reviewed. When individual patient labs were being reviewed, it was noticed that many labs were missing from the study reports – most commonly the last (third) page of labs for many patients. Though all of the lab data appeared to be present in the JMP datasets, it was sometimes more difficult to look for trends or other signals using the dataset than the individual lab profile.

#### 7.1.6.1 Overview of laboratory testing in the development program

During the acute 3 week trial labs were obtained as follows:
Clinical chemistry, electrolytes – baseline and weekly during trial
Lipids - baseline and weekly during trial; fasting glucose/lipids were obtained at baseline and end of study
Hematology - baseline and weekly during trial
Urinalysis – baseline and end of study
TSH – screening only
Prolactin – baseline and end of study
HbA1c – screening and end of study for patients with known diabetes
Hepatitis screen, urine drug screen, pregnancy test – screening only

#### 7.1.6.2 Standard analyses and explorations of laboratory data

##### *7.1.6.2.1 Analyses focused on measures of central tendency*

The mean change from baseline to endpoint for the laboratory evaluations for HGIN + HGIU Acute Database is included in Appendix 10.11. Statistically significant decreases in lab parameters in the olanzapine group compared to placebo included hematocrit, hemoglobin, erythrocyte count, basophils, mean cell volume, albumin, total bilirubin and direct bilirubin – though these mean changes were small. Statistically significant increases in lab parameters in

the olanzapine group compared to placebo included ALT, AST, GGT, fasting glucose, cholesterol, LDL cholesterol, triglycerides, uric acid, prolactin, eosinophils and urea nitrogen.

The mean change from baseline to endpoint for selected laboratory parameters is in Table 7.1.6.2.1.1 below. For ALT and AST, the standard deviation at *baseline* in these laboratory parameters for the olanzapine group was very large (SD > mean) compared to the SD at baseline in the placebo group. For change to endpoint, the SD is still quite large in the olanzapine group compared to the placebo group indicating considerable variability and some significant increases in these parameters. The fasting glucose, triglyceride and cholesterol data were converted from SI units to the more conventional mg/dL units in this table.

It should be noted that there are limitations in evaluating the mean change from baseline to endpoint for the prolactin data. Since the washout period in studies HGIN and HGIU could be as short as 2 days, some baseline prolactin concentrations were increased likely due to the effect of the prior antipsychotic. Interpretation of the effect of olanzapine on prolactin concentration is difficult if the analysis includes patients with an elevated baseline. Elevated baseline prolactin was more common in study HGIN, as would be expected. A cursory review of the JMP dataset found that approximately 17% of patients in HGIN had a baseline prolactin > 30 ng/ml (maximum baseline prolactin = 65 ng/ml). The Sponsor will be asked to perform an analysis for the subset of patients with a baseline prolactin within the normal range. Of note, the Sponsor did acknowledge this limitation and provided some additional analyses (see Section 7.1.6.3 – Special Assessments).

Table 7.1.6.2.1.1. Select Laboratory Analytes of Interest: HGIN + HGIU Acute Database

| | | | Baseline | | **Change to Endpoint** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | **Mean** | Std | LS Mean Change | LS Mean Difference | P-value |
| Alkaline Phosp (U/L) | Olanzapine | 175 | 152.3 | 82.3 | **-1.3** | 25.6 | -2.7 | | |
| | Placebo | 87 | 138.7 | 86.9 | **-4.0** | 16.6 | -5.3 | 2.6 | 0.396 |
| ALT (U/L) | Olanzapine | 175 | 24.1 | 45.9 | **19.95** | 54.84 | 28.11 | | |
| | Placebo | 87 | 20.4 | 13.0 | **-3.08** | 11.69 | 5.13 | 22.98 | < 0.001 |
| AST (U/L) | Olanzapine | 175 | 24.5 | 29.9 | **6.43** | 26.41 | 9.89 | | |
| | Placebo | 87 | 23.6 | 8.5 | **-2.47** | 7.51 | 0.98 | 8.91 | 0.002 |
| GGT (U/L) | Olanzapine | 175 | 19.0 | 12.3 | **7.47** | 20.02 | 7.73 | | |
| | Placebo | 87 | 17.7 | 8.5 | **-0.43** | 5.96 | -0.16 | 7.89 | < 0.001 |
| Glucose, fasting (mg/dL)* | Olanzapine | 135 | 88.1 | 9.91 | **2.70** | 10.4 | 2.70 | | |
| | Placebo | 64 | 89.7 | 10.27 | **-2.88** | 10.1 | -3.06 | 5.59 | < 0.001 |
| Cholesterol (mg/dL)* | Olanzapine | 175 | 161.0 | 32.0 | **13.1** | 22.78 | 12.74 | | |
| | Placebo | 87 | 160.2 | 32.8 | **-1.16** | 24.32 | -1.54 | 14.29 | < 0.001 |
| Triglycerides (mg/dL)* | Olanzapine | 175 | 104.4 | 58.4 | **29.2** | 80.53 | 26.55 | | |
| | Placebo | 87 | 110.6 | 64.6 | **-4.42** | 54.87 | -6.19 | 33.63 | < 0.001 |
| Prolactin (mcg/L) | Olanzapine | 163 | 14.06 | 9.92 | **11.44** | 14.52 | 10.51 | | |
| | Placebo | 80 | 14.95 | 11.86 | **-0.16** | 10.69 | -1.15 | 11.66 | < 0.001 |

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113

Since urinalysis for ketones, glucose and protein is noted as 1+, 2+ etc., no mean change from baseline was provided for these parameters. It was noted, however, that there were no patients with PCS changes in these parameters (defined as increase $\geq$ 2) in either the olanzapine or placebo groups. Only 1 patient exhibited a PCS change in urinalysis – protein in the Overall Combined Database.

In the HGIN + HGIU Acute Database, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes). There was no change from baseline to endpoint in this parameter – not unexpected since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months. In the Overall Combined Database, 23 patients had baseline HbA1c and there was no change at endpoint (the duration of study participation is not known for these patients).

*7.1.6.2.2 Analyses focused on outliers or shifts from normal to abnormal*

Percentage of patients with statistically significant treatment-emergent abnormal high laboratory values at any time (HGIN + HGIU Acute Database).
AST –27.6% of olanzapine and 3.8% of placebo-treated patients ($p < 0.001$)
ALT - 38.6% of olanzapine and 2.5% of placebo-treated patients ($p < 0.001$)
GGT – 10.1% of olanzapine and 1.2% of placebo-treated patients ($p = 0.008$)
Total bilirubin –0% of olanzapine and 7.1% of placebo-treated patients ($p = 0.001$)
Albumin –6.3% of olanzapine and 23.2% of placebo-treated patients ($p = 0.002$)
Fasting glucose – 3.7% of olanzapine and 3.2% of placebo-treated patients (p = NS)
Cholesterol –19.7% of olanzapine and 3.9% of placebo-treated patients ($p = 0.001$)
Triglycerides –54.7% of olanzapine and 19.6% of placebo-treated patients ($p < 0.001$)
HDL –9.7% of olanzapine and 1.2% of placebo-treated patients ($p = 0.014$) [shift to low were NS between groups]
Further analyses for shifts in fasting glucose, cholesterol, and triglycerides is included in Section 7.1.6.3 – Special Assessments.

*7.1.6.2.3 Marked outliers and dropouts for laboratory abnormalities*

In the HGIN + HGIU Acute Database, six patients discontinued due to elevations in ALT and/or AST. See Table 7.1.3.1.1 in Section 7.1.3.1 (Adverse events associated with dropouts).

The Sponsor did not provide a summary of marked outliers in the laboratory analysis. The individual patient labs and/or JMP datasets were reviewed from HGIN and HGIU study reports to identify marked outliers. It should be noted that the marked outliers in Table 7.1.6.2.3.1. may include lab values that were less than the potentially clinically significant (PCS) abnormalities defined by the Sponsor. For example, the cholesterol PCS was defined as > 15.516 mmol/L (> 599 mg/dL), whereas the values noted as marked outliers were usually lower than this PCS value. Of note, there was no defined PCS for triglycerides.

Table 7.1.6.2.3.1 includes the marked outlier (in bold font), other related analytes at the same timepoint, end of acute study value for the marked outlier (resolution?) and a column for comments which included any additional values for the marked outlier in the open-label phase. Individual patient profiles were not readily available so it is not known if resolutions in marked outlier values were related to decreases in olanzapine dose.

Table 7.1.6.2.3.1. Marked Outliers for Laboratory Values – HGIN and HGIU

| | | | **Marked Outlier** Related Analytes at Same Timepoint *(Italics = values > ULN)* | | | |
|---|---|---|---|---|---|---|
| Patient | Lab Analyte | Reference Range* | Baseline | Highest | End of Study | Comments |
| HGIU 005-501 | Triglycerides<br>Cholesterol<br>LDL | 31.8 – 124.8 mg/dL<br>129.7 – 203.9 mg/dL<br>64.1 – 132.8 mg/dL | 102.6<br>125.9<br>68.7 | **1237** (v.4)<br>*220.8*<br>NA | *389.4*<br>*205.8*<br>90.0 | TG = *160* at v.307 EOS |
| HGIU 012-1203 | ALT<br>AST<br>TBili<br>GGT | 6 – 34 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 33 U/L | 18<br>19<br>0.41<br>18 | **325** (v.5)<br>**148**<br>0.29<br>*53* | *230* (150 repeat)<br>*92* (51 repeat)<br>0.29 (0.18 repeat)<br>*48* (52 repeat) | ALT = *48*, AST = 24 at v. 501 (follow-up) |
| HGIU 012-1207 | ALT<br>AST<br>TBili<br>GGT | 6 – 34 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 33 U/L | 45<br>49<br>0.53<br>30 | **147** (v.4)<br>*60*<br>0.41<br>**163** | **147**<br>60<br>0.41<br>**163** | None |
| HGIU 013-1303 | Triglycerides<br>Cholesterol<br>LDL | 38.9 – 123.9 mg/dL<br>124.7 – 211.6 mg/dL<br>59.1 – 136.7 mg/dL | 110.6<br>178.8<br>123.9 | **261.9** (v.5)<br>179.5<br>*95.7* | **261.9**<br>179.5<br>95.7 | TG = 111 at v.306 |
| HGIU 019-1901 | Creatine Phosphokinase | 0 – 169 U/L | 83 | **256** (v.5) | *256* | CK = 168 at v. 301 (repeat 72) |
| HGIU 020-2007 | Triglycerides<br>Cholesterol<br>LDL | 38.9 – 123.9 mg/dL<br>124.7 – 211.6 mg/dL<br>59.1 – 136.7 mg/dL | 67.2<br>149.8<br>98.8 | **536.3** (v.4)<br>165.6<br>NA | *365.5*<br>*231.7*<br>120.8 | *TG = 103 at v. 307* |
| HGIU 020-2011 | ALT<br>AST<br>TBili<br>GGT | 6 – 34 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 33 U/L | 22<br>19<br>0.41<br>11 | **124** (v.6)<br>*87*<br>0.29<br>27 | **124**<br>*87*<br>0.29<br>27 | ALT = 11 at v. 309 |
| HGIU 026-2607 | Triglycerides<br>Cholesterol<br>LDL | 31.8 – 124.8 mg/dL<br>129.7 – 203.9 mg/dL<br>64.1 – 132.8 mg/dL | 59.3<br>201.5<br>125.9 | **324.8** (v.4)<br>171.8<br>62.9 | 179.6<br>164.9<br>84.9 | TG = 72 at v. 310 |
| HGIU 027-2704 | Creatine Phosphokinase | 0 – 363 U/L | 326 | **619** (v.6) | **619** | CK = 261 at v. 307 |
| HGIU 031-3103 | ALT<br>AST<br>TBili<br>GGT | 6 – 43 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 16<br>19<br>1<br>13 | **135** (v.4)<br>35<br>0.82<br>**153** | *75*<br>*62*<br>0.53<br>*87* | ALT = 33/25 at v. 302 |
| HGIU 035-3503 | Triglycerides<br>Cholesterol<br>LDL | 38.9 – 123.9 mg/dL<br>124.7 – 211.6 mg/dL<br>59.1 – 136.7 mg/dL | 62.8<br>164.9<br>120.8 | **317.7** (v.4)<br>167.6<br>74.9 | 100<br>203.9<br>*141.7* | None |
| HGIU 035-3518 | Creatine Phosphokinase | 0 – 187 U/L | 55 | **257** (v.6) | **257** | CK = 56 at v. 310 |
| HGIU | ALT | 6 – 43 U/L | 43 | **208** (v.6) | **208** | ALT = *99* at |

| | | | | | | |
|---|---|---|---|---|---|---|
| 036-3607 | AST<br>TBili<br>GGT | 10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 27<br>0.71<br>36 | *91*<br>0.29<br>*65* | *91*<br>0.29<br>*65* | v. 307 |
| HGIU 720-7202 | Creatine Phosphokinase | 0 – 363 U/L | 71 | **650** (v.5) | **650** | CK = 70 at v. 310 |
| HGIU 720-7203 | ALT<br>AST<br>TBili<br>GGT | 6 – 43 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 11<br>15<br>0.41<br>21 | **128** (v.6)<br>*58*<br>0.29<br>*98* | **128**<br>*58*<br>0.29<br>*98* | ALT = 15 at v. 310 |
| HGIU 720-7210 | Triglycerides<br>Cholesterol<br>LDL | 38.9 – 123.9 mg/dL<br>124.7 – 211.6 mg/dL<br>59.1 – 136.7 mg/dL | 108.8<br>172.6<br>109.6 | **382.3** (v.4)<br>195.7<br>88.0 | *171.7*<br>199.6<br>127.8 | TG = *148* at v. 310 |
| HGIU 720-7214 | ALT<br>AST<br>TBili<br>GGT | 6 – 43 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 38<br>31<br>0.71<br>20 | **448** (v.6)<br>**164**<br>0.41<br>46 | **448**<br>**164**<br>0.41<br>46 | ALT = *69* at v. 302 |
| HGIU 720-7217 | ALT<br>AST<br>TBili<br>GGT | 6 – 43 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 20<br>32<br>0.88<br>21 | **125** (v.6)<br>*103*<br>0.53<br>35 | **125**<br>*103*<br>0.53<br>35 | ALT = *58* at v. 308 |
| HGIU 720-7221 | Glucose, fasting | 70 – 115 mg/dL | 86.5 | **145.9 (v.4)** | 72 | Glucose = 77 at v. 306 |
| HGIU 730-7302 | ALT<br>AST<br>TBili<br>GGT | 6 – 43 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 22<br>29<br>0.29<br>13 | **123** (v.5)<br>*77*<br>0.18<br>27 | 41<br>28<br>0.18<br>22 | ALT = 16 at v. 310 |
| HGIN 003-302 | ALT<br>AST<br>TBili<br>GGT | 6 – 43 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 19<br>17<br>0.29<br>10 | **132** (v.9)<br>38<br>0.29<br>18 | **132**<br>38<br>0.29<br>18 | ALT = 27 at v. 305 |
| HGIN 004-401 | ALT<br>AST<br>TBili<br>GGT | 6 – 43 U/L<br>10 - 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 18<br>19<br>0.18<br>19 | *39*<br>**157** (v.4)<br>0.18<br>18 | 19<br>25<br>0.41<br>17 | AST = 22 at v. 309 |
| | Creatine Phosphokinase | 0 – 363 U/L | 289 | **7289** (v.4) | *610* | CPK = *781* at v. 309 (was *1766* at v. 306) |
| HGIN 006-602 | ALT<br>AST<br>TBili<br>GGT | 6 – 43 U/L<br>10-40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 22<br>27<br>0.88<br>44 | **240** (v.8)<br>**141**<br>0.29<br>**206** | *134*<br>*60*<br>0.53<br>*216* | ALT = 32<br>AST = *49*<br>GGT = 38 at v. 308 |
| | Triglycerides<br>Cholesterol<br>LDL | 37.2 – 147.8 mg/dL<br>113.9 – 197.7 mg/dL<br>61.8 – 129.7 mg/dL | 136.3<br>171.8<br>96.9 | **532.7** (v.7)<br>*210.8*<br>NA | *207.1*<br>185.7<br>102.7 | TG = 93 at v. 308 |
| HGIN 007-703 | ALT<br>AST<br>TBili<br>GGT | 6 – 34 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 33 U/L | 29<br>33<br>0.41<br>11 | **231** (v.6)<br>**142**<br>0.41<br>*34* | *199*<br>*101*<br>0.29<br>*34* | ALT = *66*,<br>AST = 33 at v. 501 (follow-up) |
| HGIN 007-705 | Creatine Phosphokinase | 0 – 408 U/L | 115 | **855** (v.8) | 189 | CK = 141 at v. 305 |
| HGIN 016-1601 | ALT<br>AST | 6 – 43 U/L<br>10 – 40 U/L | 23<br>26 | **159** (v.6)<br>*67* | 36<br>32 | ALT = 43 at v. 309 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | TBili<br>GGT | 0.18 – 1.23 mg/dL<br>0 – 51 U/L | *1.41*<br>22 | 1.23<br>*64* | 1.11<br>36 | |
| HGIN<br>017-1703 | ALT<br>AST<br>TBili<br>GGT | 6 – 43 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 33 U/L | *60*<br>40<br>0.18<br>23 | **210** (v.5)<br>*96*<br>0.18<br>29 | *79*<br>*50*<br>0.29<br>18 | ALT = 15 at v. 309 |
| HGIN<br>020-2004 | ALT<br>AST<br>TBili<br>GGT | 6 – 34 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 33 U/L | 21<br>21<br>0.29<br>29 | **163** (v.5)<br>*87*<br>0.29<br>*81* | 18<br>22<br>0.18<br>*43* | ALT = 9 at v. 309 |
| HGIN<br>021-2102 | ALT<br>AST<br>TBili<br>GGT | 6 – 34 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 33 U/L | 8<br>19<br>0.29<br>12 | **105** (v.9)<br>*90*<br>0.41<br>23 | **105**<br>*90*<br>0.41<br>23 | ALT = 13 at v. 307 |
| | Triglycerides<br>Cholesterol<br>LDL | 38.9 – 123.9 mg/dL<br>124.7 – 211.6 mg/dL<br>59.1 – 136.7 mg/dL | 84.9<br>201.5<br>102.7 | 111.5<br>**289.6** (v.6)<br>*165.6* | 109.7<br>*237.4*<br>132.8 | TG = *293*<br>Chol = *240*<br>at v. 307 |
| HGIN<br>021-2103 | ALT<br>AST<br>TBili<br>GGT | 6 – 43 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 16<br>20<br>0.41<br>18 | **396** (v.7)<br>**136**<br>0.41<br>*63* | **396**<br>**136**<br>0.41<br>*63* | ALT = *154*,<br>AST = 36 at v. 502 (follow-up) |
| HGIN<br>030-3002 | ALT<br>AST<br>TBili<br>GGT | 6 – 43 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 11<br>19<br>0.71<br>23 | **175** (v.7)<br>*69*<br>0.29<br>*72* | *61*<br>*60*<br>0.29<br>48 | ALT = 39 at v. 309 |
| HGIN<br>033-3301 | Triglycerides<br>Cholesterol<br>LDL | 31.8 – 124.8 mg/dL<br>129.7 – 203.9 mg/dL<br>64.1 – 132.8 mg/dL | 87.6<br>*214.7*<br>*139.8* | **426.5** (v.9)<br>*214.7*<br>*149.8* | **426.5**<br>*214.7*<br>*149.8* | None |
| HGIN<br>900-9003 | Triglycerides<br>Cholesterol<br>LDL | 37.2 – 147.8 mg/dL<br>113.9 – 197.7 mg/dL<br>61.8 – 129.7 mg/dL | 85.8<br>118.1<br>82.6 | **270.8** (v.8)<br>167.2<br>84.5 | *195.6*<br>147.1<br>79.5 | TG = 143 at v. 307 |
| HGIN<br>900-9006 | Triglycerides<br>Cholesterol<br>LDL | 37.2 – 147.8 mg/dL<br>113.9 – 197.7 mg/dL<br>61.8 – 129.7 mg/dL | *231*<br>194.5<br>107.3 | **363.7** (v.7)<br>*241.3*<br>130.9 | *170.8*<br>*228.2*<br>*147.9* | AST = 23 at v.309 |
| HGIN<br>900-9010 | ALT<br>AST<br>TBili<br>GGT | 6 – 43 U/L<br>10-40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 20<br>26<br>0.41<br>20 | *68*<br>**161** (v.8)<br>0.47<br>20 | 35<br>31<br>0.65<br>15 | AST = 31/29 at v. 309 |
| HGIN<br>910-9101 | ALT<br>AST<br>TBili<br>GGT | 6 – 34 U/L<br>10 – 40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 33 U/L | *65*<br>27<br>0.47<br>*36* | *51*<br>38<br>0.23<br>**95** (v.5) | 16<br>24<br>0.18<br>26 | GGT = *46* at v. 309 |
| HGIN<br>910-9103 | ALT<br>AST<br>TBili<br>GGT | 6 – 43 U/L<br>10-40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 29<br>30<br>0.35<br>22 | **141** (v.6)<br>*84*<br>0.76<br>29 | 36<br>38<br>0.53<br>20 | ALT = 23 at v. 309 |
| HGIN<br>910-9105 | Glucose, Fasting | 70 – 115 mg/dL | 108 | **127.9** (v.9) | *127.9* | Glucose, fasting = 92 at v. 309 |
| HGIN<br>910-9107 | Triglycerides<br>Cholesterol<br>LDL | 37.2 – 147.8 mg/dL<br>113.9 – 197.7 mg/dL<br>61.8 – 129.7 mg/dL | 132.7<br>190<br>128.2 | **285.8** (v.4)<br>*213.5*<br>118.9 | *178.8*<br>197.7<br>127.0 | TG = 107 at v. 309 |
| HGIN | ALT | 6-43 U/L | 40 | **117** (v.5) | 28 | ALT = 28 at |

| | | | | | | |
|---|---|---|---|---|---|---|
| 910-9108 | AST<br>TBili<br>GGT | 10-40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 20<br>0.35<br>32 | *52*<br>0.35<br>34 | 23<br>0.35<br>23 | v. 309 |
| HGIN<br>910-9110 | ALT<br>AST<br>TBili<br>GGT | 6-43 U/L<br>10-40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 25<br>25<br>0.47<br>19 | **321** (v.5)<br>**190**<br>0.59<br>37 | *128*<br>*53*<br>0.41<br>29 | ALT = 17,<br>AST = 19 at<br>v. 501<br>(follow-up) |
| HGIN<br>920-9202 | ALT<br>AST<br>TBili<br>GGT | 6-43 U/L<br>10-40 U/L<br>0.18 – 1.23 mg/dL<br>0 – 51 U/L | 15<br>19<br>1<br>27 | **393** (v.6)<br>**177**<br>1<br>*78* | **393**(231 repeat)<br>**177** (59 repeat)<br>1 (0.71 repeat)<br>*78* (82 repeat) | ALT = 20 at<br>v. 501<br>(follow-up),<br>AST NA |
| HGIN<br>920-9207 | Triglycerides<br>Cholesterol<br>LDL | 31.8 – 124.8 mg/dL<br>129.7 – 203.9 mg/dL<br>64.1 – 132.8 mg/dL | 123.9<br>*205.0*<br>*135.1* | **336.3** (v.6)<br>*233.2*<br>126.2 | **336.3**<br>*233.2*<br>126.2 | None |

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113, LDL = 0.0259, bilirubin = 17.1 (micromol/L to mg/dL)

Very few patients exhibited an increase in fasting glucose that might be considered a marked outlier in the HGIN + HGIU Acute Database. In reviewing the JMP dataset, 3 patients were noted with markedly elevated fasting glucose in the open-label phase of HGIN and HGIU:

Patient HGIN-900-9011 was randomized to placebo in the DB phase and had a baseline fasting glucose of 110 mg/dL. At visit 301, fasting glucose was 169 mg/dL on 7.5 mg olanzapine which normalized with continued dosing at 10 mg to 97 mg/dL at end of the study.
Patient HGIN 910-9108 was randomized to olanzapine in the DB phase and had a baseline fasting glucose of 95 mg/dL. At visit 7 of the acute phase, fasting glucose was 101 mg/dL, at visit 303 fasting glucose was 149 mg/dL on 20 mg olanzapine which normalized with continued dosing to 94 mg/dL at visit 309.

Patient HGIU 026-2602 was randomized to olanzapine in the DB phase and had a baseline fasting glucose of 104 mg/dL. At visit 6 of the acute phase, fasting glucose was 112 mg/dL, at visit 310 fasting glucose was 205 mg/dL on 12.5 mg olanzapine and at visit 501 (follow-up) fasting glucose was 113 mg/dL.

The Sponsor did not include prolactin in the list of analytes for definitions of potentially clinically significant changes. For purposes of this review, the laboratory data in the JMP database was reviewed and a PCS value of $\geq$ 40 ng/ml was arbitrarily chosen. Prolactin levels were obtained at screening, baseline, end of study in the double-blind acute phase of HGIN and HGIU and visit 305 (HGIN) and 307 (HGIU) (~8-10 weeks into OL) and end of OL phase.
The reference ranges used for prolactin were males 2.8 – 22 ng/ml and females 3.2 – 20 ng/ml. – per protocol amendment.
However, in the summary-clin-safe-app, the following (b) (4) adolescent reference ranges were noted:

| Gender | Age | Low (ug/L) | High (ug/L) |
|---|---|---|---|
| Male | 12<=Age<14 | 2.84 | 24.0 |
| | 14<=Age<19 | 2.76 | 16.1 |
| Female | 12<=Age<14 | 3.52 | 16.9 |
| | 14<=Age<19 | 4.20 | 39.0 |

In the double-blind phase of HGIU, 13% (13/99) olanzapine patients had prolactin elevations > 40 ng/ml at end of study [baseline and end of study prolactin levels available for 99/107 patients]. Only 3 of the 13 patients were male. The mean prolactin concentration at the end of study for this subgroup was 50.4 ± 8.3 ng/ml.

In the double-blind phase of HGIN, 17% (11/64) olanzapine patients had prolactin elevations > 40 ng/ml at end of study [baseline and end of study prolactin levels available for 64/72 patients]. Only 4 of the 11 patients were male. The mean prolactin concentration at the end of study for this subgroup was 55.8 ± 15.8 ng/ml. One patient receiving placebo in the acute HGIN study had an increase from 18.2 ng/ml at baseline to 42.4 ng/ml at end of study. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).

With the exception of one patient, it is not known whether these patients exhibited any clinical symptoms associated with hyperprolactinemia (narratives not available for these cases). Galactorrhea was not reported as an adverse event in the acute phases of HGIU or HGIN and one patient in the olanzapine group had the adverse event "gynecomastia" (see Section 7.1.4.3 Special Assessments). Patient HGIU 028-2804, who had an increase in prolactin concentration to 129.7 ng/ml, exhibited bilateral galactorrhea. Of note, one female patient in the LOAY study (data not included here) discontinued due to the adverse event galactorrhea – the narrative stated that her prolactin increased to 35 ng/ml. Therefore, clinical symptoms may have been associated with these prolactin elevations. It is possible that patients, especially adolescents, might be reluctant to report the types of adverse events associated with hyperprolactinemia.
Some patients who continued into the open-label phase had a decrease in their prolactin concentrations, others did not. Due to time constraints, this reviewer was unable to evaluate each case to determine whether decrease/resolution of hyperprolactinemia was related to a reduction in olanzapine dose.

Table 7.1.6.2.3.2. Prolactin Outliers: HGIN + HGIU Acute Database

| | | Prolactin (ng/ml) | | |
|---|---|---|---|---|
| Patient | Age/Gender | Baseline | End of Double-Blind Phase | End of Open-Label Phase |
| HGIU 010-1005 | 14 YOM | 23.4 | 60.7 | 17.6 |
| HGIU 012-1216 | 16 YOM | 18.9 | 51.1 | 51.6 |
| HGIU 019-1901 | 16 YOF | 9.2 | 43.8 | 35.0 |
| HGIU 019-1905 | 14 YOF | 18.8 | 44.5 | 32.6 |
| HGIU 020-2007 | 14 YOF | 16.5 | 57.6 | 14.5 |
| HGIU 020-2011 | 13 YOF | 8.1 | 57.5 | 10.9 |
| HGIU 020-2020 | 16 YOF | 12.7 | 44.4 | 40.3 |
| HGIU 021-2103 | 17 YOF | 20.6 | 45.1 | 13.5 |
| HGIU 024-2403 | 15 YOF | 31.1 | 49.8 | 31.5 |
| HGIU 024-2405 | 13 YOM | 15.2 | 40.3 | 24.3 |
| HGIU 026-2602 | 13 YOF | 20.2 | 50.3 | 49.5 |
| HGIU 028-2803 | 15 YOF | 31.6 | 68.1 | 11.7 |
| HGIU 035-3517 | 13 YOF | 13.8 | 42.3 | 17.4 |
| HGIN 005-503 | 14 YOF | 17.2 | 90.7 | 45.5 |
| HGIN 013-1303 | 16 YOF | 17.3 | 48.3 | NA |
| HGIN 020-2003 | 17 YOF | 26.3 | 79.9 | NA |
| HGIN 021-2102 | 16 YOF | 30.8 | 59.9 | 16.7 |
| HGIN 026-2602 | 15 YOF | 36 | 41.5 | 9.6 |
| HGIN 026-2603 | 14 YOF | 33 | 44.9 | 59.4 |
| HGIN 030-3010 | 13 YOF | 17.4 | 55 | NA |
| HGIN 034-3401 | 16 YOM | 22.7 | 43.8 | 30.4 |
| HGIN 900-9006 | 17 YOM | 28 | 55.5 | 40.1 |
| HGIN 910-9107 | 16 YOM | 45.8 | 48.2 | 43.2 |
| HGIN 940-9408 | 15 YOM | 12 | 45.8 | 21.7 |

NA = not applicable, patient was not enrolled in open-label phase

Table 7.1.6.2.3.3. Prolactin Outliers: HGIN + HGIU Open Label Phase

| Patient | Age/Gender | Treatment in DB Phase | Baseline | Visit #307(HGIU) #305 (HGIN) | End of Open-Label Phase Visit #310 (HGIU) Visit #309 (HGIN) |
|---|---|---|---|---|---|
| HGIU 007-704 | 15 YOM | Placebo | 32.5 | 36.1 | **47.3** |
| HGIU 019-1904 | 15 YOF | Placebo | 5.5 | 28.5 | **43.7** |
| HGIU 019-1907 | 15 YOF | Olanzapine | 10.1 | **40.6** | 38.5 (v. 308) |
| HGIU 020-2003 | 13 YOF | Olanzapine | 18.4 | **41.8** | 23.6 |
| HGIU 021-2102 | 17 YOF | Olanzapine | 25 | **57.7** | 10.6 |
| HGIU 026-2608 | 13 YOF | Olanzapine | 20.5 | - | **57** (v. 304) |
| HGIU 028-2804 | 15 YOF | Placebo | 11.8 | **129.7** (v.302) | **49.8** (v. 307) |
| HGIU 035-3519 | 14 YOM | Olanzapine | 28.3 | - | **41.7** (v. 302) |
| HGIU 036-3606 | 16 YOF | Placebo | 20.7 | **59.5** | **44.0** |
| HGIN 900-9009 | 17 YOF | Olanzapine | 17.5 | 17 | **110** |
| HGIN 020-2005 | 14 YOM | Olanzapine | 41.1 | - | **64.7** (v. 305) |

7.1.6.3 Special assessments

**Hyperprolactinemia**
A discussion of the adverse events potentially related to hyperprolactinemia are in Section 7.1.5 (Less Common Adverse Events). The mean change from baseline to endpoint in prolactin concentration is in Section 7.1.6.2.1 and marked outliers are in Section 7.1.6.2.3.
As was mentioned in Section 7.1.6.2.1, there are limitations in evaluating the mean change from baseline to endpoint for the prolactin data. Since the washout period in studies HGIN and HGIU could be as short as 2 days, some baseline prolactin concentrations were increased likely due to the effect of the prior antipsychotic. Interpretation of the effect of olanzapine on prolactin concentration is difficult if the analysis includes patients with an elevated baseline. The Sponsor will be asked to perform an analysis for the subset of patients with a baseline prolactin within the normal range (including treatment by gender and treatment by age analyses).

Elevations in prolactin due to antipsychotics occur more frequently in females compared to males. The Sponsor did include an analysis of these laboratory data by gender for the individual HGIU and HGIN studies. For each separate study, no significant treatment by gender interaction was found. However, there was a numerically greater mean change to endpoint in prolactin in females (16.2) compared to males (5.4) in study HGIN. Also, for the patients with an end of

study prolactin > 40 ng/ml, the majority of these patients were female (see Section 7.1.6.2.3.). For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction (see Appendix 10.12), though there was a numerically greater mean change to endpoint in females (15.6) compared to males (8.8).

Table 7.1.6.3.1. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: Study HGIU

| Laboratory Analyte | Gender | N | Therapy | Baseline n | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean | LSMean Diff. | *P-value | **P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PROLACTIN | Female | 70 | Olanzapine | 43 | 15.23 | 10.01 | 15.38 | 13.73 | 15.96 | 12.75 | <.001 | .590 |
| | | | Placebo | 27 | 14.99 | 8.00 | 2.67 | 8.60 | 3.21 | | | |
| | Male | 79 | Olanzapine | 56 | 11.36 | 5.46 | 11.50 | 9.50 | 11.91 | 10.83 | <.001 | |
| | | | Placebo | 23 | 10.00 | 6.40 | 0.66 | 3.06 | 1.08 | | | |

Table HGIU.12.13 in study report

Table 7.1.6.3.2. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: Study HGIN

| Laboratory Analyte | Gender | N | Therapy | Baseline n | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean | LSMean Diff. | *P-value | **P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PROLACTIN | Female | 30 | Olanzapine | 20 | 17.24 | 10.31 | 16.17 | 22.59 | 14.25 | 17.99 | .025 | .258 |
| | | | Placebo | 10 | 15.95 | 6.67 | -2.20 | 10.26 | -3.73 | | | |
| | Male | 64 | Olanzapine | 44 | 14.89 | 13.11 | 5.37 | 14.35 | 5.43 | 9.27 | .028 | |
| | | | Placebo | 20 | 20.10 | 19.26 | -3.91 | 16.86 | -3.84 | | | |

This reviewer could not find an analysis of prolactin concentrations by the subgroup "age". The Sponsor will be asked to provide these data.

The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIU + HGIN Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$). No significant treatment-by-gender interactions were noted in this analysis, though a higher percentage of males (41/68, 60.3%) had a high prolactin concentration at any time compared to females (14/48, 29%).

The Sponsor did evaluate prolactin concentrations over time for the Overall Combined Database. In general, there is a decrease in mean prolactin concentration over the course of the 32 weeks which approaches baseline concentrations. There are still outliers in this analysis at the 19-32 week timepoint. The Sponsor will be asked to provide a similar summary for only those patients completing the 19-32 weeks.

Table 7.1.6.3.3. Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints: Overall Combined Database

**Table APP.2.7.4.7.4.24. Mean Prolactin Values at Various Time Points Overall Olanzapine Exposure Combined Database**

| | | Summary | | | | |
|---|---|---|---|---|---|---|
| Database | Olz Exposure | N | Mean | Std | Median | Max |
| Bipolar | Baseline | 217 | 15.35 | 12.58 | 11.28 | 110.30 |
| | 1-6 weeks | 174 | 26.60 | 16.18 | 23.10 | 129.66 |
| | 7-18 weeks | 122 | 19.24 | 11.89 | 16.71 | 59.49 |
| | 19-32 weeks | 83 | 18.03 | 10.42 | 14.36 | 49.53 |
| Schizophrenia | Baseline | 214 | 18.84 | 19.97 | 11.87 | 131.57 |
| | 1-6 weeks | 190 | 31.82 | 20.75 | 26.48 | 110.84 |
| | 7-18 weeks | 88 | 22.75 | 16.24 | 18.62 | 112.00 |
| | 19-32 weeks | 93 | 19.01 | 15.60 | 14.81 | 109.97 |
| Overall | Baseline | 431 | 17.08 | 16.74 | 11.60 | 131.57 |
| | 1-6 weeks | 364 | 29.33 | 18.86 | 25.00 | 129.66 |
| | 7-18 weeks | 210 | 20.71 | 13.95 | 17.13 | 112.00 |
| | 19-32 weeks | 176 | 18.55 | 13.38 | 14.70 | 109.97 |

**Metabolic Parameters**

The Sponsor performed more detailed analyses on several adverse event profiles including "metabolic parameters".

The analyses included LOCF mean change from baseline to endpoint in fasting glucose and lipids; incidence of significant changes in fasting glucose and lipids, nonfasting glucose and lipids, weight gain-related adverse events, diabetes-related adverse events and dyslipidemia related adverse events; mean weight over time; correlations between mean changes in weight, glucose and lipids.

***HGIN + HGIU Acute Database***

LOCF mean change from baseline to endpoint:

There were statistically significant greater mean increases in fasting glucose levels (+ 2.7 mg/dL olanzapine vs. -2.9 mg/dL placebo, $p < 0.001$), total cholesterol (+ 12.7 mg/dL vs. +1.5 mg/dL, $p = 0.002$), and triglycerides (+27.4 mg/dL vs. -1.8 mg/dL, $p = 0.007$).

Significant changes in fasting glucose and lipids at any time:

There was a greater incidence of significant changes in patients treated with olanzapine than in patients treated with placebo for normal to borderline total cholesterol (15.7% vs. 3.6%, $p = 0.023$) and for normal to high fasting triglycerides (12.4% vs. 1.9%, $p = 0.039$).

The change from normal to borderline LDL cholesterol was approaching statistical significance (13.7% vs. 3.8%, $p = 0.064$).

The changes in fasting glucose were not statistically different:

Normal (< 100 mg/dL) to high (≥ 126 mg/dL) = 0% (0/122) olanzapine, 2% (1/51) placebo
Impaired glucose tolerance (≥ 100 mg/dL and < 126 mg/dL) to high (≥ 126 mg/dL): 15.4% (2/13) olanzapine, 0% (0/13) placebo
Normal/impaired glucose tolerance (< 126 mg/dL) to high (≥ 126 mg/dL): 1.5% (2/135) olanzapine, 1.6% (1/64) placebo.

The lack of a statistically significant difference in the change from impaired glucose tolerance to high fasting glucose levels (15.4% olanzapine vs. 0% placebo) is likely due to the low number of subjects enrolled with baseline impaired glucose tolerance (n = 13 each group).

Significant changes in fasting glucose and lipids at endpoint:
The only parameter that was statistically significant was normal to borderline cholesterol (14% olanzapine, 3.6% placebo, p = 0.039). The change from normal to high triglycerides was approaching statistical significance (10.6% olanzapine, 1.9% placebo, p = 0.064).

For the fasting glucose data, only 1 subject in the olanzapine treatment arm had a change from impaired glucose tolerance to high and 1 subject in the olanzapine treatment arm had a change from normal/impaired glucose tolerance to high.

In the Overall Combined Dataset, few patients had baseline impaired glucose (n = 47). Of those subjects, 6 (12.8%) had a shift from impaired glucose tolerance to high fasting glucose.
As mentioned in Section 7.1.6.2.1, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes) in the HGIN + HGIU Acute Database. There was no change from baseline to endpoint in this parameter – not unexpected since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months. In the Overall Combined Database, 23 patients had baseline HbA1c and there was no change at endpoint (the duration of study participation is not known for these patients).

The Sponsor provided correlation coefficients of change at endpoint between weight, fasting glucose, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides (it is unclear what correlation coefficient was used):
For the Overall Combined Dataset, there were statistically significant correlations between weight and total cholesterol (corr = 0.166, p = 0.005) and between weight and triglycerides (corr = 0.210, p < 0.001).
The Sponsor was asked to provide these correlations for the HGIN + HGIU Acute Database. In this database, there were statistically significant correlations between weight and total cholesterol (corr = 0.211, p = 0.003), between weight and triglycerides (corr = 0.223, p = 0.002) and between weight and fasting glucose (corr = 0.165, p = 0.021). Though these correlations are statistically significant, they are not particularly robust.

**Hepatic-related Parameters**
The Sponsor performed more detailed analyses on several adverse event profiles including "hepatic-related parameters".

For this analysis, a potentially clinically significant increase is defined as a change from a value less than or equal to the PCS high limit at all baseline visits to a value greater than the PCS high limit at endpoint or for two consecutive measures during therapy.

*HGIN + HGIU Database*
Mean change to endpoint in hepatic laboratory analytes in provided in Section 7.1.6 (Laboratory Findings).

The Sponsor analyzed treatment emergent high values at anytime (Table 7.1.6.3.4) and at endpoint (Table 7.1.6.3.5) for alkaline phosphatase, ALT, AST, GGT and total bilirubin. A higher percentage of patients in the olanzapine group had elevations in ALT, AST and GGT for both analyses.

Table 7.1.6.3.4. Sponsor's Table. Hepatic Laboratory Analytes – High Values at Anytime: HGIN + HGIU Acute Database

**Table APP.2.7.4.7.2.2. Hepatic Laboratory Analytes**
**Treatment-Emergent Abnormally High Values Anytime**
**(>1 X ULN)**
**All Randomized Patients with Normal Baseline Values**
**Acute Placebo-Controlled Combined Database**

| Hepatic Analytes | Olanzapine N | Olanzapine n | Olanzapine % | Placebo N | Placebo n | Placebo % | p-value* |
|---|---|---|---|---|---|---|---|
| ALKPH | 159 | 11 | 6.9% | 77 | 2 | 2.6% | .231 |
| ALT | 153 | 59 | 38.6% | 79 | 2 | 2.5% | <.001 |
| AST | 163 | 45 | 27.6% | 79 | 3 | 3.8% | <.001 |
| GGT | 169 | 17 | 10.1% | 83 | 1 | 1.2% | .008 |
| T. Bili | 170 | 0 | 0.0% | 85 | 6 | 7.1% | .001 |

Table 7.1.6.3.4. Sponsor's Table. Hepatic Laboratory Analytes – High Values at Endpoint: HGIN + HGIU Acute Database

**Table APP.2.7.4.7.2.24. Hepatic Laboratory Analytes**
**Treatment-Emergent Abnormally High Values at Endpoint (>1 X ULN)**
**All Randomized Patients with Normal Baseline Values**
**Acute Placebo-Controlled Combined Database**

| Hepatic Analytes | Olanzapine N | Olanzapine n | Olanzapine % | Placebo N | Placebo n | Placebo % | p-value* |
|---|---|---|---|---|---|---|---|
| ALKPH | 159 | 6 | 3.8% | 77 | 1 | 1.3% | .432 |
| ALT | 153 | 32 | 20.9% | 79 | 1 | 1.3% | <.001 |
| AST | 163 | 19 | 11.7% | 79 | 1 | 1.3% | .005 |
| GGT | 169 | 14 | 8.3% | 83 | 0 | 0.0% | .006 |
| T. Bili | 170 | 0 | 0.0% | 85 | 5 | 5.9% | .004 |

Abnormal ALT values at anytime
> 3X ULN: olanzapine 11.1% (17/153) vs. placebo 1.3% (1/79) p = 0.008
> 5X ULN : olanzapine 3.9% (6/153) vs. placebo 0% p = 0.098
> 10X ULN : olanzapine 0.7% (1/153) vs. placebo 0% p = 1.00

> 3X ULN ALT anytime for patients with ALT baseline $\leq$ 3X ULN:olanzapine 12.1% (21/174) vs. 2.3% placebo (2/87) p = 0.009. [This analysis is the one that is included in proposed labeling for ALT elevations]

Only four patients had an increase in TBili to > 1.5 times ULN – two in the olanzapine group and two in the placebo group.

The Sponsor also used Hy's rule (ALT $\geq$ 3 times and TBili $\geq$ 1.5 times ULN) to identify any patients with potential severe hepatic injury. There were no patients who met Hy's rule criteria at any time in the clinical trials or at endpoint.

## 7.1.7 Vital Signs

### 7.1.7.1 Overview of vital signs testing in the development program

Blood pressure and heart rate were taken at every visit during the acute study – supine for 5 minutes and after standing for 2 minutes
Weight and temperature were taken at every visit
Height was taken at screening, at multiple study visits and end of study.

7.1.7.2 Standard analyses and explorations of vital signs data

*7.1.7.2.1 Analyses focused on measures of central tendencies*

Mean change from baseline to endpoint (LOCF) for vital signs is included in Appendix 10.13. Data for weight change is discussed further in Section 7.1.4.4 (Common Adverse Events). Statistically significant differences in mean change from baseline to endpoint between the olanzapine and placebo groups were noted for:
Supine SBP: olanzapine + 2.94 mmHg, placebo - 0.71 mm Hg ($p = 0.009$)
Standing DBP: olanzapine + 1.42 mmHg, placebo -1.28 mmHg ($p = 0.033$)
Supine pulse: olanzapine + 7.07 bpm, placebo - 0.60 bpm ($p < 0.001$)
Standing pulse: olanzapine +6.97 bpm, placebo - 0.89 bpm ($p < 0.001$)
Orthostatic SBP and pulse were not significantly different between olanzapine and placebo.
Weight: olanzapine +3.90 kg, placebo +0.24 kg ($p < 0.001$)
BMI: olanzapine + 1.22, placebo + 0.05 ($p < 0.001$)

*7.1.7.2.2 Analyses focused on outliers or shifts from normal to abnormal*

Potentially clinically significant definitions for vital signs are in Appendix 10.14.
There were no statistically significant differences between olanzapine and placebo for percentages of patients with potentially clinically significant changes (high or low) with the exception of weight. Of note, 5.7% of olanzapine and 4.5% of placebo-treated patients exhibited orthostatic hypotension ($p = NS$).
The percentage of patients who gained $\geq$ 7% body weight was higher in the olanzapine group (43.5%) compared to the placebo group (6.8%) ($p < 0.001$). Data for weight change is discussed further in Section 7.1.4.4 (Common Adverse Events).

*7.1.7.2.3 Marked outliers and dropouts for vital sign abnormalities*

Individual vital signs were reviewed from the JMP datasets. In general, few patients had markedly abnormal vital signs. Isolated systolic BP 150 – 155 mmHg was noted in both olanzapine and placebo groups, no diastolic BPs > 110 mmHg were noted and pulse rates > 130 bpm were noted in few patients but more olanzapine-treated patients than placebo-treated patients (highest pulse was 148 bpm in placebo patient).
Patient HGIU-035-3503 (16 YOBF) receiving olanzapine discontinued study HGIU due to an elevated pulse (standing pulse 140 bpm from baseline 96 bpm).

7.1.8 Electrocardiograms (ECGs)

7.1.8.1 Overview of ECG testing in the development program

The reviewer focused mainly on the two placebo-controlled acute trials, HGIN and HGIU, for evaluation of ECG data. Though the Sponsor states that differences from baseline were analyzed, it should be noted that ECGs were not obtained at baseline (visit 2), but were obtained during the screening period (visit 1):

"Twelve-lead ECGs were collected on each patient at baseline to determine the eligibility of the patient for entry into the study, and at the Final Visits of Study Period II and Study Period III to monitor the general safety of the patient during the course of the study".
Therefore, patients could be on other medications since this was the washout period prior to randomization.
Mean "baseline" ECG parameters appear fairly similar between the olanzapine and placebo groups such that any differences between the groups with regard to concomitant medications taken during screening might have been "equalized" by randomization.

7.1.8.2 Standard analyses and explorations of ECG data

*7.1.8.2.1 Analyses focused on measures of central tendency*

Statistically significant differences were found between olanzapine and placebo on all ECG parameters except QTcF (see Table 7.1.1.2.1.1). The most notable was the increase in heart rate in the olanzapine group (+6.3 bpm) compared to the placebo (-5.1 bpm) group ($p < 0.001$). Because of this effect on heart rate, the QTcB interval was also significantly longer in the olanzapine group compared to the placebo group.

Table 7.1.8.2.1.1. Sponsor's Table. ECG Intervals and Heart Rate: HGIN + HGIU Acute Database

| ECG Intervals/ Heart Rate | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|
| Heart Rate/Minute | Olz | 158 | 72.291 | 13.183 | 6.266 | 14.039 | 4.335 | 11.624 | <.001 |
| | Placebo | 80 | 72.788 | 12.553 | -5.100 | 11.052 | -7.289 | | |
| Intervals PR/Second | Olz | 158 | 0.139 | 0.019 | 0.003 | 0.010 | 0.004 | 0.005 | .003 |
| | Placebo | 78 | 0.146 | 0.031 | -0.002 | 0.015 | -0.001 | | |
| Intervals QRS/Second | Olz | 158 | 0.088 | 0.011 | -0.001 | 0.005 | -0.001 | -0.002 | .039 |
| | Placebo | 80 | 0.087 | 0.010 | 0.001 | 0.006 | 0.001 | | |
| Intervals QT/Msec | Olz | 158 | 380.532 | 30.825 | -10.481 | 29.222 | -7.948 | -23.603 | <.001 |
| | Placebo | 80 | 378.975 | 26.752 | 12.700 | 28.247 | 15.655 | | |
| Intervals QTc/Msec-Bazett formula | Olz | 158 | 412.880 | 16.358 | 6.899 | 18.146 | 4.872 | 9.634 | <.001 |
| | Placebo | 80 | 413.362 | 17.134 | -2.475 | 16.543 | -4.762 | | |
| Intervals QTc/Msec-Fridericia formula | Olz | 158 | 401.763 | 15.537 | 0.743 | 15.165 | 0.404 | -1.974 | .345 |
| | Placebo | 80 | 401.596 | 14.722 | 2.732 | 15.219 | 2.378 | | |

*7.1.8.2.2 Analyses focused on outliers or shifts from normal to abnormal*

An analysis of the percent of patients with potentially clinically significant changes between the olanzapine and placebo groups is in Table 7.1.8.2.2.1. Though patients in the olanzapine group exhibited a mean increase in heart rate (see previous section), no PCS increases were noted for heart rate. Three patients had PCS increases in QTcB in the olanzapine group, no patients had PCS changes in QTcF. No patients had QTcB or QTcF increases $\geq$ 60 msec. No patients had QTcB or QTcF $\geq$ 500 msec.

Table 7.1.8.2.2.1. Sponsor's Table. ECG Intervals and Heart Rate – Potentially Clinically Significant Changes. HGIN + HGIU Acute Database.

| ECG Intervals/ Heart Rate | Unit | Direction | Therapy | N | n | % | *P-value |
|---|---|---|---|---|---|---|---|
| Heart Rate <=40 bpm or >=120 bpm | bpm | High | Olz | 158 | 0 | 0.0% | |
| | | | Placebo | 80 | 0 | 0.0% | |
| | | Low | Olz | 158 | 0 | 0.0% | |
| | | | Placebo | 80 | 0 | 0.0% | |
| Heart Rate < 50 bpm,Dec>=15 or >120 bpm,Inc>=15 | bpm | High | Olz | 158 | 0 | 0.0% | |
| | | | Placebo | 80 | 0 | 0.0% | |
| | | Low | Olz | 157 | 0 | 0.0% | .038 |
| | | | Placebo | 80 | 3 | 3.8% | |
| Intervals PR >=200 ms | sec | High | Olz | 158 | 0 | 0.0% | .322 |
| | | | Placebo | 75 | 1 | 1.3% | |
| Intervals QRS >=100 ms | sec | High | Olz | 132 | 7 | 5.3% | .497 |
| | | | Placebo | 72 | 2 | 2.8% | |
| Intervals QT >=450 ms | ms | High | Olz | 156 | 1 | 0.6% | .045 |
| | | | Placebo | 79 | 4 | 5.1% | |
| QTc Bazett's Male >=450 ms or Female >=470 ms | ms | High | Olz | 156 | 3 | 1.9% | .553 |
| | | | Placebo | 79 | 0 | 0.0% | |
| QTc Fridericia's Male >=450 ms or Female >=470 ms | ms | High | Olz | 158 | 0 | 0.0% | |
| | | | Placebo | 80 | 0 | 0.0% | |

*7.1.8.2.3 Marked outliers and dropouts for ECG abnormalities*

There were no dropouts due to ECG abnormalities.

## 7.1.9 Assessment of Effect on Growth

The Sponsor provided an analysis of the effect of olanzapine on growth that included data from the Overall Combined Database. Gender and age-adjusted growth in olanzapine-treated patients was compared with the expected growth seen in the general US population by using data provided by the National Center for Health Statistics. Standardized mean weight and BMI increased significantly for olanzapine-treated patients, regardless of gender, country, or disorder (schizophrenia or bipolar disorder). The changes in standardized mean height were closer to expected values based on the CDC reference population.

Table 7.1.9.1. Sponsor's Table.

**Table APP.2.7.4.7.3.2. Standardized Growth (Z-Score)**
**LOCF Mean Change in Weight, Height, and BMI from Baseline to Endpoint**
**Overall Olanzapine Exposure Combined Database**

| | | | Baseline | | Endpoint | | Change | | P-value |
|---|---|---|---|---|---|---|---|---|---|
| Measure | Value | N | Mean | Std | Mean | Std | Mean | Std | *P-value |
| Weight | Actual | 450 | 67.13 | 17.72 | 74.48 | 19.07 | 7.35 | 6.58 | <.001 |
| | Expected | 450 | 67.13 | 17.72 | 68.17 | 17.90 | 1.03 | 1.01 | <.001 |
| | Z-Score | 450 | 0.53 | 1.13 | 0.98 | 1.02 | 0.45 | 0.44 | <.001 |
| | Percentile | 450 | 63.54 | 29.54 | 75.33 | 24.50 | 11.79 | 14.19 | |
| Height | Actual | 440 | 168.24 | 9.71 | 169.27 | 9.45 | 1.03 | 2.17 | <.001 |
| | Expected | 440 | 168.24 | 9.71 | 168.92 | 9.60 | 0.67 | 0.91 | <.001 |
| | Z-Score | 440 | 0.02 | 1.02 | 0.07 | 1.00 | 0.05 | 0.24 | <.001 |
| | Percentile | 440 | 50.60 | 29.13 | 52.11 | 28.76 | 1.51 | 6.58 | |
| BMI | Actual | 439 | 23.64 | 6.07 | 25.95 | 6.21 | 2.31 | 2.31 | <.001 |
| | Expected | 439 | 23.64 | 6.07 | 23.83 | 6.01 | 0.19 | 0.30 | <.001 |
| | Z-Score | 439 | 0.50 | 1.14 | 0.99 | 0.95 | 0.49 | 0.53 | <.001 |
| | Percentile | 439 | 63.51 | 29.85 | 76.77 | 23.48 | 13.26 | 16.47 | |

Table 7.1.9.2. Sponsor's Table.

**Table APP.2.7.4.7.3.3. Standardized Growth (Z-Score)**
**LOCF Mean Change in Weight, Height, and BMI from Baseline to Endpoint by Gender**
**Overall Olanzapine Exposure Combined Database**

| | | | | Baseline | | Endpoint | | Change | | P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| Measure | Gender | Value | N | Mean | Std | Mean | Std | Mean | Std | *P-value |
| Weight | Female | Actual | 167 | 64.41 | 18.15 | 70.94 | 19.34 | 6.53 | 6.08 | <.001 |
| | | Expected | 167 | 64.41 | 18.15 | 65.05 | 18.29 | 0.64 | 0.73 | <.001 |
| | | Z-Score | 167 | 0.64 | 1.12 | 1.05 | 0.97 | 0.40 | 0.45 | <.001 |
| | | Percentile | 167 | 67.26 | 28.90 | 77.62 | 23.18 | 10.36 | 14.04 | |
| | Male | Actual | 283 | 68.74 | 17.30 | 76.58 | 18.64 | 7.83 | 6.81 | <.001 |
| | | Expected | 283 | 68.74 | 17.30 | 70.01 | 17.43 | 1.27 | 1.08 | <.001 |
| | | Z-Score | 283 | 0.47 | 1.13 | 0.94 | 1.05 | 0.47 | 0.44 | <.001 |
| | | Percentile | 283 | 61.35 | 29.74 | 73.98 | 25.20 | 12.64 | 14.23 | |
| Height | Female | Actual | 163 | 162.07 | 7.82 | 162.78 | 7.63 | 0.71 | 1.45 | <.001 |
| | | Expected | 163 | 162.07 | 7.82 | 162.35 | 7.75 | 0.27 | 0.37 | <.001 |
| | | Z-Score | 163 | 0.04 | 1.15 | 0.10 | 1.13 | 0.07 | 0.20 | <.001 |
| | | Percentile | 163 | 51.74 | 30.32 | 53.86 | 29.83 | 2.12 | 6.40 | |
| | Male | Actual | 277 | 171.88 | 8.86 | 173.09 | 8.26 | 1.21 | 2.48 | <.001 |
| | | Expected | 277 | 171.88 | 8.86 | 172.78 | 8.42 | 0.90 | 1.05 | <.001 |
| | | Z-Score | 277 | 0.00 | 0.95 | 0.04 | 0.92 | 0.04 | 0.26 | .012 |
| | | Percentile | 277 | 49.94 | 28.44 | 51.09 | 28.11 | 1.15 | 6.68 | |
| BMI | Female | Actual | 162 | 24.46 | 6.76 | 26.78 | 7.12 | 2.32 | 2.30 | <.001 |
| | | Expected | 162 | 24.46 | 6.76 | 24.66 | 6.83 | 0.20 | 0.17 | <.001 |
| | | Z-Score | 162 | 0.66 | 1.07 | 1.08 | 0.88 | 0.42 | 0.48 | <.001 |
| | | Percentile | 162 | 67.73 | 28.52 | 79.04 | 21.25 | 11.31 | 15.25 | |
| | Male | Actual | 277 | 23.16 | 5.58 | 25.46 | 5.57 | 2.30 | 2.33 | <.001 |
| | | Expected | 277 | 23.16 | 5.58 | 23.35 | 5.42 | 0.19 | 0.36 | <.001 |

The Sponsor noted a number of limitations in the evaluation of these data. Tanner Stage information was not collected during these studies, so the pubertal effects on individual standard deviation scores for height, weight or BMI are not known. The observational period of these studies (up to 8 months) did not allow for "meaningful evaluation" of the potential effect of

olanzapine on height. Additionally, the CDC reference database is based on the US population and may not be representative of patients from Germany or Russia – both countries had significant numbers of patients in this combined database.

## Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Extent of exposure (dose/duration)

Acute, placebo-controlled trials: Total exposure for olanzapine in adolescent patients was 4776 patient-days. The mean daily dose was 9.75 mg/day, the modal daily dose was 11.46 mg/day.

Overall olanzapine exposure combined database: Total exposure for olanzapine in adolescent patients was 48,946 patient-days. The mean daily dose was 10.56 mg/day, the modal daily dose was 11.36 mg/day.

The highest olanzapine dose allowed in trials HGIN and HGIU was 20 mg/day. The Sponsor provided exposure data regarding the numbers of patients taking olanzapine 20 mg at any time, who had a modal dose of 20 mg and who had a final dose of 20 mg.

**Table 2.7.4.14. Anytime, Modal Dose, and Final Dose of 20 mg**
**All Randomized Patients**
**Acute Placebo-Controlled Combined Database**

| | HGIN (N= 72) n(%) | HGIU (N= 106) n(%) | Combined (N= 178) n(%) |
|---|---|---|---|
| 20 mg Dose (Anytime) | 21 (29.17%) | 13 (12.26%) | 34 (19.10%) |
| 20 mg Modal Dose | 12 (16.67%) | 10 (9.43%) | 22 (12.36%) |
| 20 mg Final Dose | 18 (25.00%) | 11 (10.38%) | 29 (16.29%) |

**Table 2.7.4.19. Anytime, Modal Dose, and Final Dose of 20 mg
All Patients with Olanzapine Exposure
Overall Olanzapine Exposure Combined Database**

Summary of Patients Who Took >= 20 mg OLZ at Any Time

| | Schizophrenia | | | Bipolar | | | Combined | | |
|---|---|---|---|---|---|---|---|---|---|
| Dose | N | n | % | N | n | % | N | n | % |
| 20 | 227 | 81 | 35.7% | 226 | 52 | 23.0% | 453 | 133 | 29.4% |
| 25 | 227 | 0 | 0.0% | 226 | 2 | 0.9% | 453 | 2 | 0.4% |

Summary of Patients Who Had Modal Dose at 20 mg OLZ

| | Schizophrenia | | | Bipolar | | | Combined | | |
|---|---|---|---|---|---|---|---|---|---|
| Modal Dose | N | n | % | N | n | % | N | n | % |
| 20 | 227 | 46 | 20.3% | 226 | 26 | 11.5% | 453 | 72 | 15.9% |

Summary of Patients Who Had Final Dose at 20 mg OLZ

| | Schizophrenia | | | Bipolar | | | Combined | | |
|---|---|---|---|---|---|---|---|---|---|
| Final Dose | N | n | % | N | n | % | N | n | % |
| 20 | 227 | 46 | 20.3% | 226 | 30 | 13.3% | 453 | 76 | 16.8% |

## 7.2.3 Description of Secondary Clinical Data Sources Used to Evaluate Safety

### 7.2.3.1 Postmarketing experience

The Lilly Safety System was searched for spontaneously reported adverse events involving patients younger than 18 years of age treated with olanzapine for the time period of product launch through May 31, 2006. The search identified 5,633 spontaneously reported adverse events (in 2,359 case reports) for patients $\leq$ 18 years of age out of 110,529 total events (age was unknown for 25,415 events).

The Sponsor analyzed these data by using a proportional reporting ratio (PRR) and Chi square value. The PRR was used to compare events between olanzapine treated patients aged 13 to 17 years and olanzapine-treated patients aged 18 to 64 years. The Sponsor indicated that some general guidelines for interpreting a drug-event combination as a potential signal include: at least 3 reports, a PRR > 2 and a Chi-square > 4. The spontaneously reported adverse events somnolence, aggression, galactorrhea, and sedation met the PRR and Chi-square criteria and had a proportion of the event of interest $\geq$ 1% of all events in patients aged 13 – 17 years (see Table 7.2.3.1.1 ).

Table 7.2.3.1.1 Sponsor's Table. Potential Safety Signals in Postmarketing Database for Patients 13 to 17 Years of Age – Proportion, PRR and Chi-Square Criteria Met

| MedDRA Preferred Term (# of events in patients 13-17 years) | Proportion of Event in Patients 13-17 years (%) (N=3,288 events) | Proportion of Event in Patients 18-64 years (%) (N=68,450 events) | PRR[a] | Chi-Square Value |
|---|---|---|---|---|
| Somnolence (108) | 3.28 | 1.60 | 2.06 | 53.39 |
| Aggression (41) | 1.25 | 0.33 | 3.76 | 70.36 |
| Galactorrhoea (39) | 1.19 | 0.32 | 3.67 | 64.51 |
| Sedation (38) | 1.16 | 0.46 | 2.50 | 30.41 |

From Sponsor table 2.7.4.79 in summary-clin-safety document

The Sponsor also included an additional table for adverse events reported with a proportion of the event of interest > 1% of all events in patients aged 13 to 17 years not meeting additional criteria (PRR and Chi-square) (see Table 7.2.3.1.2).

Table 7.2.3.1.2. Sponsor's Table. . Potential Safety Signals in Postmarketing Database for Patients 13 to 17 Years of Age – Proportion Criteria Met

| MedDRA Preferred Term (# of events in patients 13-17 years) | Proportion of Event in Patients 13-17 years (%) (N=3,288 events) | Proportion of Event in Patients 18-64 years (%) (N=68,450 events) | PRR[a] | Chi-Square Value |
|---|---|---|---|---|
| Weight increased (320) | 9.73 | 7.74 | 1.26 | 15.98 |
| Prescribed overdose (52) | 1.58 | 1.84 | 0.86 | 1.15 |
| Overdose (42) | 1.28 | 1.23 | 1.04 | 0.05 |
| Fatigue (40) | 1.22 | 0.70 | 1.75 | 11.76 |
| Alanine aminotransferase increased (38) | 1.16 | 0.90 | 1.29 | 2.31 |
| Diabetes mellitus (36) | 1.09 | 4.75 | 0.23 | 91.49 |
| Drug ineffective (36) | 1.09 | 0.77 | 1.43 | 4.36 |
| Increased appetite (36) | 1.09 | 0.77 | 1.41 | 4.09 |
| Convulsion (33) | 1.00 | 0.55 | 1.82 | 11.26 |

Of the 2,359 case reports in patients 13 to 17 years of age, 27 had a fatal outcome (Sponsor indicated that 28 cases were fatal, upon review it was noted that one case was duplicated). These cases are from spontaneous reports or publications in the literature. The Sponsor included CIOMS line listings and MedWatch reports for each fatality. In the narrative summary for one of the fatality cases, a reference to 4 additional US fatalities was made.[3] These appear to be a cluster of deaths occurring in a county in (b) (6) Further investigation may be deemed necessary. It is not known if the reporter had contacted the FDA regarding these cases as was mentioned in the case narrative. MedWatch reports for these additional cases were not included

3 In the narrative summary for US_010158510, the following statements were noted: "This is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in (b) (6). The reporter stated he has also notified the FDA."

in the submission. The Sponsor will be asked to provide these reports as well as to submit any new reports that may have occurred since this search was last completed.

The MedWatch reports were incomplete and many details regarding the deaths (autopsy reports, pertinent laboratory values, clinical description of death) were not available. In some cases, it appears that the Sponsor attempted to obtain more information, it is not known to what extent these attempts were made. Fifteen of the cases occurred in the United States, a number of these cases were reported by an attorney via the legal department – it is not known if litigation is ongoing in these cases.
Of note, seven of the cases involved completed suicide or possible suicide and five of the cases related to diabetes mellitus, diabetic coma or diabetic ketoacidosis. A brief summary of these cases is in Appendix 10.15.

## Safety Conclusions

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIU is the pivotal trial for bipolar disorder) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events ($\geq$ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain
The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with > 7% increase in body weight.

| | Olanzapine | Placebo | LS Mean Diff | P-value |
|---|---|---|---|---|
| *HGIN + HGIU Acute Database* | | | | |
| Weight (kg)<br>Mean Change to Endpoint (LOCF) | 3.90 (n = 177) | 0.24 (n = 88) | 3.66 | < 0.001 |
| Weight (kg)<br>Mean Change to Endpoint (OC) | 3.6 (n = 154) | 0.08 (n = 67) | 3.57 | < 0.001 |
| BMI<br>Mean Change to Endpoint (LOCF) | 1.22 | 0.05 | 1.17 | < 0.001 |
| ≥ 7% increase in body weight (%) | 43.5% | 6.8% | - | < 0.001 |
| Overall Combined Database | | | | |
| Weight (kg)<br>Mean Change to Endpoint (LOCF) | 7.35 | - | - | < 0.001<br>(compared to baseline) |
| Weight (kg)<br>Mean Change to Endpoint (OC) | 10.8 | - | - | < 0.001<br>(compared to baseline) |
| BMI<br>Mean Change to Endpoint (LOCF) | 2.31 | - | - | < 0.001<br>(compared to baseline) |
| ≥ 7% increase in body weight (%) | 65% | - | - | - |

In the Acute Database, weight gain (mean change from baseline to endpoint) was similar for the groups with baseline BMI < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

Weight changes were evaluated for the subgroups gender and age (< 15, ≥ 15 years). At the time this review was finalized, mean change in weight for the age subgroup analysis was only available for study HGIN (not HGIU or the Acute Database). Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine. A treatment-by-gender interaction was noted in the Acute Database, but was likely due to differences in the placebo groups since mean change in weight was similar in the olanzapine groups for males and females.

Liver Function Abnormalities
Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline ≤ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009).
No patients met criteria for Hy's rule (ALT ≥ 3x ULN and TBili ≥ 1.5 x ULN).

Hyperprolactinemia
The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, $p < 0.001$). The washout period prior to baseline could be as short as 2 days and it was noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to perform further analyses in the subgroup of patients with baseline prolactin within normal limits. In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).

For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females (15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN + HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$).

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

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

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were also similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality
Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in bipolar disorder patients. Suicidal behaviors or ideation is not uncommon in these patients and, in the absence of a placebo comparator, it is difficult to interpret any causality to olanzapine therapy.

## General Methodology

7.4.1 Explorations for dose dependency for adverse findings

All of the clinical trials, both placebo-controlled and open-label, included a flexible dosing paradigm for olanzapine. Therefore, it is not possible to evaluate the dose-dependency of adverse events.

7.4.2 Explorations for drug-demographic interactions

The drug – demographic interactions summarized here are the adverse events occurring in HGIN + HGIU Acute Database. Subgroup analyses, particularly for gender and age, for efficacy and some safety data (prolactin, weight gain, etc.) are summarized in those relevant sections of the review. Most of the patients enrolled in the pivotal clinical trials were Caucasian, therefore any analyses by race/ethnicity are of limited usefulness.

Treatment-by-gender interactions were significant for the following adverse events: myalgia, nasal congestion, sinus congestion and tremor (see Table 7.4.2.1); though none of these adverse events were significantly different between olanzapine and placebo.

Table 7.4.2.1. Sponsor's Table. Adverse Events – Treatment-by-Gender Interactions: HGIN + HGIU Acute Database

By Subgroup: Gender

| | | Therapy | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Olanzapine | | | Placebo | | | | |
| Event Classification | Gender | N | n | % | N | n | % | *P-value | **Homogeneity of Odds Ratio |
| Myalgia | Female | 67 | 0 | 0.0% | 41 | 1 | 2.4% | .380 | .070 |
| | Male | 112 | 3 | 2.7% | 48 | 0 | 0.0% | .555 | |
| Nasal congestion | Female | 67 | 2 | 3.0% | 41 | 0 | 0.0% | .525 | .055 |
| | Male | 112 | 0 | 0.0% | 48 | 1 | 2.1% | .300 | |
| Sinus congestion | Female | 67 | 2 | 3.0% | 41 | 0 | 0.0% | .525 | .055 |
| | Male | 112 | 0 | 0.0% | 48 | 1 | 2.1% | .300 | |
| Tremor | Female | 67 | 2 | 3.0% | 41 | 0 | 0.0% | .525 | .055 |
| | Male | 112 | 0 | 0.0% | 48 | 1 | 2.1% | .300 | |

Treatment-by-age (< 15, ≥ 15 years) interactions were significant for ear pain and migraine (see Table 7.4.2.2); though none of these adverse events were significantly different between olanzapine and placebo.

Table 7.4.2.2. Sponsor's Table. Adverse Events – Treatment-by-Age Interactions: HGIN + HGIU Acute Database

By Subgroup: Age

| | | Therapy | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Olanzapine | | | Placebo | | | | |
| Event Classification | Age | N | n | % | N | n | % | *P-value | **Homogeneity of Odds Ratio |
| Ear pain | < 15 | 64 | 1 | 1.6% | 27 | 0 | 0.0% | 1.00 | .100 |
| | >=15 | 115 | 0 | 0.0% | 62 | 2 | 3.2% | .121 | |
| Migraine | < 15 | 64 | 0 | 0.0% | 27 | 1 | 3.7% | .297 | .062 |
| | >=15 | 115 | 2 | 1.7% | 62 | 0 | 0.0% | .542 | |

## Comparing adolescent and adult data

The common adverse event tables for adults in current product labeling and the common adverse events occurring in HGIN and HGIU were compared. In the schizophrenia trials, 31% of adolescent patients experienced weight gain compared to 6% of adult patients. Somnolence and sedation were experienced by 24% and 15% of adolescent patients compared to < 5% of adult patients. Similar patterns occurred in the bipolar disorder trials except that somnolence was very common in the adult population as well as the adolescent population.

Table 7.5.1. Common Adverse Events (≥ 5% incidence) – Adult versus Adolescents: 6 Week Acute Trials in *Schizophrenia*

| | Adults | |
|---|---|---|
| | Olanzapine N = 248 | Placebo N = 118 |
| Dizziness | 11% | 4% |
| Constipation | 9% | 3% |
| Personality disorder | 8% | 4% |
| Weight gain | 6% | 1% |
| Akathisia | 5% | 1% |
| Postural hypotension | 5% | 2% |

| | Adolescents | |
|---|---|---|
| | Olanzapine N = 72 | Placebo N = 35 |
| Weight increased | 31% | 9% |
| Somnolence | 24% | 3% |
| Headache | 17% | 6% |
| Increased appetite | 17% | 9% |
| Sedation | 15% | 6% |
| Dizziness | 8% | 3% |
| Pain in extremity | 6% | 3% |

Table 7.5.2. Common Adverse Events (≥ 5% incidence) – Adult versus Adolescents: 3 Week Acute Trials in *Bipolar Disorder*

| | Adults | |
|---|---|---|
| | Olanzapine N = 125 | Placebo N = 129 |
| Somnolence | 35% | 13% |
| Dry mouth | 22% | 7% |
| Dizziness | 18% | 6% |
| Asthenia | 15% | 6% |
| Constipation | 11% | 5% |
| Dyspepsia | 11% | 5% |
| Increased appetite | 6% | 3% |
| Tremor | 6% | 3% |

| Adolescents | | |
|---|---|---|
| | Olanzapine N = 107 | Placebo N = 54 |
| Weight increased | 29% | 4% |
| Increased appetite | 29% | 4% |
| Somnolence | 25% | 4% |
| Sedation | 22% | 6% |
| Headache | 17% | 17% |
| Fatigue | 14% | 6% |
| Dry mouth | 8% | 0% |
| Pain in extremity | 5% | 0% |

The Sponsor included an analysis of select adverse events occurring in the adult clinical trials databases and adolescent clinical trials databases. These analyses summarized all data including the open-label trials. The Sponsor was asked if a similar analysis could be done for the placebo-controlled studies only and they responded that none of the placebo-controlled studies included fasting glucose and lipid data so these analyses were not available.

Metabolic parameters (fasting glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides):
Mean change from baseline to endpoint – the only statistically significant differences between populations was in fasting glucose and triglycerides. Mean change to endpoint for fasting glucose was 1.8 ± 13 mg/dL for adolescents and 4.9 ± 32.8 mg/dL for adults ($p = 0.002$), triglycerides was 23.0 ± 76 mg/dL for adolescents and 20.3 ± 124 mg/dL for adults ($p = 0.007$).

Treatment-emergent significant changes at any time: statistically significant differences were noted for most of the parameters with a higher percentage of adults having significant changes at any time (see Table 7.5.3).

Table 7.5.3. Treatment-Emergent Significant Changes at Any Time – Adults vs. Adolescents

| Laboratory Analytes | Categories | Population | N | n | % | *P-value |
|---|---|---|---|---|---|---|
| Fasting Glucose | Normal to High (< 100 mg/dL to >=126 mg/dL) | Adolescent | 251 | 3 | 1.2% | .033 |
| | | Adult | 251 | 12 | 4.8% | |
| | Impaired Glucose Tolerance to High(>=100 & <126 mg/dL to >=126 mg/dL) | Adolescent | 47 | 6 | 12.8% | .066 |
| | | Adult | 121 | 32 | 26.4% | |
| | Normal/Impaired Glucose Tolerance to High(<126 mg/dL to >=126 mg/dL) | Adolescent | 298 | 9 | 3.0% | <.001 |
| | | Adult | 372 | 44 | 11.8% | |
| Total Cholesterol | Normal to Borderline(<200 mg/dL to >=200 mg/dL and <240 mg/dL) | Adolescent | 262 | 54 | 20.6% | <.001 |
| | | Adult | 216 | 82 | 38.0% | |
| | Normal to High(<200 mg/dL to >=240 mg/dL) | Adolescent | 262 | 3 | 1.1% | .001 |
| | | Adult | 216 | 15 | 6.9% | |
| LDL Cholesterol | Normal to Borderline(<130 mg/dL to >=130 mg/dL and <160 mg/dL) | Adolescent | 270 | 48 | 17.8% | <.001 |
| | | Adult | 241 | 75 | 31.1% | |
| | Normal to High(<130 mg/dL to >=160 mg/dL) | Adolescent | 270 | 4 | 1.5% | .014 |
| | | Adult | 241 | 14 | 5.8% | |
| HDL Cholesterol | Normal to Low(>=50 mg/dL to <40 mg/dL) | Adolescent | 107 | 10 | 9.3% | .052 |
| | | Adult | 155 | 28 | 18.1% | |

| Laboratory Analytes | Categories | Population | N | n | % | *P-value |
|---|---|---|---|---|---|---|
| Fasting Triglycerides | Normal to Borderline(<150 mg/dL to >=150 mg/dL and <200 mg/dL) | Adolescent | 247 | 51 | 20.6% | <.001 |
| | | Adult | 253 | 91 | 36.0% | |
| | Normal to High(<150 mg/dL to >=200 mg/dL) | Adolescent | 247 | 43 | 17.4% | .030 |
| | | Adult | 253 | 65 | 25.7% | |
| | Normal to Extremely High(<150 mg/dL to >=500 mg/dL) | Adolescent | 247 | 1 | 0.4% | 1.00 |
| | | Adult | 253 | 1 | 0.4% | |

From Sponsor table APP.2.7.4.7.1.24 in summary-clin-safe-app document

Weight Gain
Mean change from baseline to endpoint – There was a statistically significant greater mean increase in body weight for adolescents compared to adults (see Table 7.5.4).

Table 7.5.4. Sponsor's Table. Mean Change from Baseline to Endpoint - Adolescents vs. Adults. Overall Combined Databases

| | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|
| Population | N | Mean | Std | Mean | Std | LSMean Change | LSMean Difference | *P-value |
| Adolescent | 450 | 67.13 | 17.72 | 7.35 | 6.58 | 6.97 | 3.71 | <.001 |
| Adult | 7847 | 78.12 | 18.86 | 3.24 | 5.82 | 3.26 | | |

From Sponsor's table APP.2.7.4.7.1.25 in summary-clin-safe-app document

In product labeling, it is stated that in the 6-week placebo-controlled studies in adults, olanzapine patients gained an average of 2.8 kg compared to a 0.4 kg weight loss in placebo patients. In study HGIN, adolescent patients receiving olanzapine gained an average of 4.26 kg compared to 0.13 kg weight gain in placebo patients.

PCS weight increase at any time– Significantly more adolescent patients had a $\geq$ 7% increase in weight (65.1%) compared to adult patients (35.6%) ($p < 0.001$).

In the 6-week placebo controlled trials in adults, 29% of olanzapine patients had a $\geq$ 7% increase in weight compared to 3% of placebo patients. In study HGIN, 45% of olanzapine patients had a $\geq$ 7% increase in weight compared to 14.7% of placebo patients.

The Sponsor did not provide an comparison of hepatic laboratory analytes between the two populations and will be asked to provide these data. Per product labeling, in placebo-controlled olanzapine monotherapy studies in adults, elevations in ALT $\geq$ 3 x ULN were observed in 2% (6/243) olanzapine patients compared to 0/115 placebo patients. In the placebo-controlled monotherapy studies in adolescents, elevations in ALT > 3 x ULN (from baseline $\leq$ 3 x ULN) were observed in 12% (21/174) of olanzapine patients compared to 2% (2/87) of placebo patients.

Prolactin
Because of differences in reference ranges between the populations, normalized units were used in the analysis of prolactin changes (% URL = % upper range limit).

Mean change from baseline to endpoint – statistically significant differences were noted between the populations with adolescents having a mean change to endpoint of 23.0 %URL compared to -4.19 %URL in adults (p = 0.004) (see Table 7.5.5).

Table 7.5.5. Sponsor's Table. Mean Change from Baseline to Endpoint in Prolactin (Normalized Units) – Adult vs. Adolescent Patients, Overall Combined Databases

| Laboratory Evaluations | Unit | Population | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| PROLACTIN | %URL | Adolescent | 431 | 78.73 | 76.47 | 23.01 | 83.69 | 9.70 | 12.62 | .004 |
| | | Adult | 4503 | 99.42 | 126.56 | -4.19 | 125.57 | -2.92 | | |

From Sponsor's table APP.2.7.4.7.4.31 in summary-clin-app document

Treatment-emergent high prolactin concentrations at any time: a higher percentage of adolescent patients (55.5%) had high prolactin concentrations at any time compared to adult patients (29%) (p < 0.001). The Sponsor did not provide an analysis for adolescent vs. adult patients by gender.

# 8 ADDITIONAL CLINICAL ISSUES

## Dosing Regimen and Administration

The proposed labeling language for Dosage and Administration is "[redacted] (b) (4)

(b) (4)

."

(b) (4)

## Advisory Committee Meeting

No advisory committee meeting was held for this submission.

## Literature Review

The Sponsor submitted a literature review though there was no attempt to summarize key findings. The Sponsor stated that none of the reviewed articles presented safety data contradictory to the conclusions presented in the NDA. Due to time constraints for this priority application, a separate literature review was not conducted by this reviewer.

## Postmarketing Risk Management Plan

The Sponsor submitted a Risk Management document outlining their proposed actions for risk minimization. The identified risks in this document included weight gain, sedation, hepatic changes, hyperprolactinemia, glucose dysregulation, dyslipidemia. For all of these safety issues, the Sponsor has proposed the following actions for pharmacovigilance: (b) (4)

Routine pharmacovigilance was defined as periodic reporting per PSUR or as appropriate. Targeted surveillance was similar but targeted weight gain, hepatic changes, glucose dysregulation and dyslipidemia. The Sponsor has proposed (b) (4)

The Sponsor (b) (4)

The actions proposed for risk minimization include product labeling and prescriber education – no details were provided regarding the latter proposal.

# 9 OVERALL ASSESSMENT

## Recommendation on Regulatory Action

I recommend that the Division take an approvable action on NDA 20-592 SE5-040 that was filed to support the indication "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents".

A number of additional requests for safety information and analysis regarding this submission are included at the end of this review. If acceptable, these requests could be included in the action letter.

## Recommendation on Postmarketing Actions

### 9.1.1 Risk Management Activity

The Sponsor included a document discussing risk management in the submission. The actions proposed for risk minimization included product labeling and prescriber education though details for the latter were not included. These actions are the minimum steps that could be taken to manage risk associated with olanzapine therapy in this patient population. Distribution of a medication education guide could reinforce risk information to patients and their families.

### 9.1.2 Required Phase 4 Commitments

Pivotal trial HGIU (as well as HGIN – schizophrenia; SE5-041) included a flexible-dose paradigm for olanzapine. As such, a dose-response relationship for efficacy and safety cannot be determined since the important parameters of dose and time on drug can only be addressed in a fixed dose trial. To minimize risk, it would be important to use the minimum effective dose to the extent that risk may be dose-related – however, in a flexible-dose design one cannot determine the dose-response for efficacy. I recommend that the Sponsor perform a fixed dose study in adolescent patients with bipolar disorder to better characterize the relationship of dose to efficacy and adverse events so that risk may be reduced.

Since bipolar disorder is a chronic illness, patients will likely require medication for a prolonged period. Some of the adverse events occurring in this adolescent patient population are significant (see Summary of Clinical Findings). It is important not only to identify these risks but to study the effect of interventions on these adverse events. The long-term cardiovascular risk of significant weight gain, hypertriglyceridemia and hypercholesterolemia is significant and efforts

to minimize these adverse events is important. I recommend that the Sponsor perform a clinical study to evaluate interventions (e.g. dietary modification, exercise) on these adverse events.

## Labeling Review

Changes to proposed labeling are being made directly to the annotated labeling submitted by the Sponsor, this was the first PLR labeling so there were many changes from prior approved labeling. The project manager, Dr. Doris Bates, reviewed the PLR labeling against the prior approved labeling and noted any differences – especially differences that were not highlighted by the Sponsor.
In the proposed labeling, (b) (4) The Sponsor has been asked to address this and had not responded at the time this review was finalized.

This section will briefly discuss some of the labeling that may require revision:
DOSAGE AND ADMINISTRATION – In the clinical trials, it was recommended to dose olanzapine in the evening due to the potential somnolence associated with the drug. In HGIU + HGIN, somnolence occurred in 25% of patients and sedation occurred in 19% of patients.
Current proposed labeling (b) (4)

WARNINGS AND PRECAUTIONS – The team will have to discuss the order of the items under this heading.

Weight Gain: should be placed earlier in this section

Transaminase Elevations: in the adult section, the number of patients with ALT $\geq 3$ times ULN data is provided. In the adolescent section, the number of patients with ALT $> 3$ times ULN data is provided. These should be consistent (should both be $\geq 3$ x ULN). In the adult section, use ALT rather than SGPT in the discussion of the larger premarketing database. In the adolescent section, I would recommend including the number of patients who discontinued due to elevations in LFTs.

Hyperprolactinemia: I would suggest including the % of patients with elevated prolactin levels for both adolescents and adults in the placebo-controlled acute trials.

Laboratory Tests: The information with regard to glucose monitoring should be included here.

ADVERSE REACTIONS
Other Adverse Events Observed During the Clinical Trial Evaluation of Oral Olanzapine
(b) (4)

Clinical Trials in Adolescent Patients
ECG Changes – correct spelling of Frederica to Fredericia

Postmarketing Experience
When was the last time the Sponsor updated this section? There have been some postmarketing reports of death due to diabetic ketoacidosis occurring in adolescents – should this data be included in this section?

## Comments to Applicant

*Requests for information*

The Sponsor has responded to the following requests and the reviewer has reviewed the responses

1. In protocols HGIU and HGIN, height was obtained using "a measuring device supplied by the sponsor" that required calibration. Please provide a description of this measuring device.

2. The primary efficacy analysis in study HGIN excluded data from site 021 due to GCP issues at that site (it is noted that results are similar with and without this site). Please provide details regarding the GCP issues at this site or specify where this information may be found in the study report.

3. In protocol HGIN, it is noted that "The scoring of the anchored version of the BPRS-C is determined by interviews with both the patient and the parent/legal guardian at all visits. The reference score (as recorded in the CRFs) should be the higher of the two scores". Viewing the CRF, it does not appear that there is an area where the recorder could state the source of the ratings. Are both ratings, patient and parent/legal guardian, available for subjects in this study? If so, please provide these ratings and indicate the primary source for the ratings.

4. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF analysis (similar to table HGIN 14.20 for OC analysis) - with and without site 021.

5. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF and OC analysis for the US and Russia sites separately.

6. Provide patient baseline demographics and analysis for US vs. Russia sites (similar to HGIN.11.1 but comparing US vs. Russia).

7. It is noted that 50 patients were randomized at the 5 sites in Russia - 10 patients per site. Is it coincidental that 10 subjects were randomized at each of these sites? Were caps specified to the investigators such that each site could randomize no more than 10 patients?

8. Please provide patient baseline severity of illness and statistical analysis for US vs. Russia sites (similar to HGIN.11.2 but comparing US vs. Russia). Include the following variables: age of onset of illness, # of previous schizophrenia episodes, total hospitalization, length of current

episode, days since last hospitalization, psychiatric hospitalization, CGI-S, BPRS-C subscales, BPRS-C total score, PANSS subscales, and PANSS total score

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

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

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

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

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

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

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

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

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

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

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

20. For the discontinuations due to the adverse event "weight gain" in the acute and combined databases, please provide weight data for the post-study follow-up visits. Some of the narratives

have this information, but the majority indicate that the adverse event had resolved without providing weight data.

21. It is unclear whether there was greater weight gain in patients with lower BMI at baseline (and visa versa). Please provide an analysis of weight gain based on the patient's baseline BMI to address this question.

22. Please provide the numbers of patients in both the placebo and olanzapine treatment groups who were obese (BMI > 30) at baseline and at end of study. Was there a statistical difference?

23. Please provide a subgroup analysis for laboratory data (similar to the summary in Table 2.7.4.33 in summary-clin-safety). Include all olanzapine patients who gained greater than 3.9 kg (mean weight gain from baseline) compared to all placebo patients.

The following questions were submitted to the Sponsor via email on 3/19/07. The Sponsor attempted to send an email response on 3/26/07 but encountered technical difficulties. The Sponsor faxed the response on 3/27/07 and was asked to also fax the response to this reviewer (working in another location). The Sponsor did not fax the response to this reviewer. This reviewer received the response on 4/2/07 (working in office) and had insufficient time to review the responses to meet the internal NDA deadline. Of note, request #30 was not addressed in this response and the Sponsor indicated that the response will be provided at a later date.

24. For the Acute Placebo Controlled Combined Database, please provide a subgroup analysis for age (< 15, >= 15) for the variable "weight in kg" similar to Table 2.7.4.70 in the summary-clin-safety document.

25. Please provide a subgroup analysis for age (< 15 and >=15) and gender for the variable "PCS weight change (> 7%)" for the Acute Placebo Controlled Combined Database.

26. It appears that the study report for HGIN includes all vital signs analyses for all subgroups (e.g. Table HGIN.14.47) while these analyses are only included in the study report for HGIU if the treatment by subgroups analysis was significant (e.g. HGIU.12.45). Please provide the subgroup analyses for HGIU similar to that provided in Table HGIN.14.47.

27. In section 2.7.4.7.5 of the summary-clin-safe-app document, analyses are provided for suicide-related adverse events. In reviewing Table APP.2.7.4.7.5.9 (patients with possible suicidal behavior or ideation - combined database), there appear to be 3 cases that do not have narratives listed in this document or in the Table of Significant and Notable Patients document. Please provide case narratives for the following cases: HGMF-008-0805, LOAY-401-4012 and LOAY-407-4077.

28. In the summary-clin-safe-app document, section 2.7.4.7.1.3.2.6 presents correlation coefficients between weight and a number of factors for the Overall Olanzapine Exposure Combined Database. Please provide these data for the Acute Placebo Controlled Database.

29. In the summary-clin-safe-app document, section 2.7.4.7.1.3.3 compares data between the adolescent and adult populations. For these population comparisons, the Overall Olanzapine Exposure Combined Database is used. Is a comparison of these populations including only the acute, double-blind trial data available?

30. In proposed labeling, (b) (4) from proposed product labeling.

Requests for additional information from the Sponsor – may be included in action letter:

31. Please provide narrative summaries for the following: 8 cases of gynecomastia, 1 case of opisthotonus, 1 case of "oculogyration", and two cases with high prolactin concentrations (HGIN 900-9009, HGIN 005-503) and the cases with CPK > 500 U/L.

32. Please review the MedWatch reports for fatalities and submit updates where possible for incomplete data. It was noted that these MedWatch reports had "DRAFT" at the top of the page and the date of the report was 7/27/06 - have all of these reports been previously filed with the Agency?

33. For MedWatch fatality case US_010158510, the narrative states "This is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in (b) (6). The reporter stated he has also notified the FDA...". The only MedWatch report included in this submission is for US_010158510. Please provide the MedWatch reports for the additional 4 deaths indicated in this narrative.

34. Table APP.2.7.4.24 in summary-clin-safe-app provides prolactin data over time for the overall combined database. Please provide a similar table for only those patients who completed the 19-32 weeks in the study (n = 83 bipolar, n = 93 schizophrenia) - e.g. provide baseline, 1-6 week, 7-18 week and 19-32 week data for only those patients completing 19-32 weeks.

35. One of the exclusion criteria for HGIU was "patients who have been judged clinically to be at serious suicidal risk". However, a review of the CDRS-R individual item "suicidal ideation" noted a number of patients who were rated the maximum score of "7" at baseline (has made a suicide attempt within the last month or is actively suicidal". These patients include 012-1203, 012-1212, and 024-2402. Please provide more information regarding inclusion of these patients in this study.

36. Please provide an analysis of AIMs individual items and total score (change from baseline to endpoint) for the completers in the overall combined database.

37. For HGIU and HGIN, how was "treatment-emergent" parkinsonism, akathisia and dyskinesia defined by the respective rating scales?

38. For the acute phases of HGIU and HGIN, many patients had elevated prolactin at baseline, therefore the change from baseline to endpoint analyses can be difficult to interpret. Please provide additional analyses on the subset of patients with baseline prolactin within the normal range - please provide a separate analysis for gender and age.

39. For study HGIN, it is noted that 21/72 patients in the olanzapine group and 5/35 patients in the placebo group did not have any previous medications for schizophrenia (Table HGIN.14.4). How many of these patients were from the sites in Russia? How many were first-break schizophrenic patients?

40. The summary-clin-safe-app document includes comparisons of adult and adolescent data for metabolic parameters and prolactin but not for hepatic laboratory analytes. Please provide these comparisons for hepatic laboratory analytes.

41. Please provide an analysis of mean change to endpoint for prolactin by age (< 15, > 15) for HGIN + HGIU Acute Database, HGIN and HGIU.

# 10 APPENDICES

## 10.1 Investigators and Sites

| Site # | Principal Investigator | Site & Address | # Pts Randomized | # Pts Completing DB; OL |
|---|---|---|---|---|
| 1 | Gupta, Sanjay | Global Research and Consulting<br>515 Main Street<br>Olean, NY 14760<br>USA | 9 | 6;7 |
| 5 | Bastani, Bijan | Northcoast Clinical Trials<br>3733 Park East Drive, Suite 100<br>Beachwood, OH 44122<br>USA | 3 | 1;1 |
| 7 | Brams, Matthew | Bayou City Research Corp<br>550 Westcott, #310<br>Houston, TX 77007<br>USA | 11 | 6;5 |
| 9 | Childress, Ann | Nevada Behavioral Health, Inc.<br>2055 W. Charlestone Blvd, Ste B<br>Las Vegas, NV 89102<br>USA | 2 | 2;0 |
| 10 | Cueva, Jeanette | Bioscience Research, Llc<br>222 W. 14th Street<br>New York, NY 10011<br>USA | 5 | 4;3 |
| 12 | DelBello, Melissa | Univ of Cincinnati Med Center<br>231 Albert B. Sabin Way<br>Dept. of Psychiatry<br>Cincinnati, OH 45267<br>USA | 15 | 6;6 |
| 13 | Dempsey, G. Michael | Albuquerque Neurosciences<br>715 Dr. Martin Luther King Jr.<br>Ave NE ; Suite 203<br>Albuquerque, NM 87102<br>USA | 8 | 5;3 |
| 14 | Duesenberg, David | Mercy Health Research<br>12680 Olive Blvd, Suite 200<br>St. Louis, MO 63141<br>USA | 5 | 5;4 |
| 16 | Gracious, Barbara | Strong Memorial Hospital<br>300 Crittenden Blvd<br>Dept. of Psychiatry, Box PSYCH<br>Rochester, NY 14642<br>USA | 6 | 3;1 |

| | | | | |
|---|---|---|---|---|
| 17 | Gutierrez, Rosben | Psycare, Inc.<br>2120 Thibodo Court, #230<br>Vista, CA 92083<br>USA | 1 | 0;0 |
| 19 | Kaczenski, Gregory | Summit Research Group, Llc<br>1014 Autumn Rd, Suite 3<br>Little Rock, AR 72211<br>USA | 7 | 4;4 |
| 20 | Khan, Arifulla | NW Clinical Research Center<br>1900 116th Ave, NE<br>Bellevue, WA 98004<br>USA | 16 | 14;9 |
| 21 | Krishnasastry, Chandra | Tennessee Christian Med Center<br>320 Hospital Drive<br>Madison, TN 37115<br>USA | 4 | 4;2 |
| 23 | Mintz, Mark | Bancroft Neurohealth<br>201 King's Highway South<br>Cherry Hill, NJ 08034<br>USA | 2 | 2 ;2 |
| 24 | Pathak, Anjali | AP Psychiatric & Counseling Service, Inc.<br>5251 Emerson St<br>Jacksonville, FL 32207<br>USA | 5 | 5;3 |
| 26 | Plopper, Michael | Sharp Mesa Vist Hospital<br>7850 Vista Hill Avenue<br>San Diego, CA 92123<br>USA | 7 | 6;3 |
| 27 | Riesenberg, Robert | Atlanta Center of Med Research<br>811 Juniper Street<br>Atlanta, GA 30308<br>USA | 7 | 7;3 |
| 28 | Robb, Adelaide | Children's National Med Center<br>111 Michigan Ave, NW<br>Washington, DC 20010<br>USA | 4 | 3; 0 [1] |
| 31 | Soni, Poonam | Univ of Utah School of Medicine<br>Mood Disorder Clinic, Rm 5R218<br>Dept. of Psychiatry<br>30 N. 1900 East<br>Salt Lake City, UT 84132<br>USA | 4 | 3;2 |

| | | | | |
|---|---|---|---|---|
| 33 | Wozniak, Janet | Massachusetts General Hospital<br>185 Alewife Brook Parkway,<br>Suite 200<br>Cambridge, MA 02138<br>USA | 3 | 3;1 |
| 34 | Bhatia, Prakash | Synergy Clinical Research<br>5577 University Avenue<br>San Diego, CA 92105<br>USA | 1 | 1;0 |
| 35 | Yadalam, Kashinath | Institute for Neuropsychiatry<br>2829 4th Avenue<br>Lake Charles, LA 70601<br>USA | 10 | 7;3 |
| 36 | Terry, William | Mountain West Clinical Trials<br>1166 N. Cole Road, Suite D<br>Boise, ID 89704<br>USA | 8 | 7;5 |
| 720 | Varela, Alberto | Instituto Psicoterapeutico de<br>Puerto Rico<br>Hostos Avenue 405<br>San Juan, 00918<br>Puerto Rico | 17 | 15;10 |
| 730 | Velez, Jesus | RCMI-Clinic Research Center<br>University District Hospital<br>1st Floor Clinical Research<br>Center<br>Rio Piedras, 00936<br>Puerto Rico | 1 | 1;0 |

[1] Site was closed by sponsor due to protocol violations. Patients were discontinued.

## 10.2 Inclusion and Exclusion Criteria

*Inclusion Criteria*

1. Are male or female patients, 13 to 17 years of age, but must not yet have reached their 18th birthday prior to Visit 1, when informed consent is obtained.
2. Patient must have a diagnosis of bipolar I disorder and currently display an acute manic or mixed episode (with or without psychotic features) according to DSM-IV-TR and confirmed by the K-SADS-PL. Patients must meet diagnostic criteria at Visits 1 and 2.
3. Female patients of childbearing potential (not surgically sterilized) must test negative for pregnancy at the time of enrollment based on a serum pregnancy test. Furthermore, female patients must agree to abstain from sexual activity or to use a medically acceptable method of birth control during their participation in the study.
4. Each patient and the patient's parent/authorized legal representative must understand the nature of the study. The patient's parent/authorized legal representative must sign an informed consent document and the patient must sign an informed consent document/assent document as required by local regulations.

5. Each patient and the patient's parent/authorized legal representative must have a level of understanding sufficient to perform all tests and examinations required by the protocol.
6. Patients must have a YMRS total score $\geq 20$ at both Visits 1 and 2.
7. Patients must be capable of swallowing study medication whole (without crushing, dissolving, etc.).

*Exclusion criteria*

1. Are investigator site personnel directly affiliated with the study, or are immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted.
2. Are employed by Lilly (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical trials, but are not permitted to participate at a Lilly facility. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted.
3. Patients who have participated in a clinical trial of oral olanzapine or have received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry.
4. Female patients who are either pregnant or nursing.
5. Patients, who, in the opinion of the investigator, are unsuitable in any other way to participate in this study including being unable to comply with the requirements of the study for any reason.
6. Patients with acute or unstable medical conditions, including (but not limited to) inadequately controlled diabetes, hepatic insufficiency (specifically any degree of jaundice), uncorrected hypothyroidism or hyperthyroidism, acute systemic infection, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic diseases (specifically current agranulocytosis with an absolute neutrophil count $< 500\ mm^3$).
7. Patients with acute or unstable medical conditions, such that intensive care unit hospitalization for the disease is anticipated within 6 months.
8. DSM-IV-TR substance (except nicotine and caffeine) dependence within the past 30 days.
9. Patients who have undergone treatment with remoxipride within 6 months (180 days) prior to Visit 2.
10. Any concomitant medication with primarily central nervous system activity, including alternative medications, other than specified as permitted in Table HGIU.2 and HGIU.3 at Visit 2.
11. Patients who have been judged clinically to be at serious suicidal risk.
12. Patients who have experienced one or more seizures without a clear and resolved etiology.
13. Patients with a documented history of allergic reaction to olanzapine.
14. Treatment with an injectable neuroleptic $\leq 14$ days before Visit 2.
15. Prolactin level at Visit 1 $\geq 200$ ng/ml.
16. Patients who have previously not responded to an adequate dose and/or duration of olanzapine treatment.

17. Laboratory results, including serum chemistries, hematology, and urinalysis, must show no clinically significant abnormalities. In addition, there must be no clinical information that, in the judgment of a physician, should preclude a patient's participation at study entry.
18. Use of any concomitant medication(s) at Visit 2 as specified in Section 5.7 or expected to need treatment with any medication during the study other than what is allowed.
19. Patients who have a history of mental retardation, current comorbid autism, or current comorbid pervasive developmental disorder.
20. Patients who have used monoamine oxidase inhibitors (MAOIs) within 14 days prior to Visit 2 or are expected to need treatment at any time during this study.
21. Patients having psychosis or bipolar symptoms related to an underlying medical condition.
22. Current diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder as defined in the DSM-IV-TR.

10.3 Sponsor's Table. Schedule of Events – HGIU

**Table HGIU.9.4. Study Schedule, Protocol F1D-MC-HGIU**

| Description of Data | V1 | V2 | V3 | V4 | V5 | V6 | Sum. Visit SP III[i] | V301 | V302 | V303 | V304 | V305 | V306 | V307 | V308 | V309 | V310 | Sum. Visit SP III[i] | Follow-Up (V501) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Weeks until next visit | 2-14 days | 3 days | 4 days | 1 | 1 | 1 | | 1 | 1 | 2 | 2 | 2 | 2 | 4 | 4 | 4 | | | |
| **Screening and Inclusion Measures** | | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | |
| K-SADS-PL | X | | | | | | | | | | | | | | | | | | |
| Study drug compliance | | | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | |
| Study drug dispensed | | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | | | |
| **Safety Measures** | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | |
| Weight and temperature | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | |
| Height | X | | X | | | X | X | | X | | X | X | X | X | X | X | X | X | |
| Blood pressure[a] and heart rate | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | |
| Psychiatric examination | X | | | | | | | | | | | | | | | | | | |
| Physical examination | X | | | | | | | | | | | | | | | | | | |
| Electrocardiography[b] | X | | | | | | X | | | | | | | | | | | X | |
| Preexisting conditions and adverse events | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | X |
| AIMS, Barnes Akathisia, Simpson-Angus | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | |
| Historical illnesses / Previous medications Family history | X | | | | | | | | | | | | | | | | | | |

| Description of the Data | V1 | V2 | V3 | V4 | V5 | V6 | Sum. Visit SP IIi | V301 | V302 | V303 | V304 | V305 | V306 | V307 | V308 | V309 | V310 | Sum. Visit SP IIIi | Follow-Up (V501) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Weeks until next visit | 2-14 days | 3 days | 4 days | 1 | 1 | 1 | | 1 | 1 | 2 | 2 | 2 | 2 | 4 | 4 | 4 | | | |
| **Safety Measures, Cont.** | | | | | | | | | | | | | | | | | | | |
| Habits (tobacco, alcohol, drugs) | X | | | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | X |
| Visit comments | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | X |
| Patient summary including comments | | | | | | | X | | | | | | | | | | | X | |
| Adverse event follow-up, if necessary | | | | | | | | | | | | | | | | | | | X |
| **Laboratory Tests**[c] | | | | | | | | | | | | | | | | | | | |
| Clinical chemistry[d] / Electrolytes / Lipids[e] | X | X | | X | X | X | X | | X | | X | | X | X | X | X | X | X | |
| Hematology | X | X | | X | X | X | X | | X | | X | | X | X | X | X | X | X | |
| Urinalysis | X | | | | | | X | | | | | | | | | | | X | |
| Hepatitis screen, urine drug screen[f], serum pregnancy test[f], and TSH | X | | | | | | | | | | | | | | | | | | |
| Prolactin[g] | X | X | | | | | X | | | | | | | X | | | | X | |
| HgbA1c [h] | X | | | | | | X | | | | | | | X | | | | X | |
| Behavioral Intervention (optional) | | | | | | | X | X | X | X | X | X | X | X | X | X | X | | |

| Description of the Data | V1 | V2 | V3 | V4 | V5 | V6 | Sum. Visit SP IIi | V301 | V302 | V303 | V304 | V305 | V306 | V307 | V308 | V309 | V310 | Sum. Visit SP IIIi | Follow-Up (V501) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Weeks until next visit | 2-14 days | 3 days | 4 days | 1 | 1 | 1 | | 1 | 1 | 2 | 2 | 2 | 2 | 4 | 4 | 4 | | | |
| **Efficacy Measures** | | | | | | | | | | | | | | | | | | | |
| YMRS | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | |
| CGI-BP Severity of Illness | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | |
| OAS | | X | | | | | X | | | | | | | | | | | X | |
| ADHDRS-IV-PI | | X | | | | | X | | | | | | | | | | | X | |
| CDRS-R | | X | | | | | X | | | X | | | X | | | | | X | |
| **Health Outcome Measures** | | | | | | | | | | | | | | | | | | | |
| CHQ | | X | | | | | X | | | | | | | | | | | X | |
| **General** | | | | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | X |
| Visit comments | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | X |
| Patient summary including comments | | | | | | | X | | | | | | | | | | | X | |
| Adverse event follow-up, if necessary | | | | | | | | | | | | | | | | | | | X |

## 10.4 YMRS Individual Item Analyses

Table 10.4.1. Sponsor's Table. YMRS Individual Item Analyses

**Table HGIU.11.22. YMRS Individual Items**
**Mean Change from Baseline to Endpoint (LOCF)**
**Double-Blind Period**

| Efficacy Variable | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|
| YMRS1: Elevated Mood | Olanzapine | 105 | 2.79 | 0.99 | -1.50 | 1.19 | -1.40 | -0.71 | <.001 |
| | Placebo | 54 | 2.74 | 0.78 | -0.76 | 1.26 | -0.69 | | |
| YMRS2: Increased Motor Activity-Energy | Olanzapine | 105 | 2.95 | 0.90 | -1.32 | 1.44 | -1.21 | -0.70 | <.001 |
| | Placebo | 54 | 2.80 | 0.76 | -0.52 | 1.13 | -0.51 | | |
| YMRS3: Sexual Interest | Olanzapine | 105 | 1.14 | 1.08 | -0.63 | 0.95 | -0.72 | -0.14 | .249 |
| | Placebo | 54 | 1.33 | 1.13 | -0.59 | 0.94 | -0.58 | | |
| YMRS4: Sleep | Olanzapine | 105 | 2.42 | 1.08 | -1.79 | 1.43 | -1.98 | -0.71 | <.001 |
| | Placebo | 54 | 2.30 | 1.19 | -0.98 | 1.30 | -1.26 | | |
| YMRS5: Irritability | Olanzapine | 105 | 5.48 | 1.32 | -1.90 | 2.10 | -2.32 | -0.92 | .004 |
| | Placebo | 54 | 5.28 | 1.37 | -0.91 | 1.72 | -1.40 | | |
| YMRS6: Speech(Rate and Amount) | Olanzapine | 105 | 5.14 | 1.53 | -2.93 | 2.01 | -2.96 | -1.59 | <.001 |
| | Placebo | 54 | 4.69 | 1.66 | -1.07 | 2.21 | -1.37 | | |
| YMRS7: Language Thought Disorder | Olanzapine | 105 | 2.24 | 0.58 | -0.92 | 0.90 | -1.18 | -0.47 | <.001 |
| | Placebo | 54 | 2.11 | 0.66 | -0.37 | 0.90 | -0.71 | | |
| YMRS8: Content | Olanzapine | 105 | 3.41 | 2.29 | -1.86 | 2.39 | -2.08 | -0.73 | .019 |
| | Placebo | 54 | 3.11 | 2.13 | -0.94 | 2.12 | -1.35 | | |

| Efficacy Variable | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|
| YMRS9: Disruptive-Aggressive Behavior | Olanzapine | 105 | 4.84 | 1.37 | -1.84 | 2.12 | -2.10 | -0.93 | .006 |
| | Placebo | 54 | 4.74 | 1.58 | -0.87 | 1.94 | -1.18 | | |
| YMRS10: Appearance | Olanzapine | 105 | 1.18 | 1.05 | -0.52 | 0.94 | -0.61 | -0.47 | <.001 |
| | Placebo | 54 | 1.24 | 1.10 | -0.09 | 1.17 | -0.14 | | |
| YMRS11: Insight | Olanzapine | 105 | 1.49 | 1.39 | -0.69 | 1.15 | -0.96 | -0.19 | .268 |
| | Placebo | 54 | 1.70 | 1.37 | -0.61 | 1.45 | -0.77 | | |

## 10.5 Children's Depression Rating Scale - Individual Items

### Table 10.5.1. Sponsor's Table. CDRS-R Individual Items

**Table HGIU.11.25. CDRS-R Individual Items**
**Mean Change from Baseline to Endpoint (LOCF)**
**Double-Blind Period**

| Efficacy Variable | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|
| CDRS1: Impaired School Work | Olanzapine | 100 | 3.64 | 1.83 | -0.79 | 1.56 | -1.06 | -0.17 | .482 |
| | Placebo | 53 | 3.23 | 1.94 | -0.36 | 2.06 | -0.89 | | |
| CDRS2: Difficulty Having Fun | Olanzapine | 100 | 2.74 | 1.73 | -0.33 | 1.54 | -0.56 | 0.35 | .103 |
| | Placebo | 53 | 2.49 | 1.85 | -0.53 | 1.65 | -0.91 | | |
| CDRS3: Social Withdrawal | Olanzapine | 100 | 2.41 | 1.46 | -0.37 | 1.34 | -0.43 | 0.31 | .098 |
| | Placebo | 53 | 1.98 | 1.65 | -0.45 | 1.32 | -0.74 | | |
| CDRS4: Sleep Disturbance | Olanzapine | 100 | 3.36 | 1.67 | -1.56 | 1.87 | -1.59 | -0.64 | .009 |
| | Placebo | 53 | 2.87 | 1.65 | -0.55 | 1.75 | -0.96 | | |
| CDRS5: Appetite Disturbance | Olanzapine | 100 | 1.92 | 1.29 | 0.51 | 1.54 | 0.33 | 1.00 | <.001 |
| | Placebo | 53 | 1.87 | 1.23 | -0.45 | 1.32 | -0.66 | | |
| CDRS6: Excessive Fatigue | Olanzapine | 100 | 2.66 | 2.06 | -0.58 | 2.03 | -0.75 | 0.56 | .014 |
| | Placebo | 53 | 2.45 | 1.88 | -0.98 | 1.78 | -1.31 | | |
| CDRS7: Physical Complaints | Olanzapine | 100 | 1.90 | 1.47 | -0.35 | 1.42 | -0.48 | -0.02 | .925 |
| | Placebo | 53 | 1.75 | 1.25 | -0.23 | 1.38 | -0.47 | | |
| CDRS8: Irritability | Olanzapine | 100 | 4.60 | 1.44 | -1.29 | 1.87 | -1.29 | -0.38 | .124 |
| | Placebo | 53 | 4.45 | 1.53 | -0.79 | 1.79 | -0.90 | | |

| Efficacy Variable | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|
| CDRS9: Excessive Guilt | Olanzapine | 100 | 1.68 | 1.13 | -0.31 | 0.83 | -0.26 | 0.07 | .515 |
| | Placebo | 53 | 1.45 | 0.87 | -0.28 | 0.74 | -0.33 | | |
| CDRS10: Low Self-Esteem | Olanzapine | 100 | 2.76 | 1.75 | -0.37 | 1.64 | -0.49 | -0.05 | .824 |
| | Placebo | 53 | 2.23 | 1.35 | -0.11 | 1.28 | -0.44 | | |
| CDRS11: Depressed Feelings | Olanzapine | 100 | 2.57 | 1.46 | -0.45 | 1.33 | -0.56 | -0.02 | .912 |
| | Placebo | 53 | 2.02 | 1.35 | -0.13 | 1.37 | -0.54 | | |
| CDRS12: Morbid Ideation | Olanzapine | 100 | 1.81 | 1.35 | -0.33 | 1.10 | -0.37 | -0.10 | .530 |
| | Placebo | 53 | 1.62 | 1.21 | -0.13 | 1.21 | -0.27 | | |
| CDRS13: Suicidal Ideation | Olanzapine | 100 | 1.77 | 1.32 | -0.47 | 1.21 | -0.44 | 0.03 | .769 |
| | Placebo | 53 | 1.42 | 0.95 | -0.23 | 0.91 | -0.47 | | |
| CDRS14: Excessive Weeping | Olanzapine | 100 | 1.87 | 1.32 | -0.30 | 1.39 | -0.39 | 0.04 | .840 |
| | Placebo | 53 | 1.75 | 1.33 | -0.26 | 1.60 | -0.43 | | |
| CDRS15: Depressed Facial Affect | Olanzapine | 100 | 1.90 | 1.17 | -0.03 | 1.18 | -0.18 | 0.32 | .042 |
| | Placebo | 53 | 1.62 | 1.16 | -0.15 | 1.18 | -0.50 | | |
| CDRS16: Listless Speech | Olanzapine | 100 | 1.35 | 0.59 | -0.02 | 0.70 | -0.09 | 0.13 | .155 |
| | Placebo | 53 | 1.28 | 0.69 | -0.09 | 0.77 | -0.22 | | |

| Efficacy Variable | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|
| CDRS17: Hypoactivity | Olanzapine | 100 | 1.49 | 0.95 | -0.14 | 0.89 | -0.15 | 0.10 | .334 |
| | Placebo | 53 | 1.28 | 0.86 | -0.11 | 0.78 | -0.26 | | |

## 10.6 ADHDRS and OAS Analyses

### Table 10.6.1 Sponsor's Table. Mean Change from Baseline to Endpoint: ADHDRS Total Score

**Table HGIU.11.26. ADHDRS-IV-PI Total Score**
**Mean Change from Baseline to Endpoint (LOCF)**
**Double-Blind Period**

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy Variable | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Diff. | *P-value |
| ADHDRS - hyperactivity-impulsivity subtotal | Olanzapine | 100 | 13.84 | 6.81 | -4.96 | 6.19 | -5.29 | -2.42 | .008 |
| | Placebo | 50 | 11.56 | 5.39 | -1.62 | 4.33 | -2.87 | | |
| ADHDRS - Inattention subtotal | Olanzapine | 99 | 15.21 | 8.02 | -3.15 | 6.11 | -4.43 | -0.81 | .388 |
| | Placebo | 51 | 13.67 | 7.49 | -1.73 | 5.77 | -3.62 | | |
| ADHDRS-IV inv. scored total | Olanzapine | 99 | 73.46 | 16.45 | -9.47 | 13.64 | -11.36 | -3.96 | .048 |
| | Placebo | 50 | 69.72 | 13.86 | -3.97 | 10.64 | -7.40 | | |

### Table 10.6.2 Sponsor's Table. Mean Change from Baseline to Endpoint: Overt Aggression Scale

**Table HGIU.11.27. OAS Total and Subtotal Scores**
**Mean Change from Baseline to Endpoint (LOCF)**
**Double-Blind Period**

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy Variable | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Difference | *P-value |
| Verbal Aggression Total | Olanzapine | 100 | 2.74 | 1.31 | -1.17 | 1.65 | -1.43 | -0.68 | .004 |
| | Placebo | 52 | 2.73 | 1.21 | -0.48 | 1.34 | -0.75 | | |
| Physical Aggression Toward Self Total | Olanzapine | 100 | 0.84 | 1.12 | -0.58 | 1.03 | -0.54 | -0.18 | .071 |
| | Placebo | 52 | 0.58 | 0.85 | -0.19 | 0.91 | -0.36 | | |
| Physical Aggression Towards Others Total | Olanzapine | 100 | 1.18 | 1.20 | -0.72 | 1.39 | -0.65 | -0.42 | .010 |
| | Placebo | 52 | 1.00 | 1.12 | -0.15 | 1.26 | -0.23 | | |
| Physical Aggression Toward Objects | Olanzapine | 100 | 1.58 | 1.14 | -0.86 | 1.14 | -0.99 | -0.36 | .026 |
| | Placebo | 52 | 1.42 | 1.02 | -0.40 | 1.19 | -0.63 | | |
| Total of OAS01-OAS16 | Olanzapine | 100 | 6.34 | 3.67 | -3.33 | 3.92 | -3.60 | -1.70 | <.001 |
| | Placebo | 52 | 5.73 | 2.94 | -1.23 | 3.08 | -1.90 | | |

10.7 YMRS Total Score – Additional Age Subgroup Analyses

Table 10.7.1 Sponsor's Table.

**Table HGIU.11.19. YMRS Total Score Age Subgroup Analysis Mean Change from Baseline to Endpoint (LOCF) Age as a Continuous Variable**

| | | Baseline | | Change to Endpoint | | | | | **P-value |
|---|---|---|---|---|---|---|---|---|---|
| N | Therapy | Mean | Std | Mean | Std | LSMean Change | LSMean Diff. | *P-value | Age*Therapy |
| 105 | Olanzapine | 33.08 | 6.55 | -15.90 | 10.03 | -17.65 | -7.66 | <.001 | .626 |
| 54 | Placebo | 32.04 | 6.23 | -7.72 | 9.42 | -9.99 | | | |

Table 10.7.2 Sponsor's Table

**Table HGIU.11.20. YMRS Total Score Age Subgroup Analysis Mean Change from Baseline to Endpoint (LOCF) Alternative Age Subgroup Categorization**

| | | | Baseline | | | Change to Endpoint | | | | | **P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Strata | N | Therapy | n | Mean | Std | Mean | Std | LSMean Change | LSMean Diff. | *P-value | Therapy*Age |
| <16 | 118 | Olanzapine | 79 | 32.91 | 6.72 | -15.80 | 10.23 | -17.73 | -7.13 | <.001 | .577 |
| | | Placebo | 39 | 32.85 | 6.27 | -8.31 | 9.64 | -10.61 | | | |
| >=16 | 41 | Olanzapine | 26 | 33.58 | 6.09 | -16.23 | 9.59 | -17.26 | -8.37 | .010 | |
| | | Placebo | 15 | 29.93 | 5.79 | -6.20 | 8.95 | -8.88 | | | |

Table 10.7.3 Sponsor's Table.

**Table HGIU.11.21. YMRS Total Score Age Subgroup Analysis**
**Mean Change from Baseline to Endpoint (LOCF)**
**Age Subgroups Based on Age at Last Birthday**

| | | | | Baseline | | Change to Endpoint | | | | | **P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Strata | N | Therapy | n | Mean | Std | Mean | Std | LSMean Change | LSMean Diff. | *P-value | Therapy*Age |
| 13 | 31 | Olanzapine | 22 | 32.73 | 6.90 | -16.50 | 8.94 | -18.95 | -10.49 | .007 | .068 |
| | | Placebo | 9 | 31.89 | 7.52 | -4.22 | 10.23 | -8.46 | | | |
| 14 | 38 | Olanzapine | 27 | 32.81 | 7.15 | -13.11 | 11.00 | -13.58 | 0.64 | .865 | |
| | | Placebo | 11 | 32.82 | 4.00 | -13.73 | 9.98 | -14.22 | | | |
| 15 | 49 | Olanzapine | 30 | 33.13 | 6.41 | -17.70 | 10.22 | -19.73 | -10.52 | <.001 | |
| | | Placebo | 19 | 33.32 | 6.94 | -7.11 | 8.14 | -9.21 | | | |
| 16 | 27 | Olanzapine | 17 | 34.00 | 6.06 | -16.65 | 6.44 | -20.18 | -9.86 | .008 | |
| | | Placebo | 10 | 29.50 | 5.17 | -6.60 | 9.05 | -10.32 | | | |
| 17 | 14 | Olanzapine | 9 | 32.78 | 6.44 | -15.44 | 14.27 | -15.61 | -8.35 | .213 | |
| | | Placebo | 5 | 30.80 | 7.46 | -5.40 | 9.76 | -7.27 | | | |

10.8 Patient Baseline Demographics – HGIN + HGIU Acute Database and Overall Combined Database

Table 10.8.1 Sponsor's Table

**Table 2.7.4.21. Patient Demographics at Baseline**
**All Randomized Patients**
**Acute Placebo-Controlled Combined Database**

| | | Olanzapine (N=179) | Placebo (N=89) | |
|---|---|---|---|---|
| Demographic Variables | Statistics/ Category | n (%) | n (%) | *P-value |
| Gender | Male | 112(62.57) | 48(53.93) | .188 |
| | Female | 67(37.43) | 41(46.07) | |
| Age | No. of Patients | 179 | 89 | |
| | Mean | 15.54 | 15.74 | .200 |
| | Median | 15.54 | 15.62 | |
| | Std. Dev. | 1.36 | 1.42 | |
| | Minimum | 13.02 | 13.06 | |
| | Maximum | 17.99 | 18.00 | |
| Origin | African Descent | 30(16.76) | 9(10.11) | .359 |
| | Caucasian | 123(68.72) | 66(74.16) | |
| | East/Southeast Asian | 0(0.0) | 1(1.12) | |
| | Hispanic | 20(11.17) | 9(10.11) | |
| | Other | 6(3.35) | 4(4.49) | |
| Country | United States | 133(74.30) | 67(75.28) | 1.00 |
| | Puerto Rico | 12(6.70) | 6(6.74) | |
| | Russia | 34(18.99) | 16(17.98) | |

Table 10.8.2 Sponsor's Table. Age Distribution at Baseline (HGIN + HGIU)

**Table 2.7.4.22. Age Distribution at Baseline**
**All Randomized Patients**
**Acute Placebo-Controlled Combined Database**

| | HGIN | | HGIU | | Combined | |
|---|---|---|---|---|---|---|
| Age Group | n | % | n | % | n | % |
| 13 | 9 | 8.4% | 31 | 19.3% | 40 | 14.9% |
| 14 | 13 | 12.1% | 38 | 23.6% | 51 | 19.0% |
| 15 | 20 | 18.7% | 50 | 31.1% | 70 | 26.1% |
| 16 | 29 | 27.1% | 27 | 16.8% | 56 | 20.9% |
| 17 | 36 | 33.6% | 15 | 9.3% | 51 | 19.0% |
| Total | 107 | 100.0% | 161 | 100.0% | 268 | 100.0% |

Table 10.8.3 Sponsor's Table. Patient Demographics at Baseline – Overall Olanzapine Combined Database

**Table 2.7.4.24. Patient Demographics at Baseline**
**All Patients with Olanzapine Exposure**
**Overall Olanzapine Exposure Combined Database**

| | | Bipolar (N=227) | Schizophrenia (N=227) | Overall (N=454) |
|---|---|---|---|---|
| Demographic Variables | Statistics/ Category | n (%) | n (%) | n (%) |
| Gender | Male | 124(54.63) | 162(71.37) | 286(63.00) |
| | Female | 103(45.37) | 65(28.63) | 168(37.00) |
| Age | No. of Patients | 227 | 227 | 454 |
| | Mean | 15.44 | 16.38 | 15.91 |
| | Median | 15.43 | 16.67 | 16.02 |
| | Std. Dev. | 1.33 | 1.27 | 1.38 |
| | Minimum | 13.02 | 13.03 | 13.02 |
| | Maximum | 18.00 | 18.00 | 18.00 |
| Origin | African Descent | 22(9.69) | 28(12.33) | 50(11.01) |
| | Caucasian | 166(73.13) | 189(83.26) | 355(78.19) |
| | East/Southeast Asian | 1(0.44) | 0(0.0) | 1(0.22) |
| | Hispanic | 31(13.66) | 6(2.64) | 37(8.15) |
| | Other | 7(3.08) | 4(1.76) | 11(2.42) |
| Country | United States | 205(90.31) | 58(25.55) | 263(57.93) |
| | Puerto Rico | 21(9.25) | 1(0.44) | 22(4.85) |
| | Russia | 1(0.44) | 79(34.80) | 80(17.62) |
| | Germany | 0(0.0) | 89(39.21) | 89(19.60) |

## 10.9 Weight Gain – Additional Analyses

Table 10.9.1. Weight Change by Visit (OC): Overall Combined Database

| | | | | Change to Maximum | | |
|---|---|---|---|---|---|---|
| | | Visit Week | N | Mean | Std | P-value |
| Weight (kg) | Bipolar | ≤ 1 | 224 | 1.27 | 1.55 | < 0.001 |
| | Schizophrenia | | 224 | 1.75 | 1.51 | < 0.001 |
| | Overall | | 448 | 1.51 | 1.55 | < 0.001 |
| | Bipolar | > 1 ≤ 2 | 221 | 2.29 | 2.04 | < 0.001 |
| | Schizophrenia | | 219 | 2.73 | 1.96 | < 0.001 |
| | Overall | | 440 | 2.51 | 2.01 | < 0.001 |
| | Bipolar | > 2 ≤ 3 | 183 | 3.07 | 2.62 | < 0.001 |
| | Schizophrenia | | 148 | 3.46 | 2.24 | < 0.001 |
| | Overall | | 331 | 3.25 | 2.46 | < 0.001 |
| | Bipolar | > 3 ≤ 4 | 199 | 3.74 | 2.84 | < 0.001 |
| | Schizophrenia | | 201 | 4.02 | 2.51 | < 0.001 |
| | Overall | | 400 | 3.88 | 2.68 | < 0.001 |
| | Bipolar | > 4 ≤ 5 | 167 | 4.05 | 3.31 | < 0.001 |
| | Schizophrenia | | 147 | 4.66 | 2.42 | < 0.001 |
| | Overall | | 314 | 4.34 | 2.94 | < 0.001 |
| | Bipolar | > 5 ≤ 9 | 157 | 6.03 | 3.80 | < 0.001 |
| | Schizophrenia | | 130 | 7.12 | 3.80 | < 0.001 |
| | Overall | | 287 | 6.52 | 3.83 | < 0.001 |
| | Bipolar | > 9 ≤ 13 | 121 | 7.59 | 4.95 | < 0.001 |
| | Schizophrenia | | 117 | 8.17 | 4.84 | < 0.001 |
| | Overall | | 238 | 7.87 | 4.89 | < 0.001 |
| | Bipolar | > 13 ≤ 17 | 114 | 8.84 | 5.87 | < 0.001 |
| | Schizophrenia | | 103 | 9.01 | 6.03 | < 0.001 |
| | Overall | | 217 | 8.92 | 5.93 | < 0.001 |
| | Bipolar | > 17 ≤ 21 | 102 | 9.69 | 6.43 | < 0.001 |
| | Schizophrenia | | 88 | 10.2 | 6.75 | < 0.001 |
| | Overall | | 190 | 9.93 | 6.56 | < 0.001 |
| | Bipolar | > 21 ≤ 25 | 93 | 10.19 | 6.98 | < 0.001 |
| | Schizophrenia | | 81 | 10.84 | 6.92 | < 0.001 |
| | Overall | | 174 | 10.49 | 6.94 | < 0.001 |
| | Bipolar | > 25 ≤ 32 | 53 | 9.60 | 7.12 | < 0.001 |
| | Schizophrenia | | 78 | 11.68 | 7.62 | < 0.001 |
| | Overall | | 131 | 10.84 | 7.46 | < 0.001 |

From Sponsor table APP.2.7.4.7.1.18 in summary-clin-safe-app document

Table 10.9.2. Adverse Event "Weight Increased" Gender Analysis: HGIU and HGIN Acute Phases

| | | | Olanzapine | | | Placebo | | | p-value | Homogeneity of Odds Ratio |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Gender | N | n | % | N | n | % | | |
| Weight Increased | HGIU | Female | 46 | 16 | 35% | 30 | 1 | 3% | 0.001 | |
| | | Male | 61 | 15 | 25% | 24 | 1 | 4% | 0.033 | 0.628 |
| | HGIN | Female | 21 | 6 | 29% | 11 | 2 | 18% | 0.681 | |
| | | Male | 51 | 16 | 31% | 24 | 1 | 4% | 0.008 | 0.186 |
| | | | | | | | | | | |
| Weight Increased | HGIU | < 15 yrs | 49 | 14 | 29% | 20 | 0 | 0 | 0.007 | |
| | | ≥ 15 yrs | 58 | 17 | 29% | 34 | 2 | 6% | 0.008 | 0.280 |
| | HGIN | < 15 yrs | 15 | 6 | 40% | 7 | 1 | 14% | 0.350 | |
| | | ≥ 15 yrs | 57 | 16 | 28% | 28 | 2 | 7% | 0.045 | 0.868 |

From Sponsor Tables HGIN.14.28 and HGIU.14.31

Table 10.9.3. Mean Change in Weight (kg) – Subgroup Analyses: HGIN

| | | | | Baseline | | Change to Endpoint | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Subgroup | Therapy | n | Mean | St.Dev | Mean | St. Dev | LS Mean | LSMean Diff | P-value | P-value |
| **HGIN** | | | | | | | | | | | |
| Weight (kg) | Female | Olanzapine | 21 | 64.0 | 16.6 | 3.8 | 3.7 | 3.4 | | | |
| | | Placebo | 10 | 61.0 | 12.5 | 0.8 | 3.5 | 0.7 | 2.73 | 0.063 | |
| | Male | Olanzapine | 51 | 68.3 | 11.6 | 4.5 | 3.2 | 4.6 | | | |
| | | Placebo | 24 | 72.2 | 17.6 | -0.2 | 2.5 | -0.2 | 4.76 | < 0.001 | 0.140 |
| | < 15 yrs | Olanzapine | 15 | 64.7 | 14.0 | 6.3 | 4.2 | 5.2 | | | |
| | | Placebo | 7 | 62.5 | 9.6 | 1.1 | 4.1 | -0.2 | 5.37 | 0.009 | |
| | | | | | | | | | | | |
| | ≥ 15 yrs | Olanzapine | 57 | 67.7 | 13.2 | 3.7 | 2.9 | 3.8 | | | |
| | | Placebo | 27 | 70.6 | 18.1 | -0.1 | 2.4 | -0.1 | 3.84 | < 0.001 | 0.370 |
| | | | | | | | | | | | |

From Sponsor Tables HGIN.14.47

Table 10.9.4. Mean Change from Baseline to Endpoint in Laboratory Values – Patients Who Gained > 3.9 kg vs. Placebo

*The LS Mean Change and p-value for the entire population is in parenthesis for comparison purposes*

| | | | Baseline | Change to Endpoint | | | |
|---|---|---|---|---|---|---|---|
| | Therapy | n | Mean | Mean | LS Mean Change | LSMean Diff | P-value |
| AST (U/L) | Olanzapine | 84 | 21.9 | 9.5 | 11.3 | | |
| | Placebo | 87 | 23.6 | -2.5 | -0.4 | 11.7 | < 0.001 |
| | | | | | | (8.91) | (0.002) |
| ALT (U/L) | Olanzapine | 84 | 20.8 | 25.8 | 29.6 | | |
| | Placebo | 87 | 20.4 | -3.1 | 1.0 | 28.5 | < 0.001 |
| | | | | | | (23.0) | (< 0.001) |
| CPK (U/L) | Olanzapine | 84 | 125 | 18.1 | 16.8 | | |
| | Placebo | 87 | 164 | -23.6 | -21.9 | 38.7 | 0.037 |
| | | | | | | (16.1) | (0.38) |
| Glucose, fasting (mg/dL)* | Olanzapine | 58 | 88.8 | 3.2 | 4.3 | | |
| | Placebo | 64 | 89.7 | -2.9 | -2.0 | 6.3 | 0.001 |
| | | | | | | (5.6) | (< 0.001) |
| Cholesterol (mg/dL)* | Olanzapine | 84 | 164.1 | 17.4 | 13.5 | | |
| | Placebo | 87 | 160.2 | -1.1 | -4.6 | 18.5 | < 0.001 |
| | | | | | | (14.3) | (< 0.001) |
| Triglycerides (mg/dL)* | Olanzapine | 84 | 97.3 | 51.3 | 46.9 | | |
| | Placebo | 87 | 110.6 | -4.4 | -7.1 | 54.0 | < 0.001 |
| | | | | | | (33.6) | (<0.001) |
| LDL (mg/dL)* | Olanzapine | 84 | 96.1 | 6.6 | 3.1 | | |
| | Placebo | 87 | 91.5 | -0.39 | -3.5 | 6.6 | 0.038 |
| | | | | | | (6.6) | (0.016) |
| Prolactin (ng/ml) | Olanzapine | 79 | 13.3 | 12.6 | 12.0 | | |
| | Placebo | 80 | 14.9 | -0.2 | -0.9 | 12.91 | < 0.001 |
| | | | | | | (11.7) | (< 0.001) |

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113, LDL = 0.0259

## 10.10 Patients with Possible Suicidal Behavior or Ideation Events
## HGIU + HGIN Acute Database

| Patient ID (Study-Inv-Patient) | Brief Description of Event | Code | Therapy | Days to Event | Fatal? |
|---|---|---|---|---|---|
| HGIU-001-0103 | THE PATIENT HAS REPORTEDLY BEEN HAVING DIFFICULTIES WITH DYSPHORIC MOOD. IN MID TO LATE APRIL, 2003, HE TRIED TO TIE A BELT AROUND HIS NECK RESULTING IN A RASH. | 5 | Placebo | 23 | No |
| HGIU-012-1206 | INTENTIONAL SELF-INJURY / SELF-INFLICTED CUT MARKS ON FOREARM | 5 | Olz | 22 | No |
| HGIU-012-1211 | SUICIDAL IDEATION / SUICIDAL IDEATION | 4 | Olz | 14 | No |

## Overall Combined Database

| Patient ID (Study-Inv-Patient) | Brief Description of Event | Code | Days to Event | Fatal? |
|---|---|---|---|---|
| HGIN-019-1901 | SUICIDAL IDEATION / SUICIDAL IDEATION | 4 | 167 | No |
| HGIN-026-2603 | SUICIDAL IDEATION / SUICIDAL IDEATION | 4 | 135 | No |
| HGIN-030-3001 | SUBJECT IS EXPERIENCING SYMPTOMS OF DELUSIONS, AUDITORY AND VISUAL HALLUCINATIONS, AND SUICIDAL IDEATIONS SUBJECT WILL BE HOSPITALIZED FOR STABILIZATION ON TRADITIONAL MEDICATION | 4 | 51 | No |
| HGIN-930-9307 | SUICIDE ATTEMPT / SUICIDE ATTEMPT | 2 | 59 | No |
| HGIU-001-0109 | ALCOHOL POISONING / ETOH INTOXICATION. LSS: ON (b) (6), NEARLY SIX MONTHS AFTER STARTING STUDY DRUG, THE PATIENT WAS ADMITTED TO THE HOSPITAL WITH ALCOHOL ("ETOH") POISONING. THE PATIENT WAS RECEIVING 15MG OLANZAPINE AT THE TIME OF THE EVENT. THIS WAS THE FIRST PSYCHIATRIC HOSPITALIZATION FOR THIS 14-YEAR OLD WHO WAS BROUGHT TO THE EMERGENCY ROOM (ER) BY POLICE AFTER THE PATIENT BECAME INTOXICATED, VOICED SUICIDAL IDEATION, AND PASSED OUT AT SCHOOL. APPROXIMATELY (b) (6) (A WEEK AND A HALF A GO), THE PATIENT TRIED TO JUMP OUT OF HER MOTHER'S MOVING VEHICLE AT 55 MILES PER HOUR, BUT THE MOTHER PREVENTED HER FROM FALLING OUT. | 3 | 157 | No |

| Patient ID (Study-Inv-Patient) | Brief Description of Event | Code | Days to Event | Fatal? |
|---|---|---|---|---|
| HGIU-012-1206 | INTENTIONAL SELF-INJURY / SELF-INFLICTED CUT MARKS ON FOREARM | 5 | 22 | No |
| HGIU-012-1211 | SUICIDAL IDEATION / SUICIDAL IDEATION | 4 | 14 | No |
| HGIU-012-1212 | THE PATIENT HAD BEEN DRAWING PICTURES OF HOW THE PATIENT COULD DIE . . . THE PATIENT COULD NOT ASSURE THE INVESTIGATOR THAT SHE WOULDN'T HARM HERSELF. | 4 | 34 | No |
| HGIU-013-1301 | SUICIDAL IDEATION / OCCASIONAL SUICIDAL THOUGHTS | 4 | 71 | No |
| HGIU-013-1310 | INTENTIONAL SELF-INJURY / SELF INJURY | 5 | 64 | No |
| HGIU-020-2015 | SUICIDE ATTEMPT / ATTEMPTED SUICIDE | 2 | 214 | No |
| HGIU-026-2604 | SELF INJURIOUS BEHAVIOUR / SELF-INJURIOUS BEHAVIOR. LSS: THE PATIENT REPORTED THAT HIS DEPRESSION WORSENED APPROXIMATELY ONE WEEK PRIOR ( (b) (6) . ADDITIONALLY HE BEGAN FEELING SUICIDAL (WITHOUT PLAN) APPROXIMATELY THREE DAYS PRIOR ( (b) (6) . THE PATIENT'S MOTHER CALLED THE SITE TO REPORT THAT THE PATIENT HAD CUT HIMSELF THE PRIOR EVENING AND DIDN'T FEEL SAFE. THE PATIENT WAS BROUGHT TO THE HOSPITAL FOR SAFETY AND STABILIZATION. | 4 | 59 | No |

| Patient ID (Study-Inv-Patient) | Brief Description of Event | Code | Days to Event | Fatal? |
|---|---|---|---|---|
| HGIU-026-2605 | THE PATIENT WAS BEHAVING INAPPROPRIATELY AND WAS ON THE ROOF OF HIS HOME REFUSING TO COME DOWN | 9 | 53 | No |
| HGIU-026-2606 | SUICIDAL IDEATION / SUICIDAL IDEATION | 4 | 35 | No |
| HGIU-027-2705 | INTENTIONAL SELF-INJURY / SELF-INFLICTED SUPERFICIAL LACERATIONS | 5 | 76 | No |
| HGIU-028-2905 | SUICIDAL IDEATION / SUICIDAL IDEATION. LSS: THE PATIENT'S MOTHER CALLED THE INVESTIGATOR'S SITE ON 14-MAY-2004 TO STATE THAT HER DAUGHTER HAD BECOME SUICIDAL WITH A PLAN TO OVERDOSE ON LORAZEPAM (ATIVAN) DURING THE LAST WEEK OF MAY 2004, BUT ENDED UP TELLING HER PARENTS THE EVENING OF 09-MAY-2004. | 3 | 109 | No |
| HGIU-730-7302 | SUICIDAL IDEATION / PASSIVE SUICIDAL IDEATION | 4 | 177 | No |
| HGMP-003-0304 | EXACERBATION OF BIPOLAR ILLNESS WITH POSITIVE SUICIDAL IDEATION | 4 | 29 | No |
| HGMP-008-0805 | INTENTIONAL SELF-INJURY, CUTTING LEFT ARM | 5 | 93 | No |
| LOAY-400-4001 | PATIENT IS IN A DEPRESSIVE MOOD AROUND 10-11.05.99 AND EXPRESSES SUICIDALTHOUGHTS, SIGNIFICANTLY SLOWED MOVEMENT. | 4 | 44 | No |
| LOAY-401-4012 | SELF-INJURIOUS BEHAVIOR, SELF-INJURY | 5 | 16 | No |
| LOAY-407-4077 | SELF INJURIOUS BEHAVIOR, SELF-INFLICTING TENDENCIES | 5 | 55 | No |

| Patient ID (Study-Inv-Patient) | Brief Description of Event | Code | Days to Event | Fatal? |
|---|---|---|---|---|
| LOAY-407-4078 | SUICIDAL IDEATION, ACUTE SUICIDAL TENDENCIES | 4 | 4 | No |
| LOAY-413-4150 | SUICIDAL IDEATION, SUICIDAL TENDENCY | 4 | 27 | No |

## 10.11 Laboratory Evaluations – Mean Change from Baseline to Endpoint

Table 10.11.1 Sponsor's Table. Mean Change from Baseline to Endpoint: HGIN + HGIU Acute Database

**Table 2.7.4.33. Laboratory Evaluations
Mean Change from Baseline to Endpoint
Acute Placebo-Controlled Combined Database**

| Laboratory Evaluations | Unit | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| HEMATOCRIT | 1 | Olz | 174 | 0.43 | 0.03 | -0.01 | 0.03 | -0.01 | -0.01 | <.001 |
| | | Placebo | 87 | 0.43 | 0.04 | -0.00 | 0.03 | -0.00 | | |
| HEMOGLOBIN | mml/L-F | Olz | 174 | 8.93 | 0.78 | -0.30 | 0.47 | -0.30 | -0.22 | <.001 |
| | | Placebo | 87 | 8.93 | 0.83 | -0.08 | 0.41 | -0.07 | | |
| ERYTHROCYTE COUNT | TI/L | Olz | 174 | 5.00 | 0.39 | -0.15 | 0.27 | -0.15 | -0.11 | .002 |
| | | Placebo | 87 | 4.99 | 0.49 | -0.04 | 0.26 | -0.04 | | |
| MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC) | mml/L-F | Olz | 174 | 20.87 | 0.92 | -0.00 | 0.76 | 0.02 | 0.16 | .100 |
| | | Placebo | 87 | 21.00 | 0.79 | -0.17 | 0.73 | -0.14 | | |
| LEUKOCYTE COUNT | GI/L | Olz | 174 | 7.27 | 1.92 | -0.19 | 1.86 | -0.10 | -0.32 | .201 |
| | | Placebo | 87 | 7.18 | 1.91 | 0.14 | 1.99 | 0.21 | | |
| NEUTROPHILS, SEGMENTED | GI/L | Olz | 174 | 4.22 | 1.59 | -0.13 | 1.67 | -0.06 | -0.29 | .203 |
| | | Placebo | 87 | 4.29 | 1.48 | 0.17 | 1.79 | 0.23 | | |
| LYMPHOCYTES | GI/L | Olz | 174 | 2.38 | 0.66 | -0.09 | 0.49 | -0.06 | -0.07 | .297 |
| | | Placebo | 87 | 2.24 | 0.60 | -0.02 | 0.51 | 0.01 | | |
| MONOCYTES | GI/L | Olz | 174 | 0.43 | 0.14 | 0.02 | 0.17 | 0.01 | 0.01 | .544 |
| | | Placebo | 87 | 0.41 | 0.16 | 0.01 | 0.17 | 0.00 | | |

| Laboratory Evaluations | Unit | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| EOSINOPHILS | GI/L | Olz | 174 | 0.20 | 0.21 | 0.01 | 0.16 | 0.01 | 0.04 | .042 |
| | | Placebo | 87 | 0.19 | 0.14 | -0.02 | 0.10 | -0.03 | | |
| BASOPHILS | GI/L | Olz | 174 | 0.05 | 0.03 | -0.01 | 0.03 | -0.01 | -0.01 | .008 |
| | | Placebo | 87 | 0.05 | 0.03 | 0.00 | 0.03 | 0.00 | | |
| MEAN CELL VOLUME (MCV) | fL | Olz | 174 | 85.96 | 4.66 | -0.25 | 2.53 | -0.02 | -0.97 | .005 |
| | | Placebo | 87 | 85.76 | 4.59 | 0.72 | 2.78 | 0.95 | | |
| PLATELET COUNT | GI/L | Olz | 173 | 291.08 | 68.65 | 1.26 | 46.42 | 2.44 | 6.09 | .339 |
| | | Placebo | 87 | 286.54 | 63.84 | -4.68 | 52.18 | -3.66 | | |
| LYMPHOCYTES, ATYPICAL | GI/L | Olz | 1 | 0.06 | | 0.03 | | 0.03 | | |
| UA-SPECIFIC GRAVITY | NO UNIT | Olz | 156 | 1.02 | 0.01 | -0.00 | 0.01 | -0.00 | -0.00 | .292 |
| | | Placebo | 72 | 1.02 | 0.01 | -0.00 | 0.01 | -0.00 | | |
| AST/SGOT | U/L | Olz | 175 | 24.53 | 29.87 | 6.43 | 26.41 | 9.89 | 8.91 | .002 |
| | | Placebo | 87 | 23.63 | 8.46 | -2.47 | 7.51 | 0.98 | | |
| ALT/SGPT | U/L | Olz | 175 | 24.13 | 45.95 | 19.95 | 54.84 | 28.11 | 22.98 | <.001 |
| | | Placebo | 87 | 20.39 | 13.05 | -3.08 | 11.69 | 5.13 | | |
| CREATINE PHOSPHOKINASE | U/L | Olz | 175 | 141.28 | 138.78 | -7.31 | 131.11 | 2.81 | 16.06 | .376 |
| | | Placebo | 87 | 164.36 | 160.04 | -23.62 | 152.22 | -13.25 | | |

| Laboratory Evaluations | Unit | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| ALKALINE PHOSPHATASE | U/L | Olz | 175 | 152.33 | 82.35 | -1.35 | 25.61 | -2.74 | 2.57 | .396 |
| | | Placebo | 87 | 138.67 | 86.92 | -3.97 | 16.63 | -5.31 | | |
| GGT (GGPT/SGGT/YGGT) | U/L | Olz | 175 | 18.99 | 12.31 | 7.47 | 20.02 | 7.73 | 7.89 | <.001 |
| | | Placebo | 87 | 17.68 | 8.49 | -0.43 | 5.96 | -0.16 | | |
| THYROID STIMULATING HORMONE | mU/L | Olz | 6 | 2.73 | 2.32 | 0.11 | 1.02 | -0.12 | | |
| UREA NITROGEN | mmol/L | Olz | 175 | 4.40 | 1.18 | 0.22 | 1.18 | 0.14 | 0.39 | .010 |
| | | Placebo | 87 | 4.37 | 1.06 | -0.17 | 1.06 | -0.25 | | |
| CREATININE | umol/L | Olz | 175 | 93.29 | 14.47 | -2.90 | 9.85 | -2.07 | -1.80 | .147 |
| | | Placebo | 87 | 95.83 | 12.43 | -1.08 | 8.56 | -0.27 | | |
| CALCIUM | mmol/L | Olz | 175 | 2.48 | 0.08 | -0.03 | 0.09 | -0.03 | -0.02 | .215 |
| | | Placebo | 87 | 2.50 | 0.12 | -0.01 | 0.10 | -0.02 | | |
| SODIUM | mmol/L | Olz | 175 | 141.70 | 2.27 | -0.05 | 2.83 | -0.12 | 0.49 | .190 |
| | | Placebo | 87 | 141.78 | 2.44 | -0.53 | 2.94 | -0.61 | | |
| POTASSIUM | mmol/L | Olz | 175 | 4.32 | 0.33 | -0.04 | 0.36 | -0.07 | 0.04 | .462 |
| | | Placebo | 87 | 4.41 | 0.42 | -0.07 | 0.41 | -0.10 | | |
| ALBUMIN | g/L | Olz | 175 | 45.07 | 3.75 | -2.01 | 3.20 | -2.13 | -1.70 | <.001 |
| | | Placebo | 87 | 45.39 | 3.03 | -0.31 | 2.90 | -0.43 | | |

| Laboratory Evaluations | Unit | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| GLUCOSE, FASTING | mmol/L | Olz | 135 | 4.89 | 0.55 | 0.15 | 0.58 | 0.15 | 0.31 | <.001 |
| | | Placebo | 64 | 4.98 | 0.57 | -0.16 | 0.56 | -0.17 | | |
| GLUCOSE, NON-FASTING | mmol/L | Olz | 141 | 5.04 | 0.83 | 0.17 | 1.13 | 0.12 | 0.15 | .374 |
| | | Placebo | 73 | 5.01 | 0.79 | 0.03 | 1.23 | -0.03 | | |
| URIC ACID | umol/L | Olz | 175 | 331.18 | 74.27 | 25.21 | 51.54 | 30.87 | 26.95 | <.001 |
| | | Placebo | 87 | 329.40 | 84.01 | -1.86 | 53.02 | 3.92 | | |
| CHOLESTEROL | mmol/L | Olz | 175 | 4.17 | 0.83 | 0.34 | 0.59 | 0.33 | 0.37 | <.001 |
| | | Placebo | 87 | 4.15 | 0.85 | -0.03 | 0.63 | -0.04 | | |
| TRIGLYCERIDES | mmol/L | Olz | 175 | 1.18 | 0.66 | 0.33 | 0.91 | 0.30 | 0.38 | <.001 |
| | | Placebo | 87 | 1.25 | 0.73 | -0.05 | 0.62 | -0.07 | | |
| LDL CHOLESTEROL | mmol/L | Olz | 175 | 2.42 | 0.74 | 0.16 | 0.52 | 0.14 | 0.17 | .016 |
| | | Placebo | 87 | 2.37 | 0.76 | -0.01 | 0.53 | -0.02 | | |
| BILIRUBIN, TOTAL | umol/L | Olz | 175 | 7.84 | 5.27 | -1.73 | 3.82 | -2.21 | -2.52 | <.001 |
| | | Placebo | 87 | 8.56 | 5.33 | 0.78 | 5.96 | 0.31 | | |
| BILIRUBIN, DIRECT | umol/L | Olz | 175 | 1.84 | 1.07 | -0.33 | 1.07 | -0.36 | -0.38 | .005 |
| | | Placebo | 87 | 2.01 | 1.08 | 0.05 | 0.93 | 0.02 | | |
| HDL CHOLESTEROL-DEXTRAN PRECIP. | mmol/L | Olz | 175 | 1.22 | 0.31 | 0.03 | 0.23 | 0.02 | 0.03 | .331 |

| Laboratory Evaluations | Unit | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| HDL CHOLESTEROL-DEXTRAN PRECIP. | mmol/L | Placebo | 87 | 1.21 | 0.25 | -0.00 | 0.25 | -0.01 | | |
| PROLACTIN | ug/L | Olz | 163 | 14.06 | 9.92 | 11.44 | 14.52 | 10.51 | 11.66 | <.001 |
| | | Placebo | 80 | 14.95 | 11.86 | -0.16 | 10.69 | -1.15 | | |
| HEMOGLOBIN A1C | 1 | Olz | 6 | 0.05 | 0.00 | -0.00 | 0.00 | -0.00 | 0.00 | .741 |
| | | Placebo | 3 | 0.05 | 0.01 | -0.00 | 0.00 | -0.00 | | |

## 10.12 Prolactin Analysis by Gender

Table 10.12.1. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: HGIU + HGIN Acute Database.

| Laboratory Evaluations | Gender | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value | **P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PROLACTIN | Female | Olz | 63 | 15.87 | 10.06 | 15.63 | 16.86 | 14.26 | 14.25 | <.001 | .236 |
| | | Placebo | 37 | 15.25 | 7.59 | 1.35 | 9.20 | 0.00 | | | |
| | Male | Olz | 100 | 12.92 | 9.71 | 8.80 | 12.20 | 8.70 | 10.12 | <.001 | |
| | | Placebo | 43 | 14.70 | 14.67 | -1.46 | 11.78 | -1.42 | | | |

## 10.13 Vital Signs – Mean Change from Baseline to Endpoint

Table 10.13.1 Vital Signs, Weight, Height and BMI - Mean Change from Baseline to Endpoint (LOCF). HGIN + HGIU Acute Database

| Vital Signs | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|
| Systolic Blood Pressure - Supine | Olz | 177 | 111.52 | 10.95 | 2.94 | 10.57 | 1.73 | 3.66 | .009 |
| | Placebo | 89 | 112.79 | 13.18 | -0.71 | 10.90 | -1.93 | | |
| Systolic Blood Pressure - Standing | Olz | 177 | 113.33 | 12.25 | 3.14 | 12.06 | 2.16 | 1.94 | .225 |
| | Placebo | 89 | 112.18 | 13.25 | 1.22 | 12.51 | 0.23 | | |
| Systolic Blood Pressure - Orthostatic | Olz | 177 | -1.81 | 9.63 | -0.20 | 11.68 | -0.43 | 1.72 | .262 |
| | Placebo | 89 | 0.61 | 8.33 | -1.93 | 11.83 | -2.15 | | |
| Diastolic Blood Pressure - Supine | Olz | 177 | 67.71 | 9.27 | 1.24 | 9.74 | 1.56 | 2.17 | .095 |
| | Placebo | 89 | 68.19 | 8.53 | -0.92 | 10.27 | -0.61 | | |
| Diastolic Blood Pressure - Standing | Olz | 177 | 72.86 | 10.12 | 1.42 | 10.25 | -0.24 | 2.73 | .033 |
| | Placebo | 89 | 73.56 | 9.48 | -1.28 | 9.14 | -2.97 | | |
| Pulse - Supine | Olz | 177 | 73.88 | 11.40 | 7.07 | 13.99 | 7.55 | 7.71 | <.001 |
| | Placebo | 89 | 74.15 | 12.81 | -0.60 | 12.04 | -0.16 | | |
| Pulse - Standing | Olz | 177 | 83.77 | 12.73 | 6.97 | 14.83 | 6.55 | 7.90 | <.001 |
| | Placebo | 89 | 85.55 | 12.98 | -0.89 | 14.69 | -1.35 | | |
| Pulse - Orthostatic | Olz | 177 | 9.89 | 11.23 | -0.11 | 13.37 | -1.01 | 0.19 | .914 |
| | Placebo | 89 | 11.40 | 11.15 | -0.29 | 13.09 | -1.19 | | |

| Vital Signs | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|
| Temperature in Centigrade | Olz | 177 | 36.57 | 0.44 | -0.03 | 0.49 | -0.03 | -0.03 | .695 |
| | Placebo | 88 | 36.58 | 0.42 | -0.00 | 0.49 | -0.00 | | |
| Weight in Kg | Olz | 177 | 66.03 | 17.93 | 3.90 | 2.72 | 3.68 | 3.66 | <.001 |
| | Placebo | 88 | 67.63 | 17.24 | 0.24 | 2.16 | 0.01 | | |
| Height in cm | Olz | 177 | 165.84 | 10.13 | 0.48 | 1.22 | 0.46 | 0.18 | .235 |
| | Placebo | 88 | 167.59 | 9.67 | 0.31 | 1.01 | 0.28 | | |
| Body Mass Index | Olz | 177 | 23.91 | 6.01 | 1.22 | 1.01 | 1.11 | 1.17 | <.001 |
| | Placebo | 88 | 23.98 | 5.67 | 0.05 | 0.91 | -0.07 | | |

## 10.14 Potentially Clinically Significant Definitions for Safety Analyses

**Table 2.7.4.6. Criteria for Identifying Patients with Potentially Clinically Significant Changes in Vital Signs and Weight**

| Parameter | Low | High |
|---|---|---|
| Orthostatic hypotension (mm Hg) | ≥20 mm Hg decrease in systolic BP (supine to standing) and ≥10 bpm increase in pulse (supine to standing) | -- |
| Supine systolic BP (mm Hg) | ≤90 and decrease ≥20 | ≥180 and increase ≥20 |
| Standing systolic BP (mm Hg) | ≤90 and decrease ≥20 | ≥180 and increase ≥20 |
| Supine diastolic BP (mm Hg) | ≤50 and decrease ≥15 | ≥105 and increase ≥15 |
| Standing diastolic BP (mm Hg) | ≤50 and decrease ≥15 | ≥105 and increase ≥15 |
| Supine pulse (bpm) | <50 and decrease ≥15 | >120 and increase ≥15 |
| Standing pulse (bpm) | <50 and decrease ≥15 | >120 and increase ≥15 |
| Temperature (°F)[a] | -- | ≥101°F and increase ≥2 |
| Weight (kg) | decrease ≥7% | increase ≥7% |

## 10.15 Postmarketing Reports - Fatalities

Table 10.15.1. Postmarketing Reports – Fatalities

| Patient Identifier | Date of Death | Dose/Duration | Event | Concom Rx | Comments |
|---|---|---|---|---|---|
| BR200605002130 16 YOM | (b) (6) | 7.5 mg 10/05 – (b) (6) | Sudden death, cardiac arrest, prescribed overdose, suicide attempt, depression, psychosis | Alprazolam | Brazil Autopsy done, result will be available by June 2006 (per summary) |
| BE200602002031 17 YOF | (b) (6) | Unknown ~6 years | Bilateral pneumonia, gastric hemorrhagia, fever, coma | Not reported | Belgium (no autopsy) |
| US_0510123183 14 YO | (b) (6) | Unknown | Toxic exposure, completed suicide | Fluoxetine Risperidone | Literature |
| JP_051007889 17 YOM | (b) (6) | 5 mg, 8/2005 – (b) (6) | Completed suicide, suicidal ideation, apathy | Lorazepam | Japan "Police told psychiatrist about patient's death, no details provided" [prior suicide attempt per hx] |
| CA_050708496 17 YOM | (b) (6) | 15 mg 11/03 – (b) (6) | Completed suicide | Lorazepam Flupentixol decanoate | Canada 5 days after discontinuing olanzapine, committed suicide (method unknown) Not known whether |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | autopsy performed. |
| US_0506118439<br>17 YOF | Unknown<br>(b) (6)<br>estimated | Unknown,<br>7/1999 - 2004 | Death, weight increased, diabetes mellitus, hyperglycemia, multiple drug overdose, triglycerides increased, cholesterol abnormal, musculoskeletal chest pain | | Reported by attorney via legal department |
| EWC050644285<br>17 YOF | (b) (6) | 5 mg 3/5/05 –<br>(b) (6) | Endotoxic shock, kidney infection, sepsis, acute abdomen, disseminated intravascular blood coagulation, myeloid hyperplasia of spleen, pancreatitis, gastric ulcer perforation, peritoneal infection | | Russian Federation |
| US_0506118189<br>15 YOM | Unknown<br>(b) (6)<br>estimated | ~ May 2003 -<br>unknown | Death | | Reported by an attorney via the legal department<br>Cause of death not provided |
| CA_050207717<br>16 YOM | (b) (6) | Unknown | Completed suicide | Isotretinoin<br>mepha | Canada<br>No details provided |
| US_0412108962<br>16 YOM | Unknown<br>(b) (6)<br>estimated | 1-2002 –<br>unknown | Death, diabetes mellitus | | Reported by an attorney via the legal department<br>Cause of death not provided, not known if autopsy performed |
| JP_041105122<br>17 YOF | (b) (6) | 50 mg<br>11/10/2004 –<br>(b) (6) | Intentional overdose, completed suicide | Paroxetine, sulpiride, amoxapine, fluvoxamine, flunitrazepam | Japan<br>"Coroner refused to provide any information" |
| USA040979162<br>US_0402100550<br>15 YOM | (b) (6) | 10/29/2003? | Death, coma<br><br>Accidental overdose, drug toxicity, intentional drug misuse | Metronidazole, topiramate, clonazepam | Reported by an attorney via the legal department<br>Case reported in a newspaper<br>"Patient was sold olanzapine by another individual, not prescribed" |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Olanzapine Cp = 490 ng/ml postmortem |
| US_0412109585<br>15 YOF | (b) (6) | 11/2000 - unk | Diabetic ketoacidosis, diabetic coma, diabetes mellitus, pain, anxiety, drug ineffective | Methylphenidate, sertraline | Reported to company by an attorney<br>No details provided about the event, unknown if an autopsy was performed |
| EWC031237179<br>16 YOM | (b) (6) | 5 mg,<br>11/24/2003 –<br>(b) (6) | Death, pulmonary infarction | | Greece<br>Pulmonary infarction per autopsy |
| USA030742307<br>13 YOF | (b) (6) | 5 mg<br>Unknown | Diabetic ketoacidosis, loss of consciousness, dizziness | | Diabetic ketoacidosis per autopsy. No labs provided. |
| USA030741953<br>17 YOM | (b) (6) | 8/2002 –<br>(b) (6) | Convulsion, heart rate increased | Mixed amphetamine salts, trazodone | Cause of death listed as idiopathic seizure disorder, toxicology screen negative |
| GBS030413039<br>17 YOM | (b) (6) | 12.5 mg<br>10/2002 – unk | Completed suicide, sedation, eczema | Risperidone, biperiden | United Kingdom<br>Death by drowning, autopsy did not reveal other significant findings |
| US_020180581<br>15 YOM | (b) (6) | 20 mg<br>Unknown | Acute asthma | | Patient had been in blinded study 3/01 – 9/01 prior [F1D-US-X090]; did not receive olanzapine; taking marketed olanzapine at time of event. |
| US_010973481<br>17 YOM | Unknown (received by Sponsor (b) (6)) | 30 mg<br>Unknown | Prescribed overdose, drug toxicity | | No details provided, unknown if autopsy performed |
| EWC010928155<br>15 YOM | (b) (6) | 10 mg<br>8/1/2001 –<br>(b) (6) | Death | Dextro-amphetamine | Switzerland<br>Asperger's syndrome<br>Patient drowned while swimming in lake; autopsy unremarkable |
| CA_010603921<br>17 YOF | Unknown (received by Sponsor (b) (6)) | Unknown | Death | Citalopram, valproate semisodium | Canada<br>Patient "died suddenly", autopsy was completed but not available. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | "Several attempts at follow-up unsuccessful". |
| CA_010603802<br>16 YOM | Unknown (received by Sponsor (b) (6)) | 10 mg<br>90 days | Diabetic coma | Valproate sodium<br>Topiramate | Canada<br>No personal history of diabetes.<br>Weight at time of event unknown, labs not provided.<br>"Numerous attempts to obtain follow-up unsuccessful". |
| US_010566315<br>16 YOM | (b) (6) | 5 mg<br>730 days | Drug interaction, death, hepatic steatosis | Mixed amphet-Amine salts | Patient found dead.<br>Hepatic steatosis per autopsy, no cause of death provided. Autopsy never provided. |
| US_010158510<br>17 YOM | (b) (6) | 2.5 mg<br>Unknown | Accidental overdose | Citalopram, trazodone | Patient found dead by family member.<br>Cause of death presumed overdose.<br>Olanzapine Cp = 158 ng/ml. |
| US_000542556<br>15 YOM | (b) (6) | Unknown<br>1998 x 120 days | Necrotizing pancreatitis, diabetes mellitus, increased cholesterol | Carbamazepine, paroxetine | Follow-up in the literature |
| US_000236591<br>17 YOM | (b) (6) | 22.5 mg<br>Unknown | Overdose, death | Fluoxetine, valproate semisodium, nortriptyline, buspirone, haloperidol, thioridazine | Patient died while being restrained by staff in group home. |
| US97121702A<br>14 YOM | (b) (6) | 12.5 mg<br>150 days | Asphyxia, agitation | Haloperidol, sertraline | Became agitated on school bus and was restrained and died.<br>Per coroner, cause of death by mechanical asphyxia due to the restraining position. |

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/s/
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Cara Alfaro
4/12/2007 04:22:45 PM
PHARMACIST

Ni Aye Khin
4/18/2007 01:32:15 PM
MEDICAL OFFICER
I concur with Dr. Alfaro's recommendation that this application is approvable; see memo to file for additional comments.

**CLINICAL REVIEW**

| | |
|---|---|
| Application Type | NDA 20-592 |
| Submission Number | S-041 |
| Submission Code | SE5 |
| | |
| Letter Date | 10/30/06 |
| Stamp Date | 10/31/06 |
| PDUFA Goal Date | 04/30/07 |
| | |
| Reviewer Name | Cara Alfaro, Pharm.D. |
| Review Completion Date | 04/06/07 |
| | |
| Established Name | Olanzapine |
| Trade Name | Zyprexa |
| Therapeutic Class | Antipsychotic |
| Applicant | Eli Lilly |
| | |
| Priority Designation | P |
| | |
| Formulation | Oral tablets |
| Dosing Regimen | 2.5 – 5 mg starting, maximum dose 20 mg/day |
| Indication | Treatment of Schizophrenia |
| Intended Population | Adolescents |

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# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

I recommend that the Division take a non approval action on NDA 20-592 SE5-041 that was filed to support the indication "treatment of schizophrenia in adolescents".

Fifty-three percent of randomized patients in pivotal trial HGIN were from sites in the United States and 47% of randomized patients were from sites in Russia. The primary endpoint, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia ($p = 0.003$) but not the sites in the United States ($p = 0.258$). The sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia.

Though the LOCF analysis was the primary analysis, it is also concerning that the OC and MMRM analyses (the latter by recalculation by the reviewing statistician in the Division) are substantially different from the LOCF analysis and not statistically significant.

I recommend that the Sponsor conduct another clinical trial in this population if they wish to pursue this indication. The majority of patients in this clinical trial should be from sites in the United States and efficacy will need to be established in these patients. It is also strongly recommended that this clinical trial be a fixed dose design since dose-response data for efficacy or safety cannot be evaluated in a flexible dose design.

A number of additional requests for safety information and analysis regarding this submission are included at the end of this review. If acceptable, these requests could be included in the action letter.

## 1.2 Recommendation on Postmarketing Actions

Since non approval is recommended, there are no recommendations for postmarketing actions.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Study HGIN was the pivotal trial for establishing efficacy and safety for the indication "treatment of schizophrenia in adolescent patients". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with schizophrenia. The study consisted of a 6-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day ($n = 72$), or placebo ($n = 35$).

Additional open-label studies were also submitted by the Sponsor primarily in support of safety. The primary supportive studies were LOAY (n = 89 adolescents) and HGMF (n = 107), the latter study was the primary pharmacokinetic study in this population.

### 1.3.2 Efficacy

The mean modal daily dose of olanzapine was 12.5 mg and the mean daily dose was 11.1 mg. Seventy-five percent of patients in the olanzapine group and 56% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIN was change from baseline in the BPRS-C Total Score (LOCF analysis). The overall study results were statistically significant for olanzapine versus placebo (LS Mean Diff = -10.12, p = 0.003).

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy Variable | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Diff. | *P-value |
| BPRS-C Total Score | Olanzapine | 72 | 50.26 | 9.98 | -19.42 | 15.51 | -19.26 | -10.12 | .003 |
| | Placebo | 35 | 50.09 | 8.59 | -9.31 | 18.70 | -9.14 | | |

The supportive OC analysis was discordant from the LOCF analysis (LS Mean Diff = -0.26, p = 0.947). The reviewing statistician recalculated the MMRM supportive analysis and found similar results to the OC analysis (LS Mean Diff = -1.25, p = 0.72) though the Sponsor's results for the MMRM analysis were statistically significant.

When evaluating the efficacy signal for the sites in the United States and the sites in Russia, only the latter were statistically significant in favor of olanzapine. The low placebo response in the sites in Russia appears to be driving these results.

Table HGIN.14.21. BPRS-C Total Score
Mean Change from Baseline to Endpoint (LOCF) by Country
Double-Blind Period

| | | | | Baseline | | Change to Endpoint | | | | | **P-value (Therapy by Country ) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Efficacy Variable | Country | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Diff. | *P-value | |
| BPRS-C Total Score | America | Olanzapine | 38 | 53.18 | 10.10 | -21.21 | 15.30 | -20.89 | -5.26 | .258 | .146 |
| | | Placebo | 19 | 51.42 | 8.64 | -15.00 | 18.28 | -15.64 | | | |
| | Russia | Olanzapine | 34 | 47.06 | 8.88 | -17.41 | 14.55 | -17.44 | -14.95 | .003 | |
| | | Placebo | 16 | 48.50 | 8.52 | -2.56 | 17.38 | -2.49 | | | |

Since efficacy could not be demonstrated in patients in sites from the United States, this reviewer recommended a non approval action.

### 1.3.3 Safety

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIU is the pivotal trial for bipolar disorder) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events (≥ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain
The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with ≥ 7% increase in body weight.

| | Olanzapine | Placebo | LS Mean Diff | P-value |
|---|---|---|---|---|
| *HGIN + HGIU Acute Database* | | | | |
| Weight (kg)<br>Mean Change to Endpoint (LOCF) | 3.90 (n = 177) | 0.24 (n = 88) | 3.66 | < 0.001 |
| Weight (kg)<br>Mean Change to Endpoint (OC) | 3.6 (n = 154) | 0.08 (n = 67) | 3.57 | < 0.001 |
| BMI<br>Mean Change to Endpoint (LOCF) | 1.22 | 0.05 | 1.17 | < 0.001 |
| ≥ 7% increase in body weight (%) | 43.5% | 6.8% | - | < 0.001 |
| Overall Combined Database | | | | |

| | | | | |
|---|---|---|---|---|
| Weight (kg)<br>Mean Change to Endpoint (LOCF) | 7.35 | - | - | < 0.001<br>(compared to baseline) |
| Weight (kg)<br>Mean Change to Endpoint (OC) | 10.8 | - | - | < 0.001<br>(compared to baseline) |
| BMI<br>Mean Change to Endpoint (LOCF) | 2.31 | - | - | < 0.001<br>(compared to baseline) |
| ≥ 7% increase in body weight (%) | 65% | - | - | - |

In the Acute Database, weight gain (mean change from baseline to endpoint) was similar for the groups with baseline BMI < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

Weight changes were evaluated for the subgroups gender and age (< 15, ≥ 15 years). At the time this review was finalized, mean change in weight for the age subgroup analysis was only available for study HGIN (not HGIU or the Acute Database). Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine. A treatment-by-gender interaction was noted in the Acute Database, but was likely due to differences in the placebo groups since mean change in weight was similar in the olanzapine groups for males and females.

Liver Function Abnormalities
Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline ≤ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009).
No patients met criteria for Hy's rule (ALT ≥ 3x ULN and TBili ≥ 1.5 x ULN).

Hyperprolactinemia
The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, p < 0.001). The washout period prior to baseline could be as short as 2 days and it was noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to perform further analyses in the subgroup of patients with baseline prolactin within normal limits. In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin

elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).
For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females (15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN + HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$).

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

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

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were also similar between the

olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality

Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in patients with bipolar disorder. Suicidal behaviors or ideation is not uncommon in these disorders and, in the absence of a placebo comparator, it is difficult to interpret causality to olanzapine therapy.

# 2 INTRODUCTION AND BACKGROUND

## 2.1 Product Information

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

Olanzapine is not currently indicated for use in child/adolescent populations.

## 2.2 Currently Available Treatment for Indications

Other currently available atypical antipsychotics include clozapine (Clozaril), risperidone (Risperdal), aripiprazole (Abilify), quetiapine (Seroquel), ziprasidone (Geodon).
Risperidone (Risperdal) was recently approved for the indication "treatment of irritability associated with autistic disorder in children and adolescents" (5 to 16 years of age).

None of the currently available atypical antipsychotics have an approved indication for the treatment of schizophrenia in children or adolescents.

## 2.3 Important Issues With Pharmacologically Related Products

Although the atypical antipsychotics have less extrapyramidal side effects compared to typical antipsychotics, the adverse event profile is notable for weight gain, hyperglycemia, and diabetes mellitus in adults. Little data is available with regard to the adverse event profile in other populations including children and adolescents.

## 2.4 Presubmission Regulatory Activity

This summary was taken from the note to reviewer document contained in the Sponsor's submission.

On June 11, 1999, Eli Lilly and Company (Lilly) submitted a Proposed Pediatric Study Request to FDA related to the conduct of pediatric studies of Zyprexa.

In response to Lilly's proposed pediatric study request, the FDA issued to Lilly a Written Request for Pediatric Studies dated November 30, 2001 (reissued under the Best Pharmaceuticals for Children Act (BPCA) on July 3, 2002) and amended on April 9, 2002, May 7, 2004, and June 29, 2005. FDA's Written Request (WR) as amended, included a request for clinical data on the use of Zyprexa to treat adolescents with schizophrenia and adolescents with acute bipolar mania in order to make Zyprexa eligible for the pediatric exclusivity extension under Section 505A of the Federal Food, Drug, and Cosmetic Act. More details regarding FDA's WR, and Lilly's response, are provided in Item 20 of this submission.

FDA granted an indication for olanzapine for the treatment of bipolar mania in adults (NDA 20-592/S006) on March 17, 2000. As part of the approval, the FDA requested a study in pediatric patients with bipolar mania as a post-marketing commitment. Study F1D-MC-HGIU is included in this submission to fulfill this post-marketing commitment.

On January15, 2004, the FDA met with Lilly to discuss the PK package proposed by Lilly to fulfill FDA's Written Request for Pediatric Studies. At this meeting, Lilly provided an overview of the available PK data. FDA requested additional justification of

the utility of the data from Study LOAY in order to make a final decision on whether or not the data is acceptable to sufficiently meet the PK aspects of the Written Request.

On March 22, 2004 Lilly submitted to IND 28,705 additional information regarding study LOAY and requested a meeting to further discuss fulfillment of the PK aspects of the WR. In response to questions from FDA sent to Lilly on July 7, 2004, Lilly submitted additional information to IND 28,705 on July 13, 2004.

Lilly met with FDA on July 21, 2004 to again discuss the PK information needed to fulfill the WR. At that meeting, FDA agreed with Lilly's proposal to provide PK data in adolescents from Studies HGCS, HGCR, HGGC, and LOAY to address the PK requirements outlined in the Written Request.

In discussions with FDA, it was noted that information about the exact sampling time relative to the dose were not collected as part of the protocol in Study LOAY; however, extensive simulations showed that lack of data regarding timing of samples in Study LOAY should not adversely affect the ability to perform a meaningful population analysis. Nonetheless, to assure the robustness of the PK data, Lilly collected additional population PK data in adolescent patients with schizophrenia or bipolar disorder by conducting Study HGMF. Inclusion of data from Study HGMF in this submission was discussed at a pre-NDA meeting on March 17, 2006. At that meeting, FDA requested that Lilly conduct the population PK analysis both with and without the data from Study LOAY. Both analyses were conducted by Lilly and are included with this submission. The population PK analysis also includes a comparison of pediatric olanzapine PK data with the adult olanzapine PK data from Study HGAJ.

The format and content of the submission were also discussed and agreed to at the March 17, 2006 pre-sNDA meeting. The FDA indicated that, based on the pre-sNDA package and discussions, the proposed submission content appeared to be adequate to respond to FDA's Written Request and that Study HGIU appeared to be adequate to fulfill the post-marketing commitment which was part of the bipolar mania in adults approval.

In the 11/30/01 written request, the Division stated "We strongly recommend that the trial be a fixed dose study including at least two fixed doses of the study drug". The Division also recommended that a relapse prevention trial should follow the acute treatment trial. The Sponsor did not follow either recommendation and neither was required to fulfill the pediatric written request.

## 2.5 Other Relevant Background Information

The Pediatric Exclusivity Board met on January 10, 2007 to determine whether the Sponsor had fulfilled the requirements in the written request. It was determined that the requirements had been met and exclusivity was granted.

# 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

## 3.1 Statistics

The statistician (Fanhui Kong) reviewed the efficacy data from the pivotal trial, HGIN. Several significant statistical issues were identified in his review including differential efficacy in U.S. versus Russia sites and inconsistent statistical results based on LOCF, OC and MMRM analyses (see Statistical review). This reviewer has similar issues which are described in Section 6.1.3 (Efficacy Findings) of this review.

# 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

## 4.1 Tables of Clinical Studies

The Sponsor included study reports for 9 pediatric studies in this submission. HGIN is the pivotal study for adolescent schizophrenia and HGIU is the pivotal study for adolescent bipolar I disorder. HGMF is the primary study for determining pharmacokinetic parameters in the adolescent population. The other studies are supportive and provide safety and pharmacokinetic data.

Table 4.1.1 Summary of Clinical Studies

| Study | Description | Length | Age Range (years) | Number of Patients |
|---|---|---|---|---|
| HGIN | MC, DB, PC study in adolescent patients with schizophrenia.<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S. and Russia sites | 6 weeks DB<br>26 weeks OL extension | 13 to 17 | 107<br>(n = 72 olanzapine, n = 35 placebo) |
| HGIU | MC, DB, PC study in adolescent patients with mixed/manic episode of bipolar I disorder.<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S., Puerto Rico | 3 weeks DB<br>26 weeks OL extension | 13 – 17 | 161<br>(n = 107 olanzapine, n = 54 placebo) |
| LOAY | OL study in patients with schizophrenia, schizoaffective, and schizophreniform disorders<br>Flexible dose olanzapine (5 – 20 mg)<br>German sites | 24 weeks | 12 – 21 | 96<br>(n = 89, 13-17 years) |
| HGMF | OL study in adolescent patients with schizophrenia or bipolar I disorder<br>Flexible dose olanzapine (2.5 | 4.5 weeks | 13 – 17 | 107<br>(n = 37 schizophrenia, n = 70 bipolar) |

| | | | | |
|---|---|---|---|---|
| | – 20 mg)<br>U.S., Puerto Rico, Russia | | | |
| HGCS | OL study in adolescent patients with schizophrenia<br>Dosing: 2.5 to 20 mg/day<br>Single site | 8 weeks | 10 – 18 | 8 |
| HGCR | DB study in adolescent patients with schizophrenia, haloperidol as active comparator<br>Dosing: 2.5 qod – 20 mg/day<br>Single site | 8 weeks | 12 – 16 | 2 |
| HGGC | OL study in children and adolescents with bipolar disorder<br>Dosing: 2.5 to 20 mg/day<br>Single site (U.S.) | 8 weeks | 5 – 14 | 23 |

Modified from Sponsor Table 2.5.1.1 clinical-overview.
MC = multicenter, DB = double-blind, PC = placebo-controlled, OL = open-label

## 4.2 Data Quality and Integrity

The Division of Scientific Investigations was asked to inspect a number of sites for studies HGIN and HGIU – some sites enrolled patients for both studies. DSI was asked to audit one site in Georgia (n = 7 HGIU, n = 5 HGIN) and one site in Ohio (n = 15 HGIU, n = 6 HGIN).

For pivotal trial HGIN, DSI was also asked to inspect two sites in Russia. This request was made since the sites in Russia, that enrolled approximately 50% of patients in study HGIN, were driving the overall efficacy signal in that trial. The final DSI report was not available at the time this review was completed, but preliminary comments from the investigator did not indicate any major issues thought to effect efficacy.

## 4.3 Compliance with Good Clinical Practices

Per protocols, the studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Of note, one clinical trial site was omitted from the primary efficacy analyses due to significant GCP issues. This site enrolled patients in both HGIU (site 028) and HGIN (site 021). Details regarding the GCP issues is in Section 6.1.3 (Efficacy Findings) of this review.

## 4.4 Financial Disclosures

Financial disclosure information was provided for the study HGIN. No investigators were noted to have received significant monies from the Sponsor.

# 5 CLINICAL PHARMACOLOGY

## 5.1 Pharmacokinetics

The pharmacokinetics of oral olanzapine were evaluated primarily in study HGMF (see Table 4.1.1 in Section 4.1 Tables of Clinical Studies) via population pharmacokinetic analyses. These data have been extensively reviewed by the biopharmaceutical reviewer (see Biopharm review).

# 6 INTEGRATED REVIEW OF EFFICACY

One pivotal trial, F1D-MC-HGIN, was submitted to support the efficacy of olanzapine in the treatment of schizophrenia in adolescents.

## 6.1 Indication

The Sponsor proposes the following indication "indicated for the treatment of schizophrenia in adolescents".

### 6.1.1 General Discussion of Endpoints

The primary efficacy endpoint for the clinical trial was the change from baseline to endpoint on the Anchored version of the Brief Psychiatric Rating Scale for Children. The BPRS, in general, is a standard rating scale used to evaluate efficacy in adult schizophrenia populations and is appropriate for evaluating efficacy in this clinical trial. The BPRS-C is slightly different from the BPRS and has been validated in the adolescent population.

The scoring of the Anchored BPRS-C was determined by interviews with both the patient and the parent/legal guardian at all visits. Investigators were told to record the "reference score" on the CRF and that this score is the higher of the two scores. This reviewer asked if the ratings were recorded separately for the patient and parent/legal guardian so that disparate ratings might be reviewed. The Sponsor indicated that the investigators were instructed to collect both ratings and retain the sheets as source documentation but not to enter them on the CRF. Therefore, the separate ratings are not available.

The Sponsor also included the Clinical Global Impression-Severity and Clinical Global Impression-Improvement scales to rate overall symptomatology. These are standard rating scales in clinical trials for psychiatric illnesses, including schizophrenia.

### 6.1.2 Study Design

Protocol F1D-MC-HGIN is the pivotal study submitted to support the indication "for the treatment of adolescents with schizophrenia". The other studies submitted as supportive studies

in this population are open-label trials and are supportive primarily from a safety and not efficacy perspective. Therefore, only study HGIN is reviewed here.

**Protocol HGIN**
**"Olanzapine versus placebo in the treatment of adolescents with schizophrenia"**
First patient enrolled 11/26/02, last patient completed 4/29/05.

*Investigators and sites*
This study enrolled patients at 20 sites in the United States and 5 sites in Russia. It is noteworthy that 107 patients were randomized and 50 (47%) of those were randomized from the 5 sites in Russia. Investigator and site information (including numbers of patients randomized and completing the trial) are included in Appendix 10.1.

*Study Objectives*
Primary objective: To assess the efficacy of a flexible dose of olanzapine (2.5 to 20 mg/day) compared to placebo in the treatment of adolescents (ages 13 – 17) with schizophrenia as measured by the difference between treatment groups in mean change from baseline to endpoint in the Anchored Version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score.

Secondary objectives:
To assess secondary efficacy measures 1) Clinical Global Impression: Improvement Scale, (CGI-I); 2) Clinical Global Impression: Severity Scale (CGI-S); 3) Positive and Negative Syndrome Scale (PANSS) total, positive subscale, and negative subscale scores; and 4) Overt Aggression Scale (OAS).

To assess the efficacy of olanzapine compared with placebo in improving clinical symptoms in terms of rate of response, with response defined as a reduction of 30% or more in the Anchored BPRS-C total score and a CGI Severity score of 3 or less.

To assess the safety of olanzapine compared with placebo for up to 6 weeks of double-blind treatment and for up to an additional 26 weeks of open-label olanzapine treatment.

To assess the health-related quality of life and cognition associated with olanzapine compared with placebo for up to 6 weeks of double-blind treatment and for up to an additional 26 weeks of open-label olanzapine treatment.

*Study Population*
The study population consisted of generally healthy adolescents, ages 13 to 17 inclusive, with a DSM-IV-TR diagnosis of schizophrenia. The diagnosis of schizophrenia was confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime (K-SADS-PL). The inclusion and exclusion criteria are listed in Appendix 10.2. Patients must have obtained an Anchored BPRS-C total score $\geq$ 35 with a minimum score of 3 on at least one of the following items at Visit 1 and Visit 2: hallucinations, delusions or peculiar fantasies. The patient's parent/authorized legal representative must sign an informed consent document and the patient must sign an informed consent document/assent document as required

by local regulations. Exclusion criteria included patients who have been judged clinically to be at serious suicidal risk; patients who have previously not responded to an adequate dose and/or duration of olanzapine treatment; patients currently meeting DSM-IV-TR criteria for delusional disorder, psychotic disorder, schizophreniform disorder, schizoaffective disorder, bipolar disorder, attention deficit/hyperactivity disorder, or major depressive disorder.

*Design*
This was a multicenter, randomized, double-blind, parallel, placebo-controlled trial consisting of three periods: screening/washout, 6-week double-blind trial, 26-week open-label olanzapine treatment. The screening/washout period was 2-14 days, patients who were on previous antipsychotic therapy had to undergo a taper allowing the patient to be free of antipsychotic therapy for at least 2 days prior to randomization. Patients were then randomized to olanzapine flexible dose (2.5 to 20 mg/day) or placebo treatment (2:1 randomization) for the 6-week acute double-blind trial. Olanzapine was initiated at 2.5 or 5 mg/day and the dose could be increased by 2.5 or 5 mg/day dose increments at the investigator's discretion. If no tolerability or safety issues were apparent, the dose had to be titrated to at least 10 mg/day by Visit 4 (end of first week). The investigator could continue to increase the dose by 2.5 or 5 mg/day to the maximum tolerable dose not to exceed 20 mg/day. The investigator could decrease the dose at any time and in any number of dose decrements if patients experienced an adverse event. The minimum allowable olanzapine dose was 2.5 mg/day. During this 6-week acute trial, 3 study visits occurred in the first week (including baseline visit) and then weekly thereafter.

Patients who did not respond after at least 3 weeks during the 6-week double-blind trial could participate in the optional 26-week open-label extension study and receive open-label olanzapine therapy (2.5 to 20 mg/day). Response was defined as having a $\geq$ 20% decrease in the Anchored version of the BPRS-C compared to baseline and a CGI-S score $\leq$ 3. Study visits occurred weekly x 1 visit, biweekly x 2 visits and then monthly until the end of the 26-week study.

*Assessments* (The Schedule of Events is in Appendix 10.3)
Rating scales – efficacy:
Primary efficacy endpoint: Anchored version of the Brief Psychiatric Rating Scale for Children (BPRS-C)
Secondary efficacy endpoints: Clinical Global Impression – Severity (CGI-S), Clinical Global Impression – Improvement (CGI-I), Positive and Negative Syndrome Scale (PANSS), Overt Aggression Scale (OAS), Child Health Questionnaire (CHQ), Brief Assessment of Cognition Scale (BACS)

Safety assessments:
Vital signs (blood pressure, pulse, weight, height, temperature) – including orthostatic assessments, ECG, Labs (hematology, clinical chemistry, urinalysis, lipid panel, hepatitis screen and panel, serum pregnancy test, prolactin, thyroid stimulating hormone, HgbA1c, urine drug screen.
Fasting glucose at baseline, end of 6-week study and end of 26-week open-label study.
HbA1c was only obtained for patients with diabetes.

Rating scales: Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BAS), Abnormal Involuntary Movement Scale (AIMS)
Spontaneous reporting of adverse events.

### 6.1.3 Efficacy Findings

One hundred seven patients were randomized, 72 to the olanzapine group and 35 to the placebo group. In the olanzapine group, 23 patients discontinued with lack of efficacy as the primary reason for discontinuation for 43.5% of drop-outs. In the placebo group, 20 patients discontinued with lack of efficacy as the primary reason for discontinuation for 90% of drop-outs. Drop-outs due to adverse events was the primary reason for discontinuation for 5 patients in the olanzapine group and no patients in the placebo group.

Table 6.1.3.1 Patient Disposition

| | Olanzapine N = 72 | Placebo N = 35 | P-value |
|---|---|---|---|
| Completers | 49 (68.1%) | 15 (42.9%) | 0.020 |
| Drop Outs | 23 (31.9%) | 20 (57.1%) | |
| Adverse Event | 5 (6.9%) | 0 | 0.170 |
| Lack of Efficacy | 10 (13.9%) | 18 (51.4%) | < 0.001 |
| Lost to Follow-up | 1 (1.4%) | 0 | 1.00 |
| Patient Decision | 4 (5.6%) | 1 (2.9%) | 1.00 |
| Criteria Not Met/Compliance | 2 (2.8%) | 1 (2.9%) | 1.00 |
| Sponsor Decision | 1 (1.4%) | 0 | 1.00 |

Modified from Sponsor table HGIN.10.1 in study report
*Percent - number of drop-outs is denominator

*Demographics and Baseline Disease Severity*

There were no statistically significant differences between the olanzapine and placebo groups with regard to baseline demographics or baseline disease severity. Information regarding the subtypes of schizophrenia was not included in the study report.

Table 6.1.3.2 Baseline Demographics and Severity of Disease

| | | Olanzapine N = 72 | Placebo N = 35 | P-value |
|---|---|---|---|---|
| Gender | Male | 51 (70.8%) | 24 (68.6%) | 0.825 |
| | Female | 21 (29.2%) | 11 (31.4%) | |
| Age (years) | Mean | 16.14 | 16.30 | 0.536 |
| | Median | 16.31 | 17.00 | |
| | St. Dev | 1.25 | 1.55 | |
| | Minimum | 13.03 | 13.06 | |
| | Maximum | 17.99 | 18.00 | |
| Origin | African descent | 17 (23.6%) | 7 (20.0%) | 0.656 |
| | Caucasian | 52 (72.2%) | 25 (71.4%) | |
| | Hispanic | 2 (2.8%) | 1 (2.9%) | |
| | Other | 1 (1.4%) | 2 (5.7%) | |
| Country | America | 38 (52.8%) | 19 (54.3%) | 1.00 |

| | | | | |
|---|---|---|---|---|
| | Russia | 34 (47.2%) | 16 (45.7%) | |
| Age of onset of illness (years)* | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 12.54<br>13.00<br>3.18<br>5.0<br>17.0 | 13.40<br>13.00<br>2.79<br>5.0<br>17.0 | 0.175 |
| No. of Prev. Schizophrenia episodes | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 2.53<br>2.00<br>4.18<br>0.00<br>30.00 | 2.25<br>2.00<br>1.80<br>0.00<br>6.00 | 0.672 |
| Total hospitalization for the past year (months) | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 2.43<br>2.00<br>2.43<br>0.20<br>11.00 | 2.21<br>1.50<br>1.96<br>0.10<br>6.50 | 0.957 |
| Length of current episode (days) | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 274.3<br>109.0<br>483.0<br>0.00**<br>2742 | 233.5<br>92.0<br>435.2<br>4.00<br>2139 | 0.675 |
| Days since last hospitalization | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 335.4<br>88.0<br>618.4<br>1.00<br>2889 | 250.9<br>37.0<br>494.0<br>1.00<br>2045 | 0.678 |
| Psychiatric hospitalization within the past year | Yes<br>No | 38 (52.78%)<br>34 (47.22%) | 22 (62.86%)<br>13 (37.14%) | 0.407 |
| CGI-S | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 4.83<br>5.00<br>0.69<br>4.00<br>6.00 | 4.94<br>5.00<br>0.80<br>4.00<br>7.00 | 0.471 |
| BPRS-C Thinking Disturbance | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 10.49<br>10.00<br>3.16<br>4.00<br>18.00 | 10.29<br>10.00<br>3.12<br>6.00<br>17.00 | 0.730 |
| BPRS-C Total Score | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 50.26<br>49.50<br>9.98<br>36.00<br>79.00 | 50.09<br>49.00<br>8.59<br>35.00<br>68.00 | 0.894 |
| PANSS Positive Score | Mean<br>Median<br>St. Dev.<br>Minimum<br>Maximum | 22.75<br>22.50<br>5.22<br>11.00<br>36.00 | 22.66<br>22.00<br>4.17<br>17.00<br>32.00 | 0.885 |
| PANSS Total Score | Mean<br>Median<br>St. Dev.<br>Minimum | 95.25<br>96.50<br>14.06<br>66.00 | 95.54<br>94.00<br>14.11<br>68.00 | 0.902 |

| | | | | |
|---|---|---|---|---|
| | Maximum | 122.00 | 123.0 | |

Modified from Sponsor table HGIN.11.1 and HGIN.11.2 in study report
*The Sponsor was asked to provide a list of patients with age of onset < 10 along with CRFs. Seventeen patients had age of onset < 10 years of age, only two patients had age of onset = 5 years of age (both from U.S. sites).
**Only 1 patient had length of current episode = 0. This patient entered the study when he had just started his most recent episode – the month was in the CRF, the actual date was imputed.

## *Efficacy Analyses*

*Site Issues*

In the efficacy analysis, the sponsor included analyses with and without site 021. Per the sponsor, site 021 had significant GCP issues and patients from this site were dropped from the primary analyses (efficacy analyses were similar with and without this site). The study report did not specify what the GCP issues were with this site. The sponsor was asked to provide details and indicated the following:

Lilly discontinued site 021 (Dr. Robb) from study HGIN, and also discontinued Dr Robb's site (site 028) from study HGIU. Lilly informed FDA of the discontinuation of Dr Robb's site from these studies in a submission to IND 28,705; serial number 953, dated May 21, 2004. In a letter dated May 2, 2004 sent to Dr Robb, Lilly listed the following GCP issues that occurred at this site related to studies HGIN and HGIU:

- Not following the randomization procedures outlined in the protocol
- Not submitting protocol amendment A, approved by Lilly on October 17, 2002, to the Institutional Review Board (IRB) for approval before use
- Not submitting revised informed consent documents to IRB
- Not communicating to patients about safety issues in risk profile of study drug. The risk profile was updated by Lilly on December 4, 2003 and faxed to the site on January 6, 2004 and a reminder fax was sent on January 28, 2004.
- Significant problems with drug accountability
- Not being able to reconstruct the regulatory document in the Clinical Trial Record Binder
- Violation of inter-active voice response system (IVRS) security personal identification number process.

*Concomitant Medications*

Interestingly, 29.2% (21/72) patients in the olanzapine group and 14.3% (5/35) patients in the placebo group did not have any previous medications for schizophrenia.

There were no statistically significant differences in the frequency of concomitant benzodiazepine use between the olanzapine and placebo groups. Concomitant lorazepam use occurred in 18.1% (13/72) patients in the olanzapine group and 34.3% (12/35) patients in the placebo group (p = 0.088). Concomitant diazepam use occurred in 12.5% (9/72) patients in the

olanzapine group and 8.6% (3/35) patients in the placebo group. A few patients in both groups had concomitant clonazepam, temazepam and phenazepam use. The mean number of days of benzodiazepine use did not differ between the treatment groups: 6.25 days in the olanzapine group and 7.39 days in the placebo group. The mean dose of benzodiazepines (using equivalent doses) did not differ between the treatment groups: 1.64 ± 0.80 mg in the olanzapine group and 1.80 ± 0.64 mg in the placebo group.

There were no statistically significant differences in the frequency of concomitant anticholinergic medication use between the olanzapine and placebo groups. Three patients had concomitant benztropine mesylate use – 2 in the olanzapine group and 1 in the placebo group. One patient in the olanzapine group had concomitant dimenhydrinate use. One patient in the placebo group had concomitant trihexyphenidyl use. There was a statistically significant difference in the number of days of concomitant anticholinergic use: 22.5 ± 0.7 days in the olanzapine group and 6.5 ± 6.4 days in the placebo group. The mean dose of anticholinergic medication did not differ between the treatment groups: 2.6 ± 2.0 mg in the olanzapine group and 2.0 ± 1.4 mg in the placebo group.

*Primary Endpoint*
*Primary Analysis - LOCF*
The mean modal daily dose of olanzapine was 12.5 mg and the mean daily dose was 11.1 mg.

The Sponsor was asked to provide statistical analysis for the weekly visits for the primary endpoint (BPRS-C total score). Statistical differences favoring the olanzapine group occurred beginning at visit 5 and were maintained to the end of study (visit 9). The analysis including site 021 was similar, least square mean difference was 10.38 favoring the olanzapine group (p = 0.003).

Table 6.1.3.3 Sponsor's Table. BPRS-C Total Score Mean Change from Baseline to Endpoint by Visit– LOCF. (without site 021)

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Visit | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Diff. | *P-value |
| 3 | Olanzapine | 72 | 50.26 | 9.98 | -5.39 | 6.88 | -5.30 | -2.25 | .132 |
| | Placebo | 35 | 50.09 | 8.59 | -3.17 | 8.30 | -3.05 | | |
| 4 | Olanzapine | 72 | 50.26 | 9.98 | -10.13 | 9.56 | -9.97 | -1.80 | .370 |
| | Placebo | 35 | 50.09 | 8.59 | -8.37 | 11.50 | -8.16 | | |
| 5 | Olanzapine | 72 | 50.26 | 9.98 | -14.33 | 10.78 | -14.15 | -5.50 | .017 |
| | Placebo | 35 | 50.09 | 8.59 | -8.89 | 13.43 | -8.65 | | |
| 6 | Olanzapine | 72 | 50.26 | 9.98 | -16.65 | 15.27 | -16.46 | -9.14 | .003 |
| | Placebo | 35 | 50.09 | 8.59 | -7.54 | 15.55 | -7.32 | | |
| 7 | Olanzapine | 72 | 50.26 | 9.98 | -17.46 | 15.64 | -17.27 | -8.52 | .008 |
| | Placebo | 35 | 50.09 | 8.59 | -8.97 | 16.63 | -8.75 | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 8 | Olanzapine | 72 | 50.26 | 9.98 | -18.81 | 16.06 | -18.59 | -9.91 | .003 |
| | Placebo | 35 | 50.09 | 8.59 | -8.94 | 18.05 | -8.68 | | |
| 9 | Olanzapine | 72 | 50.26 | 9.98 | -19.42 | 15.51 | -19.26 | -10.12 | .003 |
| | Placebo | 35 | 50.09 | 8.59 | -9.31 | 18.70 | -9.14 | | |

Sponsor provided LOCF analyses by visit upon request

*Supportive Analyses – OC and MMRM*

By contrast, the OC analysis (Table 6.1.3.4) found statistically significant differences favoring olanzapine treatment only at visits 5 and 6. The MMRM analysis (Table 6.1.3.5) was also statistically significant, however, the statistician has also performed an MMRM analysis and the results from his analysis are very different from the Sponsor's analysis. The statistician calculated a p-value of 0.72 at endpoint for his MMRM analysis (see Statistician's review).

Table 6.1.3.4. Sponsor's Table. BPRS-C Total Score Mean Change from Baseline to Endpoint by Visit– OC.

**Table HGIN.14.20. BPRS-C Total Score**
**Mean Change from Baseline to Each Visit (OC)**
**Double-Blind Period**

| | | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Efficacy Variable | Visit | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Diff. | *P-value |
| BPRS-C Total Score | 3 | Olanzapine | 72 | 50.26 | 9.98 | -5.39 | 6.88 | -5.30 | -2.25 | .132 |
| | | Placebo | 35 | 50.09 | 8.59 | -3.17 | 8.30 | -3.05 | | |
| | 4 | Olanzapine | 70 | 50.07 | 9.94 | -10.00 | 9.61 | -9.83 | -1.42 | .490 |
| | | Placebo | 34 | 49.74 | 8.46 | -8.53 | 11.63 | -8.41 | | |
| | 5 | Olanzapine | 69 | 50.12 | 10.00 | -14.77 | 10.31 | -14.52 | -4.92 | .032 |
| | | Placebo | 33 | 49.76 | 8.59 | -9.64 | 13.37 | -9.60 | | |
| | 6 | Olanzapine | 66 | 50.24 | 10.16 | -17.42 | 15.33 | -17.17 | -7.49 | .021 |
| | | Placebo | 30 | 49.50 | 8.84 | -9.83 | 15.20 | -9.68 | | |
| | 7 | Olanzapine | 57 | 49.63 | 10.59 | -20.19 | 14.74 | -20.07 | -4.08 | .250 |
| | | Placebo | 21 | 49.05 | 9.51 | -16.38 | 15.30 | -15.99 | | |
| | 8 | Olanzapine | 52 | 50.23 | 10.56 | -23.02 | 14.73 | -23.08 | -4.52 | .253 |
| | | Placebo | 18 | 49.11 | 9.51 | -18.72 | 18.10 | -18.55 | | |
| | 9 | Olanzapine | 50 | 50.64 | 10.57 | -24.52 | 13.47 | -24.38 | -0.26 | .947 |
| | | Placebo | 15 | 49.00 | 8.49 | -23.73 | 14.62 | -24.12 | | |

Table 6.1.3.5 Sponsor's Table. BPRS-C Total Score Mean Change from Baseline to Endpoint by Visit– MMRM.

**Table HGIN.14.23. BPRS-C Total Score Repeated Measures ANOVA Analysis
Mean Change from Baseline to Each Visit
Double-Blind Period**

| Efficacy Variable | Visit (Week) | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean StdErr | LSMean Difference | Diff StdErr | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BPRS-C Total Score | Combined | Olanzapine | | | | | | -15.17 | 1.36 | -6.55 | 2.42 | .008 |
| | | Placebo | | | | | | -8.62 | 2.00 | | | |
| | 3 (0.5) | Olanzapine | 72 | 50.26 | 9.98 | -5.39 | 6.88 | -5.26 | 0.85 | -2.26 | 1.48 | .131 |
| | | Placebo | 35 | 50.09 | 8.59 | -3.17 | 8.30 | -3.01 | 1.22 | | | |
| | 4 (1) | Olanzapine | 70 | 50.07 | 9.94 | -10.00 | 9.61 | -10.12 | 1.17 | -1.76 | 2.05 | .392 |
| | | Placebo | 34 | 49.74 | 8.46 | -8.53 | 11.63 | -8.36 | 1.68 | | | |
| | 5 (2) | Olanzapine | 69 | 50.12 | 10.00 | -14.77 | 10.31 | -14.49 | 1.33 | -5.50 | 2.33 | .020 |
| | | Placebo | 33 | 49.76 | 8.59 | -9.64 | 13.37 | -8.98 | 1.92 | | | |
| | 6 (3) | Olanzapine | 66 | 50.24 | 10.16 | -17.42 | 15.33 | -16.98 | 1.85 | -9.79 | 3.27 | .004 |
| | | Placebo | 30 | 49.50 | 8.84 | -9.83 | 15.20 | -7.19 | 2.69 | | | |
| | 7 (4) | Olanzapine | 57 | 49.63 | 10.59 | -20.19 | 14.74 | -18.10 | 1.90 | -7.90 | 3.42 | .023 |
| | | Placebo | 21 | 49.05 | 9.51 | -16.38 | 15.30 | -10.20 | 2.84 | | | |
| | 8 (5) | Olanzapine | 52 | 50.23 | 10.56 | -23.02 | 14.73 | -19.96 | 2.02 | -9.76 | 3.69 | .010 |
| | | Placebo | 18 | 49.11 | 9.51 | -18.72 | 18.10 | -10.21 | 3.08 | | | |
| | 9 (6) | Olanzapine | 50 | 50.64 | 10.57 | -24.52 | 13.47 | -21.29 | 1.93 | -8.90 | 3.58 | .015 |
| | | Placebo | 15 | 49.00 | 8.49 | -23.73 | 14.62 | -12.39 | 3.02 | | | |

*U.S. vs. Russia sites*

Since almost half of the patients were from sites in Russia, the Sponsor provided an analysis of mean change from baseline to endpoint (LOCF) on the BPRS-C total score between the two sites (Table 6.1.3.6). Interestingly, the overall efficacy signal comes entirely from the sites in Russia and is driven by the very low mean change from baseline to endpoint in the placebo group.

Table 6.1.3.6. Sponsor's Table. BPRS-C Total Score Mean Change from Baseline to Endpoint by Country– U.S. vs. Russian sites.

**Table HGIN.14.21. BPRS-C Total Score
Mean Change from Baseline to Endpoint (LOCF) by Country
Double-Blind Period**

| Efficacy Variable | Country | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Diff. | *P-value | **P-value (Therapy by Country) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BPRS-C Total Score | America | Olanzapine | 38 | 53.18 | 10.10 | -21.21 | 16.30 | -20.89 | -5.26 | .258 | .146 |
| | | Placebo | 19 | 51.42 | 8.64 | -15.00 | 18.28 | -15.64 | | | |
| | Russia | Olanzapine | 34 | 47.00 | 8.88 | -17.41 | 14.55 | -17.44 | -14.95 | .003 | |
| | | Placebo | 16 | 48.50 | 8.52 | -2.56 | 17.38 | -2.49 | | | |

Because of these differences in efficacy, this reviewer asked the Sponsor to analyze the baseline psychiatric illness variables of patients between the U.S. and Russia sites. This analysis is in Appendix 10.4. In general, patients from the U.S. sites had fewer days since last hospitalization (149 vs. 477 days, p = 0.012) [other differences between the countries may account for this difference], higher baseline BPRS-C scores (52.6 vs. 47.5, p = 0.005) and higher baseline scores on several BPRS-C subscales including behavioral problems, depression, thinking disturbance

(11.04 vs. 9.72, p = 0.030), and psychomotor excitation. The PANSS total scores were not different between the sites though there were some inconsistent differences on the subscales. Although not statistically significant, the PANSS total scores were numerically higher in the Russia sites (97.6 vs. 93.3, p = 0.116). Therefore, it does not appear that there is a consistent signal indicating that the patients enrolled in the Russia sites are more severely ill compared to the patients enrolled in the U.S. sites.

*Secondary Analyses*

BPRS-C Individual Items and Composite Scores

When evaluating the BPRS-C individual items, statistical differences favoring olanzapine were found only for uncooperativeness (p = 0.003), hostility (p < 0.001), manipulativeness (p = 0.035), hyperactivity (p = 0.004) and sleep difficulties (p < 0.001) (see Appendix 10.5). Although there were statistical differences favoring olanzapine for the Thinking Disturbance composite (p = 0.050), the effect is only significant for peculiar fantasies (p = 0.014) but not delusions (p = 0.151) or hallucinations (p = 0.249) – despite the similar severity ratings at baseline for all three symptoms. Interestingly, the "peculiar fantasies" item is one that has been noted to have poor interrater reliability in psychometric testing.[1]

*Subgroup Analyses*

The Sponsor evaluated the following subgroups: gender, age (< 15, ≥ 15), Caucasian vs. nonCaucasian.

Statistically significant differences favoring olanzapine were found for all subgroups except females (p = 0.203), < 15 years of age (p = 0.302) and nonCaucasians – the greater change to endpoint in the placebo group in these subgroups may have contributed to these findings. However, the treatment-by-subgroup analyses were not significant.

Table 6.1.3.6. Sponsor's Table. BPRS-C Total Score - Subgroup Analyses

| | | | | | Baseline | | Change to Endpoint | | | | **P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Efficacy Variable | Subgroup | Strata | N | Therapy | n | Mean | Std | Mean | Std | LSMean Change | LSMean Diff. | *P-value | (Therapy*Subgroup) |
| BPRS-C Total Score | Gender | Female | 32 | Olanzapine | 21 | 51.90 | 11.92 | -18.67 | 12.77 | -17.66 | -8.08 | .203 | .682 |
| | | | | Placebo | 11 | 53.36 | 7.58 | -10.45 | 21.88 | -9.58 | | | |
| | | Male | 75 | Olanzapine | 51 | 49.59 | 9.10 | -19.73 | 16.61 | -20.03 | -10.99 | .009 | |
| | | | | Placebo | 24 | 48.58 | 8.75 | -8.79 | 17.55 | -9.03 | | | |
| | Age | < 15 | 22 | Olanzapine | 15 | 50.73 | 9.27 | -17.27 | 17.80 | -10.20 | -6.01 | .302 | .561 |
| | | | | Placebo | 7 | 54.71 | 8.88 | -12.57 | 20.40 | -2.19 | | | |
| | | >=15 | 85 | Olanzapine | 57 | 50.14 | 10.23 | -19.98 | 14.97 | -19.95 | -11.07 | .004 | |
| | | | | Placebo | 28 | 48.93 | 8.27 | -8.50 | 18.56 | -8.88 | | | |

1 Lachar D, Randle SL, Harper RA et al. The Brief Psychiatric Rating Scale for Children (BPRS-C): validity and reliability of an anchored version. J Am Acad Child Adolesc Psychiatry 2001;40:333-340.

| Efficacy Variable | Subgroup | Strata | N | Therapy | Baseline n | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Diff. | *P-value | **P-value (Therapy*Subgroup) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BPRS-C Total Score | Origin | Caucasian | 77 | Olanzapine | 52 | 50.02 | 10.08 | -17.65 | 15.02 | -18.22 | -10.92 | .007 | .802 |
| | | | | Placebo | 25 | 49.08 | 8.33 | -6.72 | 18.42 | -7.30 | | | |
| | | Non-Caucasian | 30 | Olanzapine | 20 | 50.90 | 9.92 | -24.00 | 16.21 | -24.55 | -9.85 | .092 | |
| | | | | Placebo | 10 | 52.60 | 9.16 | -15.80 | 18.73 | -14.70 | | | |

*Efficacy issues*

1. It is troubling to this reviewer that the efficacy signal appears to be coming entirely from the sites in Russia ($p = 0.003$), whereas the efficacy data is far from significant in the sites in the U.S. ($p = 0.258$). The mean change to endpoint in the BPRS-C total score in the olanzapine groups are similar between the sites and the difference in efficacy signal appears to be driven by the very low mean change in the placebo group in the Russia sites.
2. Because of this discrepancy in efficacy findings, DSI was sent to inspect two of the sites in Russia. Although a final report has not been issued, they did not find any major compliance issues.
3. It is interesting that all 5 of the sites in Russia randomized 10 patients each while most of the 20 U.S. sites (80%) randomized between 1 and 3 patients. Only one of the 20 U.S. sites randomized 10 patients (no sites randomized more than 10). It is not surprising that many U.S. sites did not enroll a high number of patients since adolescent schizophrenia is a rare disorder. It is surprising that the sites in Russia were able to randomize that many patients. This reviewer asked the Sponsor if enrollment was capped at 10 for the Russia sites – the Sponsor indicated that the "target number of patients for each site in Russia was 10 patients for a total of 50 patients".
4. The efficacy results from the clinical trial are not consistent among different analyses. While the LOCF analysis is significant ($p = 0.003$), the OC analysis is not ($p = 0.947$). Significant numbers of patients were still in the study at endpoint (50/72, 69% in the olanzapine group and 15/35, 43% in the placebo group). The least squares mean difference was -10.12 in the LOCF analysis, -8.90 in the MMRM analysis and -0.26 in the OC analysis.
5. The statistician reanalyzed the dataset per MMRM and obtained very different results compared to the Sponsor's MMRM analysis. The statistician calculated a LS Mean Difference of -1.25, $p = 0.72$ (see Statistician's review).

### 6.1.4 Efficacy Conclusions

The mean modal daily dose of olanzapine was 12.5 mg and the mean daily dose was 11.1 mg. Seventy-five percent of patients in the olanzapine group and 56% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIN was change from baseline in the BPRS-C Total Score (LOCF analysis). The overall study results were statistically significant for olanzapine versus placebo (LS Mean Diff = -10.12, $p = 0.003$).

The supportive OC analysis was discordant from the LOCF analysis (LS Mean Diff = -0.26, p = 0.947). The reviewing statistician recalculated the MMRM supportive analysis and found similar results to the OC analysis (LS Mean Diff = -1.25, p = 0.72) though the Sponsor's results for the MMRM analysis were statistically significant.

When evaluating the efficacy signal for the sites in the United States and the sites in Russia, only the latter were statistically significant in favor of olanzapine. The LS Mean Diff for United States sites -5.26 (p = 0.258) and for Russia -14.95 (p = 0.003). The low placebo response in the sites in Russia appears to be driving these results. Since efficacy could not be demonstrated in patients in sites from the United States, this reviewer recommended a non approval action.

# 7 INTEGRATED REVIEW OF SAFETY

The Sponsor used the following databases for assessment of safety (see Table 4.1.1 in Section 4.1 – Tables of Clinical Studies for more information on individual studies). For studies HGCS (n = 8), HGCR (n = 2), and HGGC (n = 23), the Sponsor included only information regarding deaths, serious adverse events and discontinuations due to adverse events.

Sponsor's Table. Databases for Summary of Clinical Safety

**Table 2.7.4.1. Databases for Summary of Clinical Safety**

| Database | Indication | Studies Used | Number of Patients |
|---|---|---|---|
| Acute Placebo-Controlled Databases | Schizophrenia | HGIN | N=107 (Olz=72, Pla=35) |
| | Bipolar | HGIU | N=161 (Olz=107, Pla=54) |
| | Combined | HGIN, HGIU | N=268 (Olz=179, Pla=89) |
| Overall Olanzapine Exposure Databases | Schizophrenia | HGIN, LOAY, HGMF[a] | N=227 |
| | Bipolar | HGIU, HGMF[a] | N=227 |
| | Combined | HGIN, HGIU, LOAY, HGMF | N=454 |

a Because Study HGMF enrolled patients with schizophrenia or bipolar disorder, some patients from Study HGMF were included in the Overall Olanzapine Exposure Bipolar Database and some patients from Study HGMF were included in the Overall Olanzapine Exposure Schizophrenia Database.

The Sponsor also included information on serious adverse events and discontinuations due to adverse events for the 37 adolescent patients who participated in the olanzapine adult studies:

Study HGBG and HGCL were clinical trials for adult patients aged 18 or older – two adolescent patients were enrolled in those trials (17.9 and 17.8 years of age).
Study HGDH – acute and long-term efficacy of olanzapine in first-episode psychotic patients aged 16 – 40 years (n = 7 adolescents).
Study HGGF – delaying or preventing psychosis onset in persons aged 12 to 45 years prodromal to psychosis (n = 24 adolescents).

Study HGKL – clinical trial in patients aged 15 to 65 years with borderline personality disorder (n = 4 adolescents).

**"Acute Placebo Controlled Database" hereafter called HGIN + HGIU Acute Database**
A total of 268 patients were included in the HGIN + HGIU Acute Database. Eight (4.5%) patients discontinued due to adverse events in the olanzapine treatment group.

Patient Disposition (HGIN + HGIU)

| | Olanzapine N = 179 | Placebo N = 89 | P-value |
|---|---|---|---|
| Completers | 134 (74.9%) | 50 (56.2%) | 0.003 |
| Drop Outs | 45 (25%) | 39 (44%) | |
| Adverse Event | 8 (4.5%) | 1 (1.1%) | 0.279 |
| Lack of Efficacy | 22 (12.3%) | 34 (38.2%) | < 0.001 |
| Lost to Follow-up | 1 (0.6%) | 0 | 1.00 |
| Patient Decision | 8 (4.5%) | 2 (2.2%) | 0.504 |
| Criteria Not Met/Compliance | 2 (1.1%) | 2 (2.2%) | 0.602 |
| Sponsor Decision | 1 (0.6%) | 0 | 1.00 |
| Physician Decision | 1 (0.6%) | 0 | 1.00 |
| Other | 2 (1.1%) | 0 | 1.00 |

Modified from Sponsor table 2.7.4.20 in summary-clin-safety document

Patient demographics (HGIN + HGIU): The majority of patients were male (60%), Caucasian (70%) with a mean age of ~ 15.6 years (see Appendix 10.6). For study HGIN, the majority of patients were 16 and 17 years of age at baseline (61%); for study HGIU, the majority of patients were 14 and 15 (55%). This is expected and consistent with the psychiatric diagnoses in these two trials. A table of age distribution at baseline is in Appendix 10.6.

**"Overall Olanzapine Exposure Combined Database" hereafter called Overall Combined Database**
A total of 454 patients were included in the Overall Combined Database. The patient disposition by diagnoses (bipolar vs. schizophrenia) is given in Table 6.1.4.2. Twice as many patients with bipolar disorder discontinued due to an adverse event compared to patients with schizophrenia (14.5% vs. 7.9%). More than twice as many patients with schizophrenia discontinued due to lack of efficacy compared to patients with bipolar disorder (16.3% vs. 5.7%).

Sponsor's Table. Patient Disposition (Overall Combined Database)

**Table 2.7.4.23. Patient Disposition**
**All Patients with Olanzapine Exposure**
**Overall Olanzapine Exposure Combined Database**

| | Bipolar | | Schizophrenia | | Overall | |
|---|---|---|---|---|---|---|
| Patient Disposition | N | % | N | % | N | % |
| Reporting Interval Completed | 130 | 57.3% | 119 | 52.4% | 249 | 54.8% |
| Adverse Event | 33 | 14.5% | 18 | 7.9% | 51 | 11.2% |
| Lack of Efficacy | 13 | 5.7% | 37 | 16.3% | 50 | 11.0% |
| Lost To Follow-Up | 9 | 4.0% | 4 | 1.8% | 13 | 2.9% |
| Patient Decision | 24 | 10.6% | 10 | 4.4% | 34 | 7.5% |
| Criteria Not Met/Compliance/Protocol Violation | 2 | 0.9% | 28 | 12.3% | 30 | 6.6% |
| Sponsor Decision | 3 | 1.3% | 5 | 2.2% | 8 | 1.8% |
| Physician Decision | 10 | 4.4% | 4 | 1.8% | 14 | 3.1% |
| Other | 3 | 1.3% | 2 | 0.9% | 5 | 1.1% |
| Total | 227 | 100.0% | 227 | 100.0% | 454 | 100.0% |

The patient demographics in the Overall Combined Database were fairly consistent with the demographics of the HGIU + HGIN Acute Database with the exception of country – 89 additional patients with schizophrenia from study LOAY (German sites) were included in the Overall Combined Database. Patient demographics for the Overall Combined Database are included in Appendix 10.6.

## 7.1 Methods and Findings

### 7.1.1 Deaths

No deaths occurred in the HGIU + HGIN Acute Database, Overall Combined Database, studies HGCS, HGCR, HGGC or in adolescent patients from the adult studies.

### 7.1.2 Other Serious Adverse Events

The following tables for serious adverse events were compiled from narratives provided by the Sponsor.

A total of 7 serious adverse events occurred in 6 patients in the olanzapine treatment arm in the HGIU + HGIN Acute Database (see Table 7.1.2.1).
One serious adverse event (schizophrenia) occurred in 1 patient in the placebo arm of study HGIN (no SAEs in the placebo group in study HGIU).

Table 7.1.2.1. Serious Adverse Events: HGIN + HGIU Acute Database

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Severity Outcome |
|---|---|---|---|---|---|
| HGIN 025-2504 | 15 YOWF | Olanzapine DB phase | Migraine | Migraine | Severe Worsened from baseline; failed to restart study med and discontinued from study |
| HGIN 930-9301 | 15 YOWM | Olanzapine DB phase | Closed fracture of right forearm | Forearm fracture | Severe Fracture from fall, treated in hospital |
| HGIN 026-2603 | 14 YOWF | Olanzapine DB phase | Weight gain | Weight increased | Mild/moderate Onset of AE in DB phase, patient discontinued OL phase due to weight gain of 18.3 kg over 4 months |
| HGIU 012-1211 | 14 YOWF | Olanzapine DB phase | Exacerbation of bipolar symptoms | Bipolar disorder | Severe Discontinued during OL phase |
| HGIU 035-3501 | 14 YOWF | Olanzapine DB phase | Relapse of bipolar disorder | Bipolar disorder | Moderate Hospitalized, Discontinued due to weight gain |
| HGIU 031-3103 | 14 YOWM | Olanzapine DB phase | Decreased WBC count and decreased neutrophils | WBC count decreased, neutrophil count decreased | Moderate WBC 4.04 to 2.52; ANC 1.63 to 0.83; Discontinued in OL phase due to persistently low counts |

A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database (see Table 7.1.2.2). The majority of these SAEs, 19/35 patients, were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

Table 7.1.2.2 Serious Adverse Events: Overall Combined Database

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Severity Outcome |
|---|---|---|---|---|---|
| HGIN 007-0704 | 15 YOBM | Olanzapine OL phase | Exacerbation of schizophrenia | Schizophrenia | Severe Hospitalization, discontinuation from study |
| HGIN 013-1302 | 17 YOM | Olanzapine OL phase | Wosening of schizophrenia symptoms | Schizophrenia | Moderate |
| HGIN 019-1901 | 15 YOWF | Olanzapine OL phase | Depressive with psychotic features, weight gain | Major depression, weight increased | Severe Hospitalization, discontinuation from study |
| HGIN 021-2101 | 14 YOBM | Olanzapine OL phase | Worsening of schizophrenia | Schizophrenia | Severe |
| HGIN 026-2603 | 14 YOWF | Olanzapine OL phase | Exacerbation of schizophrenia, | Schizophrenia, weight | Severe (schiz) Moderate (weight) |

| | | | | | |
|---|---|---|---|---|---|
| | | | suicidal ideation, weight gain | increased | Hospitalization, weight gain of 18.3 kg over 4 months |
| HGIN 030-3001 | 17 YOWM | Olanzapine OL phase, 1st visit | Exacerbation of psychosis | Psychotic disorder | Severe Hospitalized |
| HGIN 910-9101 | 16 YOWF | Olanzapine OL phase | Worsening of Schizophrenia | Schizophrenia | Moderate Hospitalized |
| HGIN 930-9301 | 15 YOWM | Olanzapine OL phase | Closed fracture of right forearm | Forearm fracture | Severe Fracture from fall, treated in hospital |
| HGIN 930-9307 | 15 YOWF | Olanzapine OL phase | Attempted suicide | Suicide attempt | Severe Attempted overdose with Phenobarbital, hospitalized, discontinued from study |
| HGIU 001-0103 | 13 YOWM | Olanzapine OL phase | Increased agitation | Agitation | Severe Hospitalized, completed study |
| HGIU 001-0107 | 13 YOWM | Olanzapine OL phase | Agitation, aggression | Agitation, aggression | Severe Hospitalized, completed study |
| HGIU 001-0108 | 14 YOWF | Olanzapine OL phase | Alcohol intoxication, suicidal ideation | Alcohol poisoning, suicidal ideation | Severe (alcohol) Moderate (SI) Discontinued from study |
| HGIU 012-1202 | 15 YOWF | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized, completed study |
| HGIU 012-1211 | 14 YOWF | Olanzapine OL phase | Exacerbation of bipolar symptoms | Bipolar disorder | Severe Discontinued study |
| HGIU 012-1212 | 14 YOBF | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized, discontinued "patient decision" |
| HGIU 020-2016 | 14 YOWF | Olanzapine OL phase | Attempted suicide | Suicide attempt | Mild Overdose of Benadryl and ibuprofen, recovered without treatment; completed study |
| HGIU 026-2604 | 16 YOHM** | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized, completed study |
| HGIU 026-2605 | 14 YOM | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized and discontinued study |
| HGIU 026-2608 | 13 YOWF | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized, discontinued study |
| HGIU 027-2705 | 15 YOBM | Olanzapine OL period | Worsening of bipolar disorder, self-inflicted superficial lacerations | Bipolar disorder, Intentional self-injury | Severe (BP) Moderate (SIB) Hospitalized, discontinued study (cut arms with fingernails) |
| HGIU | 14 YOBF | Olanzapine | Worsening of | Bipolar disorder | Severe |

| | | | | | |
|---|---|---|---|---|---|
| 027-2707 | | OL phase | bipolar disorder | | Hospitalized, completed study |
| HGIU 028-2804 | 15 YOWF | Olanzapine OL phase | Recurrence of bipolar symptoms | Bipolar disorder | Severe Hospitalized, discontinued study "sponsor's decision" – GCP issues at site |
| HGIU 028-2805 | 14 YOWF | Olanzapine OL phase | Suicidal ideation | Suicidal ideation | Severe Hospitalized, discontinued – GCP issues at site |
| HGIU 028-2806 | 15 YOBF | Olanzapine OL phase | Bipolar mania | Bipolar disorder | Severe Hospitalized, discontinued study |
| HGIU 031-3103 | 14 YOWM | Olanzapine OL phase | Decreased WBC count and decreased neutrophils | WBC count decreased, neutrophil count decreased | See Table 7.1.2.1. |
| HGIU 033-3304 | 15 YOWF | Olanzapine OL phase | Intensifying aggressiveness and irritability | Aggression, irritability | Severe Hospitalized, discontinued study |
| HGIU 035-3519 | 14 YOWM | Olanzapine OL phase | Violent behavior | Aggression | Severe Hospitalized, discontinued study |
| HGIU 730-7302 | 13 YOHM | Olanzapine OL phase | Oppositional defiant behavior | Oppositional defiant disorder | Severe Hospitalized, discontinued due to noncompliance |
| HGMF 003-0303 | 17 YOWF | Olanzapine OL | Acute appendicitis | Appendicitis | Severe Hospitalized, completed study |
| HGMF 003-0304 | 16 YOWF | Olanzapine OL | Exacerbation of bipolar illness with positive suicidal ideation | Bipolar disorder | Severe Hospitalized, discontinued study |
| LOAY 407-4078 | 17 YOWM | Olanzapine OL | Recurrence of acute psychotic symptoms | Psychotic disorder | Severe Hospitalized |
| LOAY 407-4207 | 14 YOWM | Olanzapine OL | Borrelia infection | Borrelia infection | Mild Discontinued study |
| LOAY 413-4145 | 16 YOWM | Olanzapine OL | Worsening of underlying disease schizophrenia | Schizophrenia | Severe Hospitalized Discontinued study |

Table 7.1.2.3 Serious Adverse Events: HGCR, HGCS, HGGC

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Severity Outcome |
|---|---|---|---|---|---|
| HGCR 001-2001 | 12 YOWM | Olanzapine OL | Headache lumbar puncture | Headache | Moderate Completed study |
| HGCS 001-1001 | 14 YOHF | Olanzapine OL | Mallory Weiss tear, vomiting blood | Esophageal hemorrhage, hematemesis | Severe Completed study |
| HGGC 001-2023 | 14 YOWF | Olanzapine | Suicidality | Depression | Hospitalized and discontinued from study |

The Sponsor was asked to provide narratives for the adolescent patients in the adult studies who experienced serious adverse events (Table 7.1.2.4).

Table 7.1.2.4 Serious Adverse Events: Adolescent Patients from Adult Studies (n = 37)

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Comments |
|---|---|---|---|---|---|
| HGDH 007-1607 | 17 YOWM | Olanzapine | Overdose | Overdose | Ingested 175 mg olanzapine, completed the study |
| HGGF 001-0102 | 15 YOWM | Olanzapine | Worsening depression with suicidal ideation | Depression, affective disorder, suicidal ideation | Gained significant amount of weight- 14 kg in 17 weeks; patient discontinued |
| HGGF 001-113 | 16 YOWF | Olanzapine | Dysphoria, Superficial self-mutilation | Dysphoria, self mutilation | Cuts on upper arm made with piece of glass, discontinued from study |
| HGGF 004-405 | 17 YOWF | Olanzapine | Auditory perceptual abnormalities, depersonalization, depressed mood, suicidal ideation, worsening psychosis | Auditory hallucination, depersonalization, depressed mood, illusion, suicidal ideation, psychotic disorder | |
| HGGF 004-406 | 17 YOWF | Olanzapine | Depressed mood, suicidal ideation | Depressed mood, suicidal ideation | Discontinued study |

Narratives were provided by Sponsor upon request

## 7.1.3 Dropouts and Other Significant Adverse Events

### 7.1.3.1 Adverse events associated with dropouts

Table 7.1.3.1.1 Discontinuations Due to Adverse Events: HGIN + HGIU Acute Database

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Comments |
|---|---|---|---|---|---|
| HGIN 007-703 | 13 YOBF | Olanzapine DB phase | Clinically significant increased ALT | ALT increased | ALT up to 231<br>(AST up to 142)<br>Returned to WNL after discontinuation from study |
| HGIN 010-1001 | 17 YOWM | Olanzapine DB phase | Elevated liver function | Liver function test abnormal | ALT = up to 597<br>AST = up to 410<br>GGT = up to 129<br>Noted at randomization visit (was taking olanzapine prior to study)<br>Discontinued study |
| HGIN 021-2103 | 17 YOBM | Olanzapine DB phase | Elevated transaminases | Transaminases increased | AST up to 136<br>ALT up to 396 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Returned to WNL after discontinuation from study |
| HGIN 910-9110 | 17 YOWM | Olanzapine DB phase | AST increased | AST increased | AST up to 190 (ALT up to 321) Returned to WNL after discontinuation from study |
| HGIN 920-9202 | 17 YOWM | Olanzapine DB phase | Rise ALT | ALT increased | ALT up to 393 (AST up to 179 GGT up to 82) ALT and GGT returned to WNL after discontinuation from study (AST N/A) |
| HGIU 035-3503 | 16 YOBF | Olanzapine DB phase | Heart rate increased | Elevated pulse | Holter noted sinus tachycardia Discontinued from study, pulse WNL at 4th follow-up visit |
| HGIU 012-1203 | 15 YOWF | Olanzapine DB phase | Hepatic enzyme increased | Elevated liver enzymes | AST up to 148 ALT up to 325 GGT up to 53 Returned to near WNL after discontinuation from study (ALT 48) |
| HGIU 035-3501 | 14 YOWF | Olanzapine DB phase | Weight increased | Weight gain | Weight increase of 4.5 kg in ~ 15 days |

Table 7.1.3.1.2 Discontinuations Due to Adverse Events: Overall Combined Database

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Comments |
|---|---|---|---|---|---|
| HGIN 003-0302 | 17 YOWM | Olanzapine OL | Weight increased | Weight gain | Gained 12.7 kg in 3 months |
| HGIN 019-1901 | 15 YOWF | Olanzapine OL | Weight increased | Weight gain | Gained 6.62 kg during DB phase, Gained 15.88 kg over 5.7 months |
| HGIN 020-2002 | 15 YOBM | Olanzapine OL | Sedation | Sedation | |
| HGIN 025-2502 | 16 YOWM | Olanzapine OL | Weight increased | Weight gain | Gained 12.2 kg over 183 days |
| HGIN 027-2701 | 17 YOWM | Olanzapine OL | Weight increased | Weight gain | Gained 12 kg over 92 days |
| HGIN 027-2702 | 13 YOWF | Olanzapine OL | Weight increased | Weight gain | Gained 17.5 kg over 148 days |
| HGIN 030-3007 | 13 YOWF | Olanzapine OL | Increased appetite | Increased appetite | Gained 21.8 kg over 94 days |
| HGIN 900-9003 | 16 YOWM | Olanzapine OL | Weight increased | Weight gain | Gained 12.8 kg over 169 days |
| HGIN 930-9307 | 15 YOWF | Olanzapine OL | Suicide attempt | Suicide attempt | See Table 7.1.2.2. |
| HGIN 940-9403 | 16 YOWM | Olanzapine OL | Weight increased | Weight gain | Gained 13.4 kg over 152 days |
| HGIU | 14 YOWF | Olanzapine | Alcohol | Alcohol | See Table 7.1.2.2. |

| | | | | | |
|---|---|---|---|---|---|
| 001-108 | | OL | intoxication | poisoning | |
| HGIU 007-708 | 15 YOWM | Olanzapine OL | Drowsiness | Somnolence | |
| HGIU 009-902 | 15 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 14.2 kg over 78 days |
| HGIU 013-1303 | 17 YOWF | Olanzapine OL | Syncope | Syncope | 100/60 mm Hg, 88 bpm supine, 98/62 mmHg, 100 bpm standing |
| HGIU 013-1308 | 14 YOHF | Olanzapine OL | Weight gain | Weight increased | Gained 9.1 kg over 103 days |
| HGIU 013-1310 | 16 YOWF | Olanzapine OL | Increased appetite | Increased appetite | Gained 9.5 kg over ~ 56 days (at time of weight patient had been off drug for 11 days) |
| HGIU 013-1311 | 13 YOHM | Olanzapine OL | Worsened aggressive behavior | Aggression | |
| HGIU 019-1901 | 16 YOBF | Olanzapine OL | Pregnancy | Pregnancy | |
| HGIU 019-1907 | 15 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 17.7 kg over 170 days |
| HGIU 020-2007 | 14 YOWF | Olanzapine OL | Elevated liver function test | Liver function test abnormal | AST up to 204, ALT up to 330<br>Resolved after discontinuation from study |
| HGIU 020-2008 | 15 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 9.3 kg over 58 days |
| HGIU 020-2019 | 16 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 9.5 kg over 81 days |
| HGIU 024-2404 | 13 YOWF | Olanzapine OL | Fear of more weight gain | Fear of weight gain | Gained 5.9 kg over 34 days |
| HGIU 026-2608 | 13 YOWF | Olanzapine OL | Exacerbation of bipolar disorder | Bipolar disorder | |
| HGIU 027-2701 | 15 YOWF | Olanzapine OL | Sedation | Sedation | |
| HGIU 027-2704 | 15 YOBM | Olanzapine OL | Weight gain | Weight increased | Gained 18.6 kg over 119 days |
| HGIU 027-2705 | 15 YOBM | Olanzapine OL | Worsening of bipolar disorder | Bipolar disorder | |
| HGIU 028-2806 | 15 YOBF | Olanzapine OL | Bipolar mania | Bipolar disorder | |
| HGIU 031-3103 | 14 YOWM | Olanzapine OL | Decreased WBC | WBC count decreased | See Table 7.1.2.1 |
| HGIU 033-3304 | 15 YOWF | Olanzapine OL | Intensifying aggressiveness | Aggression | See Table 7.1.2.2. |
| HGIU 035-3510 | 15 YOWM | Olanzapine OL | Weight gain | Weight increased | Gained 5.4 kg over 89 days |
| HGIU 035-3517 | 13 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 5 kg over ~6 weeks |
| HGIU 720-7217 | 15 YOHM | Olanzapine OL | Hepatic enzymes increases | Hepatic enzyme increased | AST up to 103, ALT up to 125<br>(also had significant weight gain, 21 kg over ~ 5 months) |

| | | | | | |
|---|---|---|---|---|---|
| HGIU 720-7219 | 14 YOHF | Olanzapine OL | Pregnancy | Pregnancy | |
| HGMF 002-0211 | 17 YOWF | Olanzapine OL | Somnolence | Somnolence | |
| HGMF 003-0304 | 16 YOWF | Olanzapine OL | Exacerbation of bipolar illness with positive suicidal ideation | Bipolar disorder | See Table 7.1.2.2. |
| HGMF 008-0806 | 15 YOWM | Olanzapine OL | Increased depression | Depression | |
| HGMF 014-1400 | 17 YOBF | Olanzapine OL | Elevated CK level lab | Blood creatine phosphokinase | CK up to 690 U/L |
| HGMF 025-2501 | 15 YOWM | Olanzapine OL | Drowsiness | Somnolence | |
| HGMF 028-2801 | 18 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 8.9 kg over 27 days |
| LOAY 405-4057 | 13 YOWF | Olanzapine OL | Weight gain | Weight increased | Gained 10.1 kg over 42 days |
| LOAY 407-4207 | 14 YOWM | Olanzapine OL | Suspicion of neuroborreliosis | Neuroborreliosis | See Table 7.1.2.2. |
| LOAY 407-4218 | 15 YOWF | Olanzapine OL | Galactorrhea | Galactorrhea | Prolactin up to 35 mcg/L (ULN = 29) |

There were no discontinuations due to adverse events for studies HGCS, HGCR and HGGC.

The Sponsor was asked to provide narratives for the adolescent patients in the adult studies who discontinued due to adverse events (Table 7.1.3.1.3).

Table 7.1.3.1.3 Discontinuations Due to Adverse Events: Adolescent Patients from Adult Studies

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Comments |
|---|---|---|---|---|---|
| HGGF 001-127 | 13 YOWM | Olanzapine | Weight gain | Weight increased | Gained 23 kg in ~5 months (BMI from 32 to 39) |
| HGKL 014-1416 | 15 YOWM | Olanzapine | Weight gain | Weight increased | Gained 12.5 kg over 3 months; triglycerides also increased from 260 to 508 mg/dL |

## 7.1.4 Common Adverse Events

### 7.1.4.1 Eliciting adverse events data in the development program

Adverse events were obtained by spontaneous reports, patient observation and investigator query at every study visit. Rating scales were included for evaluation of extrapyramidal symptoms (SAS), akathisia (BAS) and dyskinesias (AIMS). Vital signs, ECGs and laboratory tests were obtained at intervals throughout the study.

7.1.4.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using the MedDRA version 8.0 coding dictionary. A sample of patient narratives was reviewed and the coding of verbatim terms to preferred terms was appropriate.

7.1.4.3 Common adverse event tables

Adverse events occurring in ≥ 2% of patients in the HGIU + HGIN Acute Database is in Table 7.1.4.3.1. The majority of adverse events in this table occurred more than twice as frequently in the olanzapine group compared to the placebo group, that adverse events that were statistically more frequent in the olanzapine group were weight increased (30% vs. 6%), somnolence (25% vs. 3%), increased appetite (24% vs. 6%) and sedation (24% vs. 6%).

Table 7.1.4.3.1 Sponsor's Table. Adverse Events Occurring in ≥ 2% of Patients: HGIU + HGIN Acute Database

| | Therapy | | | | | | |
|---|---|---|---|---|---|---|---|
| | Olanzapine | | | Placebo | | | |
| Event Classification | N | n | % | N | n | % | *P-value |
| Patients with >=1 TEAS | 179 | 158 | 88.3% | 89 | 54 | 60.7% | <.001 |
| Weight increased | 179 | 53 | 29.6% | 89 | 5 | 5.6% | <.001 |
| Somnolence | 179 | 44 | 24.6% | 89 | 3 | 3.4% | <.001 |
| Increased appetite | 179 | 43 | 24.0% | 89 | 5 | 5.6% | <.001 |
| Sedation | 179 | 34 | 19.0% | 89 | 5 | 5.6% | .003 |
| Headache | 179 | 30 | 16.8% | 89 | 11 | 12.4% | .374 |
| Fatigue | 179 | 17 | 9.5% | 89 | 4 | 4.5% | .227 |
| Dizziness | 179 | 13 | 7.3% | 89 | 2 | 2.2% | .155 |
| Dry mouth | 179 | 11 | 6.1% | 89 | 0 | 0.0% | .018 |
| Dysmenorrhoea | 67 | 4 | 6.0% | 41 | 4 | 9.8% | .475 |
| Pain in extremity | 179 | 9 | 5.0% | 89 | 1 | 1.1% | .173 |
| Vomiting | 179 | 9 | 5.0% | 89 | 6 | 6.7% | .580 |
| Constipation | 179 | 8 | 4.5% | 89 | 0 | 0.0% | .055 |
| Nausea | 179 | 8 | 4.5% | 89 | 8 | 9.0% | .172 |
| Nasopharyngitis | 179 | 7 | 3.9% | 89 | 2 | 2.2% | .722 |
| Abdominal pain upper | 179 | 6 | 3.4% | 89 | 5 | 5.6% | .514 |
| Diarrhoea | 179 | 6 | 3.4% | 89 | 0 | 0.0% | .183 |
| Irritability | 179 | 6 | 3.4% | 89 | 4 | 4.5% | .735 |
| Pharyngolaryngeal pain | 179 | 6 | 3.4% | 89 | 3 | 3.4% | 1.00 |
| Restlessness | 179 | 6 | 3.4% | 89 | 2 | 2.2% | 1.00 |
| Alanine aminotransferase increased | 179 | 5 | 2.8% | 89 | 0 | 0.0% | .174 |
| Dyspepsia | 179 | 5 | 2.8% | 89 | 1 | 1.1% | .667 |
| Epistaxis | 179 | 5 | 2.8% | 89 | 0 | 0.0% | .174 |
| Hepatic enzyme increased | 179 | 5 | 2.8% | 89 | 0 | 0.0% | .174 |
| Insomnia | 179 | 5 | 2.8% | 89 | 10 | 11.2% | .009 |
| Sinusitis | 179 | 5 | 2.8% | 89 | 0 | 0.0% | .174 |

Sponsor's Table 2.7.4.27 from summary-clin-safety document

The common adverse events for the two trials are listed separately in Table 7.1.4.3.2 since the trials differed in duration (6 vs. 3 weeks) and study population. For study HGIN, the adverse events that were statistically different between olanzapine and placebo included weight increased ($p = 0.014$) and somnolence ($p = 0.0006$). For study HGIU, the adverse events that were statistically different between olanzapine and placebo included weight increased ($p < 0.001$), increased appetite ($p < 0.001$), somnolence ($p < 0.001$) and sedation ($p = 0.011$). The adverse events and frequencies occurring in the olanzapine group between the two clinical trials were fairly similar though more patients in HGIU exhibited somnolence (25% vs. 17%), increased

appetite (29% vs. 17%), sedation (22% vs. 15%), dry mouth (8% vs. 4%) and fatigue (14% vs. 3%)

Table 7.1.4.3.2 Adverse Events Occurring in > 2% of Patients with Olanzapine > 2x Placebo: HGIU and HGIN Clinical Trials

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | 6 Week Trial % Schizophrenia Patients | | 3 Week Trial % Bipolar Patients | |
| Adverse Event | Olanzapine (N = 72) | Placebo (N = 35) | Olanzapine (N = 107) | Placebo (N = 54) |
| Weight increased | 31%* | 9% | 29%* | 4% |
| Somnolence | 17%* | 3% | 25%* | 4% |
| Headache | 17% | 6% | 17% | 17% |
| Increased appetite | 17% | 9% | 29%* | 4% |
| Sedation | 15% | 6% | 22%* | 6% |
| Dizziness | 8% | 3% | 7% | 2% |
| Pain in extremity | 6% | 3% | 5% | 0 |
| Abdominal pain | 4% | 0 | 5% | 7% |
| ALT increase | 4% | 0 | - | - |
| AST increase | 4% | 1% | 1% | 0 |
| Constipation | 4% | 0 | 5% | 0 |
| Dry mouth | 4% | 0 | 8% | 0 |
| Fatigue | 3% | 3% | 14% | 6% |
| Diarrhea | 1% | 0 | 5% | 0 |
| Dyspepsia | - | - | 5% | 0 |
| Hepatic enzyme increased | 1% | 0 | 4% | 0 |
| Sinusitis | 1% | 0 | 4% | 0 |

From Tables HGIN.12.4, HGIN.14.27 and HGIU.12.4 clinical study reports
*p < 0.05

7.1.4.4 Common adverse events – further analysis

**Weight Gain**
Weight gain was a significant adverse event occurring in these clinical trials and is further analyzed and discussed in this section along with the weight data.

*HGIU + HGIN Acute Database*
In the HGIU + HGIN Acute Database, patients in the olanzapine treatment group had significantly greater weight gain and increase in BMI compared to the placebo group (see Table 7.1.4.4.1).

Table 7.1.4.4.1 Weight and BMI Data (LOCF): HGIN + HGIU Database

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | LS Mean Change | LS Mean Difference | P-value |
| Weight (kg) | Olanzapine | 177 | 66.03 | 17.93 | 3.90 | 2.72 | 3.68 | | |
| | Placebo | 88 | 67.63 | 17.24 | 0.24 | 2.16 | 0.01 | 3.66 | < 0.001 |
| BMI | Olanzapine | 177 | 23.91 | 6.01 | 1.22 | 1.01 | 1.11 | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo | 88 | 23.98 | 5.67 | 0.05 | 0.91 | -0.07 | 1.17 | < 0.001 |

From Table 2.7.4.43 in summary-clin-safety document

The visit wise weight change for observed cases was similar to the LOCF analysis. The mean change at visit 6 was + 3.63 kg for olanzapine (n = 154) and + 0.08 kg for placebo (n = 67) (LS Mean Diff = 3.57, $p < 0.001$).

A $\geq$ 7% increase in body weight from baseline was considered a potentially clinically significant change. Seventy-seven (43.5%) patients in the olanzapine group and 6 (6.8%) of patients in the placebo group had a $\geq$ 7% increase in body weight ($p < 0.001$). Only 2 patients, both randomized to placebo, had a $\geq$ 7% decrease in body weight.

Since studies HGIN and HGIU were different with respect to types of patients and duration of the double-blind period (HGIN 6 weeks, HGIU 3 weeks), the weight and BMI data were also evaluated separately:

Table 7.1.4.4.2. Weight and BMI Data: Study HGIU

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | LS Mean Change | LS Mean Difference | P-value |
| Weight (kg) | Olanzapine | 105 | 65.33 | 20.55 | 3.66 | 2.18 | 3.51 | | |
| | Placebo | 54 | 66.83 | 17.55 | 0.30 | 1.67 | 0.16 | 3.36 | < 0.001 |
| BMI | Olanzapine | 105 | 24.21 | 6.82 | 1.18 | 0.85 | 1.15 | | |
| | Placebo | 54 | 24.05 | 5.44 | 0.02 | 0.62 | 0.00 | 1.15 | < 0.001 |

From Table HGIU.12.44 in study report

A $\geq$ 7% increase in body weight from baseline was considered a potentially clinically significant change. Forty-four (41.9%) patients in the olanzapine group and 1 (1.9%) patient in the placebo group had a $\geq$ 7% increase in body weight ($p < 0.001$). No patients in the study had a $\geq$ 7% decrease in body weight.

Table 7.1.4.4.3. Weight and BMI Data: Study HGIN

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | LS Mean Change | LS Mean Difference | P-value |
| Weight (kg) | Olanzapine | 72 | 67.04 | 13.31 | 4.26 | 3.33 | 4.22 | | |
| | Placebo | 34 | 68.91 | 16.93 | 0.13 | 2.80 | 0.08 | 4.13 | < 0.001 |
| BMI | Olanzapine | 72 | 23.45 | 4.59 | 1.39 | 1.21 | 1.37 | | |
| | Placebo | 34 | 24.02 | 6.12 | -0.05 | 1.03 | -0.07 | 1.44 | < 0.001 |

From Table HGIN.12.42 in study report

The results for the OC analysis for change in weight and BMI were similar to the LOCF analysis. At end of study, patients in the olanzapine group (n = 50) gained 4.95 kg from baseline and patients in the placebo group (n = 15) gained 0.61 kg [LS mean diff = 4.65, $p < 0.001$]. BMI

increased by 1.56 in the olanzapine group and decreased by 0.04 in the placebo group [LS mean diff = 1.62, $p < 0.001$].

A $\geq$ 7% increase in body weight from baseline was considered a potentially clinically significant change. Thirty-three (45%) patients in the olanzapine group and 5 (14.7%) of patients in the placebo group had a $\geq$ 7% increase in body weight ($p = 0.002$). Only 2 patients in the study, both randomized to placebo, had a $\geq$ 7% decrease in body weight.

Only 1 of the 8 discontinuations due to adverse events was due to weight gain in the HGIU + HGIN Acute Database (4.5 kg increase over ~15 days).
Unfortunately, insufficient data were collected during the follow-up visits to adequately address weight loss after patients completed the clinical trial (if they switched to a different antipsychotic). Though many of the investigators noted that the adverse event of "weight gain" had resolved at some of the follow-up visits, no actual weights were obtained for the majority of patients (or at least not recorded in the CRFs).

*Overall Combined Database*
Though no placebo comparison is available in this database, weight change over longer duration of time could be evaluated in general terms. Similar to the acute data, weight did appear to increase over time. This patient population (adolescents) are expected to increase in height and weight during this developmental period, however, the increases in weight are well above what would be considered expected (see Section 7.1.9 - Assessment of Effect on Growth).

Table 7.1.4.4.4. Weight and BMI Data (LOCF): Overall Combined Database

| | | | Baseline | | Change to Endpoint | | |
|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Mean | Std | P-value |
| Weight (kg) | Bipolar | 224 | 68.58 | 21.21 | 7.63 | 6.62 | < 0.001 |
| | Schizophrenia | 226 | 65.71 | 13.30 | 7.07 | 6.53 | < 0.001 |
| | Overall | 450 | 67.13 | 17.72 | 7.35 | 6.58 | < 0.001 |
| BMI | Bipolar | 216 | 24.92 | 7.34 | 2.37 | 2.39 | < 0.001 |
| | Schizophrenia | 223 | 22.40 | 4.17 | 2.24 | 2.25 | < 0.001 |
| | Overall | 439 | 23.64 | 6.07 | 2.31 | 2.31 | < 0.001 |

From Table 2.7.4.45 in summary-clin-safety document

Sixty-five percent of patients in the Overall Combined Database gained $\geq$ 7% body weight.

The Sponsor provided a summary of weight change by visit for observed cases for the Overall Combined Database (see Appendix 10.7). For the 131 patients who completed visits > 25 and $\leq$ 32 weeks, the mean increase in weight was 10.8 kg ($p < 0.001$ compared to baseline).

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months. The patient who gained 21.8 kg did so over a period of 3 months.

For those patients in the Overall Combined Database who participated in HGIU or HGIN, the weight gain for the acute phase of these trials was also evaluated to determine whether they gained a greater amount of weight early in the trial. These data were readily available for only 10 patients (some of the patients had been randomized to placebo and are not included here). The mean weight gain at the end of the double-blind phase of the study (or early termination) was 4.8 ± 2.6 kg, similar to the overall mean weight gain of 3.9 ± 2.7 kg in the acute database (see Table 7.1.4.4.1).

*Weight – Subgroup Analyses*
Because of the different duration of dosing in the HGIN and HGIU acute phases, these data were reviewed separately for each study.
The Sponsor evaluated weight changes for the subgroups gender and age (< 15, ≥ 15 years) for the adverse event "weight increased". Approximately 30% of females and males had this adverse event in the olanzapine group in both HGIU and HGIN acute studies while this adverse event was ~4% for the placebo group (with the exception of females in HGIN). No significant differences were noted between the gender subgroups (see Appendix 10.7). For the age subgroups, 28-40% had the adverse event "weight increased" in the olanzapine group compared to 0 – 14% in the placebo group. No significant differences were noted between the age subgroups (see Appendix 10.7).

Mean change in weight (kg) was also evaluated between the subgroups gender and age. These data were not included in the study report for HGIU, the Sponsor has been asked to submit these data (per the study report, only those data where results were significant were included). Data from HGIN are included in Appendix 10.7. Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine.
The Sponsor also did not include mean change in weight for the age subgroup for the HGIN + HGIU Acute Database (per the study reports, only those data where results were significant were included). The Sponsor has been asked to provide these data. In the HGIN + HGIU Acute Database, significant treatment-by-gender differences were noted (see Table 7.1.4.4.5). However, these findings are likely due to the differences in the placebo group since the weight gain (mean change to endpoint) in the olanzapine group was similar between females and males.

Table 7.1.4.4.5 Sponsor's Table. Mean Change in Weight (kg) – Gender Subgroup Analysis: HGIU + HGIN Acute Database

By Subgroup: Gender

| | | | | Baseline | | Change to Endpoint | | | LSMean | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Vital Signs | Subgroup | N Therapy | n | Mean | Std | Mean | Std | LSMean | Diff. | *P-value | **P-value |
| Weight in Kg | Female | 106 Olz | 66 | 61.79 | 16.68 | 3.66 | 2.65 | 3.63 | 3.05 | <.001 | .083 |
| | | Placebo | 40 | 62.83 | 13.65 | 0.55 | 2.27 | 0.59 | | | |
| | Male | 159 Olz | 111 | 68.54 | 18.25 | 4.05 | 2.76 | 3.79 | 4.16 | <.001 | |
| | | Placebo | 48 | 71.64 | 18.97 | -0.03 | 2.95 | -0.36 | | | |

Table 2.7.4.70 in Summary-clin-safety

Only four patients had an increase in TBili to > 1.5 times ULN – two in the olanzapine group and two in the placebo group.

The Sponsor also used Hy's rule (ALT ≥ 3 times and TBili ≥ 1.5 times ULN) to identify any patients with potential severe hepatic injury. There were no patients who met Hy's rule criteria at any time in the clinical trials or at endpoint.

## 7.1.7 Vital Signs

### 7.1.7.1 Overview of vital signs testing in the development program

Blood pressure and heart rate were taken at every visit during the acute study – supine for 5 minutes and after standing for 2 minutes
Weight and temperature were taken at every visit
Height was taken at screening, at multiple study visits and end of study.

### 7.1.7.2 Standard analyses and explorations of vital signs data

#### *7.1.7.2.1 Analyses focused on measures of central tendencies*

Mean change from baseline to endpoint (LOCF) for vital signs is included in Appendix 10.11.
Data for weight change is discussed further in Section 7.1.4.4 (Common Adverse Events).
Statistically significant differences in mean change from baseline to endpoint between the olanzapine and placebo groups were noted for:
Supine SBP: olanzapine + 2.94 mmHg, placebo - 0.71 mm Hg ($p = 0.009$)
Standing DBP: olanzapine + 1.42 mmHg, placebo -1.28 mmHg ($p = 0.033$)
Supine pulse: olanzapine + 7.07 bpm, placebo - 0.60 bpm ($p < 0.001$)
Standing pulse: olanzapine +6.97 bpm, placebo - 0.89 bpm ($p < 0.001$)
Orthostatic SBP and pulse were not significantly different between olanzapine and placebo.
Weight: olanzapine +3.90 kg, placebo +0.24 kg ($p < 0.001$)
BMI: olanzapine + 1.22, placebo + 0.05 ($p < 0.001$)

#### *7.1.7.2.2 Analyses focused on outliers or shifts from normal to abnormal*

Potentially clinically significant definitions for vital signs are in Appendix 10.12.
There were no statistically significant differences between olanzapine and placebo for percentages of patients with potentially clinically significant changes (high or low) with the exception of weight. Of note, 5.7% of olanzapine and 4.5% of placebo-treated patients exhibited orthostatic hypotension (p = NS).
The percentage of patients who gained ≥ 7% body weight was higher in the olanzapine group (43.5%) compared to the placebo group (6.8%) ($p < 0.001$). Data for weight change is discussed further in Section 7.1.4.4 (Common Adverse Events).

#### *7.1.7.2.3 Marked outliers and dropouts for vital sign abnormalities*

Individual vital signs were reviewed from the JMP datasets. In general, few patients had markedly abnormal vital signs. Isolated systolic BP 150 – 155 mmHg was noted in both olanzapine and placebo groups, no diastolic BPs > 110 mmHg were noted and pulse rates > 130 bpm were noted in few patients but more olanzapine-treated patients than placebo-treated patients (highest pulse was 148 bpm in placebo patient).
Patient HGIU-035-3503 (16 YOBF) receiving olanzapine discontinued study HGIU due to an elevated pulse (standing pulse 140 bpm from baseline 96 bpm).

## 7.1.8 Electrocardiograms (ECGs)

### 7.1.8.1 Overview of ECG testing in the development program

The reviewer focused mainly on the two placebo-controlled acute trials, HGIN and HGIU, for evaluation of ECG data. Though the Sponsor states that differences from baseline were analyzed, it should be noted that ECGs were not obtained at baseline (visit 2), but were obtained during the screening period (visit 1):
"Twelve-lead ECGs were collected on each patient at baseline to determine the eligibility of the patient for entry into the study, and at the Final Visits of Study Period II and Study Period III to monitor the general safety of the patient during the course of the study".
Therefore, patients could be on other medications since this was the washout period prior to randomization.
Mean "baseline" ECG parameters appear fairly similar between the olanzapine and placebo groups such that any differences between the groups with regard to concomitant medications taken during screening might have been "equalized" by randomization.

### 7.1.8.2 Standard analyses and explorations of ECG data

#### *7.1.8.2.1 Analyses focused on measures of central tendency*

Statistically significant differences were found between olanzapine and placebo on all ECG parameters except QTcF (see Table 7.1.8.2.1.1). The most notable was the increase in heart rate in the olanzapine group (+6.3 bpm) compared to the placebo (-5.1 bpm) group ($p < 0.001$). Because of this effect on heart rate, the QTcB interval was also significantly longer in the olanzapine group compared to the placebo group.

Table 7.1.8.2.1.1. Sponsor's Table. ECG Intervals and Heart Rate: HGIN + HGIU Acute Database

| ECG Intervals/ Heart Rate | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|
| Heart Rate/Minute | Olz | 158 | 72.291 | 13.183 | 6.266 | 14.039 | 4.335 | 11.624 | <.001 |
| | Placebo | 80 | 72.788 | 12.553 | -5.100 | 11.052 | -7.289 | | |
| Intervals PR/Second | Olz | 158 | 0.139 | 0.019 | 0.003 | 0.010 | 0.004 | 0.005 | .003 |
| | Placebo | 78 | 0.146 | 0.031 | -0.002 | 0.015 | -0.001 | | |
| Intervals QRS/Second | Olz | 158 | 0.088 | 0.011 | -0.001 | 0.005 | -0.001 | -0.002 | .039 |
| | Placebo | 80 | 0.087 | 0.010 | 0.001 | 0.006 | 0.001 | | |
| Intervals QT/Msec | Olz | 158 | 380.532 | 30.825 | -10.481 | 29.222 | -7.948 | -23.603 | <.001 |
| | Placebo | 80 | 378.975 | 26.752 | 12.700 | 28.247 | 15.655 | | |
| Intervals QTc/Msec-Bazett formula | Olz | 158 | 412.880 | 16.358 | 6.899 | 18.146 | 4.872 | 9.634 | <.001 |
| | Placebo | 80 | 413.362 | 17.134 | -2.475 | 16.543 | -4.762 | | |
| Intervals QTc/Msec-Fridericia formula | Olz | 158 | 401.763 | 15.537 | 0.743 | 15.165 | 0.404 | -1.974 | .345 |
| | Placebo | 80 | 401.596 | 14.722 | 2.732 | 15.219 | 2.378 | | |

### *7.1.8.2.2 Analyses focused on outliers or shifts from normal to abnormal*

An analysis of the percent of patients with potentially clinically significant changes between the olanzapine and placebo groups is in Table 7.1.8.2.2.1. Though patients in the olanzapine group exhibited a mean increase in heart rate (see previous section), no PCS increases were noted for heart rate. Three patients had PCS increases in QTcB in the olanzapine group, no patients had PCS changes in QTcF. No patients had QTcB or QTcF increases $\geq$ 60 msec. No patients had QTcB or QTcF $\geq$ 500 msec.

Table 7.1.8.2.2.1. Sponsor's Table. ECG Intervals and Heart Rate – Potentially Clinically Significant Changes. HGIN + HGIU Acute Database.

| ECG Intervals/ Heart Rate | Unit | Direction | Therapy | N | n | % | *P-value |
|---|---|---|---|---|---|---|---|
| Heart Rate <=40 bpm or >=120 bpm | bpm | High | Olz | 158 | 0 | 0.0% | |
| | | | Placebo | 80 | 0 | 0.0% | |
| | | Low | Olz | 158 | 0 | 0.0% | |
| | | | Placebo | 80 | 0 | 0.0% | |
| Heart Rate < 50 bpm,Dec>=15 or >120 bpm,Inc>=15 | bpm | High | Olz | 158 | 0 | 0.0% | |
| | | | Placebo | 80 | 0 | 0.0% | |
| | | Low | Olz | 157 | 0 | 0.0% | .038 |
| | | | Placebo | 80 | 3 | 3.8% | |
| Intervals PR >=200 ms | sec | High | Olz | 158 | 0 | 0.0% | .322 |
| | | | Placebo | 75 | 1 | 1.3% | |
| Intervals QRS >=100 ms | sec | High | Olz | 132 | 7 | 5.3% | .497 |
| | | | Placebo | 72 | 2 | 2.8% | |
| Intervals QT >=450 ms | ms | High | Olz | 156 | 1 | 0.6% | .045 |
| | | | Placebo | 79 | 4 | 5.1% | |
| QTc Bazett's Male >=450 ms or Female >=470 ms | ms | High | Olz | 156 | 3 | 1.9% | .553 |
| | | | Placebo | 79 | 0 | 0.0% | |
| QTc Fridericia's Male >=450 ms or Female >=470 ms | ms | High | Olz | 158 | 0 | 0.0% | |
| | | | Placebo | 80 | 0 | 0.0% | |

### *7.1.8.2.3 Marked outliers and dropouts for ECG abnormalities*

There were no dropouts due to ECG abnormalities.

## 7.1.9 Assessment of Effect on Growth

The Sponsor provided an analysis of the effect of olanzapine on growth that included data from the Overall Combined Database. Gender and age-adjusted growth in olanzapine-treated patients was compared with the expected growth seen in the general US population by using data provided by the National Center for Health Statistics. Standardized mean weight and BMI increased significantly for olanzapine-treated patients, regardless of gender, country, or disorder (schizophrenia or bipolar disorder). The changes in standardized mean height were closer to expected values based on the CDC reference population.

Table 7.1.9.1. Sponsor's Table.

**Table APP.2.7.4.7.3.2. Standardized Growth (Z-Score)
LOCF Mean Change in Weight, Height, and BMI from Baseline to Endpoint
Overall Olanzapine Exposure Combined Database**

| | | | Baseline | | Endpoint | | Change | | P-value |
|---|---|---|---|---|---|---|---|---|---|
| Measure | Value | N | Mean | Std | Mean | Std | Mean | Std | *P-value |
| Weight | Actual | 450 | 67.13 | 17.72 | 74.48 | 19.07 | 7.35 | 6.58 | <.001 |
| | Expected | 450 | 67.13 | 17.72 | 68.17 | 17.90 | 1.03 | 1.01 | <.001 |
| | Z-Score | 450 | 0.53 | 1.13 | 0.98 | 1.02 | 0.45 | 0.44 | <.001 |
| | Percentile | 450 | 63.54 | 29.54 | 75.33 | 24.50 | 11.79 | 14.19 | |
| Height | Actual | 440 | 168.24 | 9.71 | 169.27 | 9.45 | 1.03 | 2.17 | <.001 |
| | Expected | 440 | 168.24 | 9.71 | 168.92 | 9.60 | 0.67 | 0.91 | <.001 |
| | Z-Score | 440 | 0.02 | 1.02 | 0.07 | 1.00 | 0.05 | 0.24 | <.001 |
| | Percentile | 440 | 50.60 | 29.13 | 52.11 | 28.76 | 1.51 | 6.58 | |
| BMI | Actual | 439 | 23.64 | 6.07 | 25.95 | 6.21 | 2.31 | 2.31 | <.001 |
| | Expected | 439 | 23.64 | 6.07 | 23.83 | 6.01 | 0.19 | 0.30 | <.001 |
| | Z-Score | 439 | 0.50 | 1.14 | 0.99 | 0.95 | 0.49 | 0.53 | <.001 |
| | Percentile | 439 | 63.51 | 29.85 | 76.77 | 23.48 | 13.26 | 16.47 | |

Table 7.1.9.2. Sponsor's Table.

**Table APP.2.7.4.7.3.3. Standardized Growth (Z-Score)**
**LOCF Mean Change in Weight, Height, and BMI from Baseline to Endpoint by Gender**
**Overall Olanzapine Exposure Combined Database**

| | | | | Baseline | | Endpoint | | Change | | P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| Measure | Gender | Value | N | Mean | Std | Mean | Std | Mean | Std | *P-value |
| Weight | Female | Actual | 167 | 64.41 | 18.15 | 70.94 | 19.34 | 6.53 | 6.08 | <.001 |
| | | Expected | 167 | 64.41 | 18.15 | 65.05 | 18.29 | 0.64 | 0.73 | <.001 |
| | | Z-Score | 167 | 0.64 | 1.12 | 1.05 | 0.97 | 0.40 | 0.45 | <.001 |
| | | Percentile | 167 | 67.26 | 28.90 | 77.62 | 23.18 | 10.36 | 14.04 | |
| | Male | Actual | 283 | 68.74 | 17.30 | 76.58 | 18.64 | 7.83 | 6.81 | <.001 |
| | | Expected | 283 | 68.74 | 17.30 | 70.01 | 17.43 | 1.27 | 1.08 | <.001 |
| | | Z-Score | 283 | 0.47 | 1.13 | 0.94 | 1.05 | 0.47 | 0.44 | <.001 |
| | | Percentile | 283 | 61.35 | 29.74 | 73.98 | 25.20 | 12.64 | 14.23 | |
| Height | Female | Actual | 163 | 162.07 | 7.82 | 162.78 | 7.63 | 0.71 | 1.45 | <.001 |
| | | Expected | 163 | 162.07 | 7.82 | 162.35 | 7.75 | 0.27 | 0.37 | <.001 |
| | | Z-Score | 163 | 0.04 | 1.15 | 0.10 | 1.13 | 0.07 | 0.20 | <.001 |
| | | Percentile | 163 | 51.74 | 30.32 | 53.86 | 29.83 | 2.12 | 6.40 | |
| | Male | Actual | 277 | 171.88 | 8.86 | 173.09 | 8.26 | 1.21 | 2.48 | <.001 |
| | | Expected | 277 | 171.88 | 8.86 | 172.78 | 8.42 | 0.90 | 1.05 | <.001 |
| | | Z-Score | 277 | 0.00 | 0.95 | 0.04 | 0.92 | 0.04 | 0.26 | .012 |
| | | Percentile | 277 | 49.94 | 28.44 | 51.09 | 28.11 | 1.15 | 6.68 | |
| BMI | Female | Actual | 162 | 24.46 | 6.76 | 26.78 | 7.12 | 2.32 | 2.30 | <.001 |
| | | Expected | 162 | 24.46 | 6.76 | 24.66 | 6.83 | 0.20 | 0.17 | <.001 |
| | | Z-Score | 162 | 0.66 | 1.07 | 1.08 | 0.88 | 0.42 | 0.48 | <.001 |
| | | Percentile | 162 | 67.73 | 28.52 | 79.04 | 21.25 | 11.31 | 15.25 | |
| | Male | Actual | 277 | 23.16 | 5.58 | 25.46 | 5.57 | 2.30 | 2.33 | <.001 |
| | | Expected | 277 | 23.16 | 5.58 | 23.35 | 5.42 | 0.19 | 0.36 | <.001 |

The Sponsor noted a number of limitations in the evaluation of these data. Tanner Stage information was not collected during these studies, so the pubertal effects on individual standard deviation scores for height, weight or BMI are not known. The observational period of these studies (up to 8 months) did not allow for "meaningful evaluation" of the potential effect of olanzapine on height. Additionally, the CDC reference database is based on the US population and may not be representative of patients from Germany or Russia – both countries had significant numbers of patients in this combined database.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1.1 Extent of exposure (dose/duration)

Acute, placebo-controlled trials: Total exposure for olanzapine in adolescent patients was 4776 patient-days. The mean daily dose was 9.75 mg/day, the modal daily dose was 11.46 mg/day.

Overall olanzapine exposure combined database: Total exposure for olanzapine in adolescent patients was 48,946 patient-days. The mean daily dose was 10.56 mg/day, the modal daily dose was 11.36 mg/day.

The highest olanzapine dose allowed in trials HGIN and HGIU was 20 mg/day. The Sponsor provided exposure data regarding the numbers of patients taking olanzapine 20 mg at any time, who had a modal dose of 20 mg and who had a final dose of 20 mg.

**Table 2.7.4.14. Anytime, Modal Dose, and Final Dose of 20 mg**
**All Randomized Patients**
**Acute Placebo-Controlled Combined Database**

| | HGIN (N= 72) n(%) | HGIU (N= 106) n(%) | Combined (N= 178) n(%) |
|---|---|---|---|
| 20 mg Dose(Anytime) | 21(29.17%) | 13(12.26%) | 34(19.10%) |
| 20 mg Modal Dose | 12(16.67%) | 10(9.43%) | 22(12.36%) |
| 20 mg Final Dose | 18(25.00%) | 11(10.38%) | 29(16.29%) |

**Table 2.7.4.19. Anytime, Modal Dose, and Final Dose of 20 mg**
**All Patients with Olanzapine Exposure**
**Overall Olanzapine Exposure Combined Database**

Summary of Patients Who Took >= 20 mg OLZ at Any Time

| | Schizophrenia | | | Bipolar | | | Combined | | |
|---|---|---|---|---|---|---|---|---|---|
| Dose | N | n | % | N | n | % | N | n | % |
| 20 | 227 | 81 | 35.7% | 226 | 52 | 23.0% | 453 | 133 | 29.4% |
| 25 | 227 | 0 | 0.0% | 226 | 2 | 0.9% | 453 | 2 | 0.4% |

Summary of Patients Who Had Modal Dose at 20 mg OLZ

| | Schizophrenia | | | Bipolar | | | Combined | | |
|---|---|---|---|---|---|---|---|---|---|
| Modal Dose | N | n | % | N | n | % | N | n | % |
| 20 | 227 | 46 | 20.3% | 226 | 26 | 11.5% | 453 | 72 | 15.9% |

Summary of Patients Who Had Final Dose at 20 mg OLZ

| | Schizophrenia | | | Bipolar | | | Combined | | |
|---|---|---|---|---|---|---|---|---|---|
| Final Dose | N | n | % | N | n | % | N | n | % |
| 20 | 227 | 46 | 20.3% | 226 | 30 | 13.3% | 453 | 76 | 16.8% |

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

### 7.2.2.1 Postmarketing experience

The Lilly Safety System was searched for spontaneously reported adverse events involving patients younger than 18 years of age treated with olanzapine for the time period of product launch through May 31, 2006. The search identified 5,633 spontaneously reported adverse events (in 2,359 case reports) for patients ≤18 years of age out of 110,529 total events (age was unknown for 25,415 events).

The Sponsor analyzed these data by using a proportional reporting ratio (PRR) and Chi square value. The PRR was used to compare events between olanzapine treated patients aged 13 to 17 years and olanzapine-treated patients aged 18 to 64 years. The Sponsor indicated that some general guidelines for interpreting a drug-event combination as a potential signal include: at least 3 reports, a PRR > 2 and a Chi-square > 4. The spontaneously reported adverse events somnolence, aggression, galactorrhea, and sedation met the PRR and Chi-square criteria and had a proportion of the event of interest ≥ 1% of all events in patients aged 13 – 17 years (see Table 7.2.2.1.1 ).

Table 7.2.2.1.1 Sponsor's Table. Potential Safety Signals in Postmarketing Database for Patients 13 to 17 Years of Age – Proportion, PRR and Chi-Square Criteria Met

| MedDRA Preferred Term (# of events in patients 13-17 years) | Proportion of Event in Patients 13-17 years (%) (N=3,288 events) | Proportion of Event in Patients 18-64 years (%) (N=68,450 events) | PRR[a] | Chi-Square Value |
|---|---|---|---|---|
| Somnolence (108) | 3.28 | 1.60 | 2.06 | 53.39 |
| Aggression (41) | 1.25 | 0.33 | 3.76 | 70.36 |
| Galactorrhoea (39) | 1.19 | 0.32 | 3.67 | 64.51 |
| Sedation (38) | 1.16 | 0.46 | 2.50 | 30.41 |

From Sponsor table 2.7.4.79 in summary-clin-safety document

The Sponsor also included an additional table for adverse events reported with a proportion of the event of interest > 1% of all events in patients aged 13 to 17 years not meeting additional criteria (PRR and Chi-square) (see Table 7.2.1.1.2).

Table 7.2.2.1.2. Sponsor's Table. Potential Safety Signals in Postmarketing Database for Patients 13 to 17 Years of Age – Proportion Criteria Met

| MedDRA Preferred Term (# of events in patients 13-17 years) | Proportion of Event in Patients 13-17 years (%) (N=3,288 events) | Proportion of Event in Patients 18-64 years (%) (N=68,450 events) | PRR[a] | Chi-Square Value |
|---|---|---|---|---|
| Weight increased (320) | 9.73 | 7.74 | 1.26 | 15.98 |
| Prescribed overdose (52) | 1.58 | 1.84 | 0.86 | 1.15 |
| Overdose (42) | 1.28 | 1.23 | 1.04 | 0.05 |
| Fatigue (40) | 1.22 | 0.70 | 1.75 | 11.76 |
| Alanine aminotransferase increased (38) | 1.16 | 0.90 | 1.29 | 2.31 |
| Diabetes mellitus (36) | 1.09 | 4.75 | 0.23 | 91.49 |
| Drug ineffective (36) | 1.09 | 0.77 | 1.43 | 4.36 |
| Increased appetite (36) | 1.09 | 0.77 | 1.41 | 4.09 |
| Convulsion (33) | 1.00 | 0.55 | 1.82 | 11.26 |

Of the 2,359 case reports in patients 13 to 17 years of age, 27 had a fatal outcome (Sponsor indicated that 28 cases were fatal, upon review it was noted that one case was duplicated). These cases are from spontaneous reports or publications in the literature. The Sponsor included CIOMS line listings and MedWatch reports for each fatality. In the narrative summary for one of the fatality cases, a reference to 4 additional US fatalities was made.[3] These appear to be a cluster of deaths occurring in a county in (b) (4) Further investigation may be deemed necessary. It is not known if the reporter had contacted the FDA regarding these cases as was mentioned in the case narrative. MedWatch reports for these additional cases were not included in the submission. The Sponsor will be asked to provide these reports as well as to submit any new reports that may have occurred since this search was last completed.

The MedWatch reports were incomplete and many details regarding the deaths (autopsy reports, pertinent laboratory values, clinical description of death) were not available. In some cases, it appears that the Sponsor attempted to obtain more information, it is not known to what extent these attempts were made. Fifteen of the cases occurred in the United States, a number of these cases were reported by an attorney via the legal department – it is not known if litigation is ongoing in these cases.
Of note, seven of the cases involved completed suicide or possible suicide and five of the cases related to diabetes mellitus, diabetic coma or diabetic ketoacidosis. A brief summary of these cases is in Appendix 10.13.

## 7.3 Safety Conclusions

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIU is the pivotal trial for bipolar

3 In the narrative summary for US_010158510, the following statements were noted: "This is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in (b) (4). The reporter stated he has also notified the FDA."

disorder) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events (≥ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain
The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with > 7% increase in body weight.

| | Olanzapine | Placebo | LS Mean Diff | P-value |
|---|---|---|---|---|
| *HGIN + HGIU Acute Database* | | | | |
| Weight (kg) Mean Change to Endpoint (LOCF) | 3.90 (n = 177) | 0.24 (n = 88) | 3.66 | < 0.001 |
| Weight (kg) Mean Change to Endpoint (OC) | 3.6 (n = 154) | 0.08 (n = 67) | 3.57 | < 0.001 |
| BMI Mean Change to Endpoint (LOCF) | 1.22 | 0.05 | 1.17 | < 0.001 |
| ≥ 7% increase in body weight (%) | 43.5% | 6.8% | - | < 0.001 |
| Overall Combined Database | | | | |
| Weight (kg) Mean Change to Endpoint (LOCF) | 7.35 | - | - | < 0.001 (compared to baseline) |
| Weight (kg) Mean Change to Endpoint (OC) | 10.8 | - | - | < 0.001 (compared to baseline) |

| | | | | |
|---|---|---|---|---|
| BMI<br>Mean Change to Endpoint (LOCF) | 2.31 | - | - | < 0.001<br>(compared to baseline) |
| ≥ 7% increase in body weight (%) | 65% | - | - | - |

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

Weight changes were evaluated for the subgroups gender and age (< 15, ≥ 15 years). At the time this review was finalized, mean change in weight for the age subgroup analysis was only available for study HGIN (not HGIU or the Acute Database). Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine. A treatment-by-gender interaction was noted in the Acute Database, but was likely due to differences in the placebo groups since mean change in weight was similar in the olanzapine groups for males and females.

Liver Function Abnormalities
Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline ≤ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009).
No patients met criteria for Hy's rule (ALT ≥ 3x ULN and TBili ≥ 1.5 x ULN).

Hyperprolactinemia
The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, p < 0.001). The washout period prior to baseline could be as short as 2 days and it was noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to perform further analyses in the subgroup of patients with baseline prolactin within normal limits. In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).

For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females (15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN +

HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$).

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

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

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were also similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality
Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown

and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in bipolar disorder patients. Suicidal behaviors or ideation is not uncommon in these patients and, in the absence of a placebo comparator, it is difficult to interpret any causality to olanzapine therapy.

## 7.4 General Methodology

### 7.4.1.1 Explorations for dose dependency for adverse findings

All of the clinical trials, both placebo-controlled and open-label, included a flexible dosing paradigm for olanzapine. Therefore, it is not possible to evaluate the dose-dependency of adverse events.

### 7.4.1.2 Explorations for drug-demographic interactions

The drug – demographic interactions summarized here are the adverse events occurring in HGIN + HGIU Acute Database. Subgroup analyses, particularly for gender and age, for efficacy and some safety data (prolactin, weight gain, etc.) are summarized in those relevant sections of the review. Most of the patients enrolled in the pivotal clinical trials were Caucasian, therefore any analyses by race/ethnicity are of limited usefulness.

Treatment-by-gender interactions were significant for the following adverse events: myalgia, nasal congestion, sinus congestion and tremor (see Table 7.4.1.2.1); though none of these adverse events were significantly different between olanzapine and placebo.

Table 7.4.1.2.1. Sponsor's Table. Adverse Events – Treatment-by-Gender Interactions: HGIN + HGIU Acute Database

By Subgroup: Gender

| | | Therapy | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Olanzapine | | | Placebo | | | | |
| Event Classification | Gender | N | n | % | N | n | % | *P-value | **Homogeneity of Odds Ratio |
| Myalgia | Female | 67 | 0 | 0.0% | 41 | 1 | 2.4% | .380 | .070 |
| | Male | 112 | 3 | 2.7% | 48 | 0 | 0.0% | .555 | |
| Nasal congestion | Female | 67 | 2 | 3.0% | 41 | 0 | 0.0% | .525 | .055 |
| | Male | 112 | 0 | 0.0% | 48 | 1 | 2.1% | .300 | |
| Sinus congestion | Female | 67 | 2 | 3.0% | 41 | 0 | 0.0% | .525 | .055 |
| | Male | 112 | 0 | 0.0% | 48 | 1 | 2.1% | .300 | |
| Tremor | Female | 67 | 2 | 3.0% | 41 | 0 | 0.0% | .525 | .055 |
| | Male | 112 | 0 | 0.0% | 48 | 1 | 2.1% | .300 | |

Treatment-by-age (< 15, ≥ 15 years) interactions were significant for ear pain and migraine (see Table 7.4.1.2.2); though none of these adverse events were significantly different between olanzapine and placebo.

Table 7.4.1.2.2. Sponsor's Table. Adverse Events – Treatment-by-Age Interactions: HGIN + HGIU Acute Database

By Subgroup: Age

| | | Therapy | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Olanzapine | | | Placebo | | | | |
| Event Classification | Age | N | n | % | N | n | % | *P-value | **Homogeneity of Odds Ratio |
| Ear pain | < 15 | 64 | 1 | 1.6% | 27 | 0 | 0.0% | 1.00 | .100 |
| | >=15 | 115 | 0 | 0.0% | 62 | 2 | 3.2% | .121 | |
| Migraine | < 15 | 64 | 0 | 0.0% | 27 | 1 | 3.7% | .297 | .062 |
| | >=15 | 115 | 2 | 1.7% | 62 | 0 | 0.0% | .542 | |

## 7.5 Comparing adolescent and adult data

The common adverse event tables for adults in current product labeling and the common adverse events occurring in HGIN and HGIU were compared. In the schizophrenia trials, 31% of adolescent patients experienced weight gain compared to 6% of adult patients. Somnolence and sedation were experienced by 24% and 15% of adolescent patients compared to < 5% of adult patients. Similar patterns occurred in the bipolar disorder trials except that somnolence was very common in the adult population as well as the adolescent population.

Table 7.5.1. Common Adverse Events (≥ 5% incidence) – Adult versus Adolescents: 6 Week Acute Trials in *Schizophrenia*

| | Adults | |
|---|---|---|
| | Olanzapine N = 248 | Placebo N = 118 |
| Dizziness | 11% | 4% |
| Constipation | 9% | 3% |
| Personality disorder | 8% | 4% |
| Weight gain | 6% | 1% |
| Akathisia | 5% | 1% |
| Postural hypotension | 5% | 2% |

| | Adolescents | |
|---|---|---|
| | Olanzapine N = 72 | Placebo N = 35 |
| Weight increased | 31% | 9% |
| Somnolence | 24% | 3% |
| Headache | 17% | 6% |
| Increased appetite | 17% | 9% |
| Sedation | 15% | 6% |
| Dizziness | 8% | 3% |
| Pain in extremity | 6% | 3% |

Table 7.5.2. Common Adverse Events (≥ 5% incidence) – Adult versus Adolescents: 3 Week Acute Trials in *Bipolar Disorder*

| | Adults | |
|---|---|---|
| | Olanzapine N = 125 | Placebo N = 129 |
| Somnolence | 35% | 13% |
| Dry mouth | 22% | 7% |
| Dizziness | 18% | 6% |

| | Adolescents | |
|---|---|---|
| | Olanzapine N = 107 | Placebo N = 54 |
| Weight increased | 29% | 4% |
| Increased appetite | 29% | 4% |
| Somnolence | 25% | 4% |

| | | |
|---|---|---|
| Asthenia | 15% | 6% |
| Constipation | 11% | 5% |
| Dyspepsia | 11% | 5% |
| Increased appetite | 6% | 3% |
| Tremor | 6% | 3% |

| | | |
|---|---|---|
| Sedation | 22% | 6% |
| Headache | 17% | 17% |
| Fatigue | 14% | 6% |
| Dry mouth | 8% | 0% |
| Pain in extremity | 5% | 0% |

The Sponsor included an analysis of select adverse events occurring in the adult clinical trials databases and adolescent clinical trials databases. These analyses summarized all data including the open-label trials. The Sponsor was asked if a similar analysis could be done for the placebo-controlled studies only and they responded that none of the placebo-controlled studies included fasting glucose and lipid data so these analyses were not available.

Metabolic parameters (fasting glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides):
Mean change from baseline to endpoint – the only statistically significant differences between populations was in fasting glucose and triglycerides. Mean change to endpoint for fasting glucose was 1.8 ± 13 mg/dL for adolescents and 4.9 ± 32.8 mg/dL for adults (p = 0.002), triglycerides was 23.0 ± 76 mg/dL for adolescents and 20.3 ± 124 mg/dL for adults (p = 0.007).

Treatment-emergent significant changes at any time: statistically significant differences were noted for most of the parameters with a higher percentage of adults having significant changes at any time (see Table 7.5.3).

Table 7.5.3. Treatment-Emergent Significant Changes at Any Time – Adults vs. Adolescents

| Laboratory Analytes | Categories | Population | N | n | % | *P-value |
|---|---|---|---|---|---|---|
| Fasting Glucose | Normal to High (< 100 mg/dL to >=126 mg/dL) | Adolescent | 251 | 3 | 1.2% | .033 |
| | | Adult | 251 | 12 | 4.8% | |
| | Impaired Glucose Tolerance to High(>=100 & <126 mg/dL to >=126 mg/dL) | Adolescent | 47 | 6 | 12.8% | .066 |
| | | Adult | 121 | 32 | 26.4% | |
| | Normal/Impaired Glucose Tolerance to High(<126 mg/dL to >=126 mg/dL) | Adolescent | 298 | 9 | 3.0% | <.001 |
| | | Adult | 372 | 44 | 11.8% | |
| Total Cholesterol | Normal to Borderline(<200 mg/dL to >=200 mg/dL and <240 mg/dL) | Adolescent | 262 | 54 | 20.6% | <.001 |
| | | Adult | 216 | 82 | 38.0% | |
| | Normal to High(<200 mg/dL to >=240 mg/dL) | Adolescent | 262 | 3 | 1.1% | .091 |
| | | Adult | 216 | 15 | 6.9% | |
| LDL Cholesterol | Normal to Borderline(<130 mg/dL to >=130 mg/dL and <160 mg/dL) | Adolescent | 270 | 48 | 17.8% | <.001 |
| | | Adult | 241 | 75 | 31.1% | |
| | Normal to High(<130 mg/dL to >=160 mg/dL) | Adolescent | 270 | 4 | 1.5% | .014 |
| | | Adult | 241 | 14 | 5.8% | |
| HDL Cholesterol | Normal to Low(>=50 mg/dL to <40 mg/dL) | Adolescent | 107 | 10 | 9.3% | .052 |
| | | Adult | 155 | 28 | 18.1% | |

| Laboratory Analytes | Categories | Population | N | n | % | *P-value |
|---|---|---|---|---|---|---|
| Fasting Triglycerides | Normal to Borderline(<150 mg/dL to >=150 mg/dL and <200 mg/dL) | Adolescent | 247 | 51 | 20.6% | <.001 |
| | | Adult | 253 | 91 | 36.0% | |
| | Normal to High(<150 mg/dL to >=200 mg/dL) | Adolescent | 247 | 43 | 17.4% | .030 |
| | | Adult | 253 | 65 | 25.7% | |
| | Normal to Extremely High(<150 mg/dL to >=500 mg/dL) | Adolescent | 247 | 1 | 0.4% | 1.00 |
| | | Adult | 253 | 1 | 0.4% | |

Weight Gain
Mean change from baseline to endpoint – There was a statistically significant greater mean increase in body weight for adolescents compared to adults (see Table 7.5.4).

Table 7.5.4. Sponsor's Table. Mean Change from Baseline to Endpoint - Adolescents vs. Adults. Overall Combined Databases

| | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|
| Population | N | Mean | Std | Mean | Std | LSMean Change | LSMean Difference | *P-value |
| Adolescent | 450 | 67.13 | 17.72 | 7.35 | 6.58 | 6.97 | 3.71 | <.001 |
| Adult | 7847 | 78.12 | 18.86 | 3.24 | 5.82 | 3.26 | | |

From Sponsor's table APP.2.7.4.7.1.25 in summary-clin-safe-app document

In product labeling, it is stated that in the 6-week placebo-controlled studies in adults, olanzapine patients gained an average of 2.8 kg compared to a 0.4 kg weight loss in placebo patients. In study HGIN, adolescent patients receiving olanzapine gained an average of 4.26 kg compared to 0.13 kg weight gain in placebo patients.

PCS weight increase at any time– Significantly more adolescent patients had a $\geq$ 7% increase in weight (65.1%) compared to adult patients (35.6%) ($p < 0.001$).

In the 6-week placebo controlled trials in adults, 29% of olanzapine patients had a $\geq$ 7% increase in weight compared to 3% of placebo patients. In study HGIN, 45% of olanzapine patients had a $\geq$ 7% increase in weight compared to 14.7% of placebo patients.
The Sponsor did not provide an comparison of hepatic laboratory analytes between the two populations and will be asked to provide these data. Per product labeling, in placebo-controlled olanzapine monotherapy studies in adults, elevations in ALT $\geq$ 3 x ULN were observed in 2% (6/243) olanzapine patients compared to 0/115 placebo patients. In the placebo-controlled monotherapy studies in adolescents, elevations in ALT > 3 x ULN (from baseline $\leq$ 3 x ULN) were observed in 12% (21/174) of olanzapine patients compared to 2% (2/87) of placebo patients.

Prolactin
Because of differences in reference ranges between the populations, normalized units were used in the analysis of prolactin changes (% URL = % upper range limit).

Mean change from baseline to endpoint – statistically significant differences were noted between the populations with adolescents having a mean change to endpoint of 23.0 %URL compared to -4.19 %URL in adults ($p = 0.004$) (see Table 7.5.5).

Table 7.5.5. Sponsor's Table. Mean Change from Baseline to Endpoint in Prolactin (Normalized Units) – Adult vs. Adolescent Patients, Overall Combined Databases

| Laboratory Evaluations | Unit | Population | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| PROLACTIN | %URL | Adolescent | 431 | 78.73 | 76.47 | 23.01 | 83.69 | 9.70 | 12.62 | .004 |
| | | Adult | 4503 | 99.42 | 126.56 | -4.19 | 125.57 | -2.92 | | |

From Sponsor's table APP.2.7.4.7.4.31 in summary-clin-app document

Treatment-emergent high prolactin concentrations at any time: a higher percentage of adolescent patients (55.5%) had high prolactin concentrations at any time compared to adult patients (29%) ($p < 0.001$). The Sponsor did not provide an analysis for adolescent vs. adult patients by gender.

# 8 ADDITIONAL CLINICAL ISSUES

## 8.1 Dosing Regimen and Administration

The proposed labeling language for Dosage and Administration is "(b) (4) (b) (4) (b) (4)".

(b) (4)

## 8.2 Advisory Committee Meeting

No advisory committee meeting was held for this submission.

## 8.3 Literature Review

The Sponsor submitted a literature review though there was no attempt to summarize key findings. The Sponsor stated that none of the reviewed articles presented safety data contradictory to the conclusions presented in the NDA. Due to time constraints for this priority application, a separate literature review was not conducted by this reviewer.

## 8.4 Postmarketing Risk Management Plan

The Sponsor submitted a Risk Management document outlining their proposed actions for risk minimization. The identified risks in this document included weight gain, sedation, hepatic changes, hyperprolactinemia, glucose dysregulation, dyslipidemia. For all of these safety issues, the Sponsor has proposed the following actions for pharmacovigilance: (b) (4)

Routine pharmacovigilance was defined as periodic reporting per PSUR or as appropriate. Targeted surveillance was similar but targeted weight gain, hepatic changes, glucose dysregulation and dyslipidemia. The Sponsor has proposed a long-term safety study to evaluate the safety of olanzapine in adolescent patients with schizophrenia or bipolar disorder and to estimate the incidence and prevalence of identified and potential risks associated with olanzapine treatment. The study is still in the planning phase.

(b) (4)

. It is unknown whether these protocols have been submitted to the Division.

The actions proposed for risk minimization include product labeling and prescriber education – no details were provided regarding the latter proposal.

# 9 OVERALL ASSESSMENT

## 9.1 Recommendation on Regulatory Action

I recommend that the Division take a non approval action on NDA 20-592 SE5-041 that was filed to support the indication "treatment of schizophrenia in adolescent patients".

Fifty-three percent of randomized patients in pivotal trial HGIN were from sites in the United States and 47% of randomized patients were from sites in Russia. The primary endpoint, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia ($p = 0.003$) but not the sites in the United States ($p = 0.258$). The sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia.

Though the LOCF analysis was the primary analysis, it is also concerning that the OC and MMRM analyses (the latter by recalculation by the reviewing statistician in the Division) are substantially different from the LOCF analysis and not statistically significant.

I recommend that the Sponsor conduct another clinical trial in this population if they wish to pursue this indication. The majority of patients in this clinical trial should be from sites in the United States and efficacy will need to be established in these patients. It is also strongly recommended that this clinical trial be a fixed dose design since dose-response data for efficacy or safety cannot be evaluated in a flexible dose design.

A number of additional requests for safety information and analysis regarding this submission are included at the end of this review. If acceptable, these requests could be included in the action letter.

## 9.2 Recommendation on Postmarketing Actions

Since non approval is recommended, there are no recommendations for postmarketing actions.

## 9.3 Labeling Review

Changes to proposed labeling are being made directly to the annotated labeling submitted by the Sponsor, this was the first PLR labeling so there were many changes from prior approved labeling. The project manager, Dr. Doris Bates, reviewed the PLR labeling against the prior approved labeling and noted any differences – especially differences that were not highlighted by the Sponsor.
In the proposed labeling, (b) (4) The Sponsor has been asked to address this and had not responded at the time this review was finalized.

This section will briefly discuss some of the labeling that may require revision:
DOSAGE AND ADMINISTRATION – In the clinical trials, it was recommended to dose olanzapine in the evening due to the potential somnolence associated with the drug. In HGIU + HGIN, somnolence occurred in 25% of patients and sedation occurred in 19% of patients. Current proposed labeling (b) (4)

WARNINGS AND PRECAUTIONS – The team will have to discuss the order of the items under this heading.

Weight Gain: should be placed earlier in this section

Transaminase Elevations: in the adult section, the number of patients with ALT $\geq 3$ times ULN data is provided. In the adolescent section, the number of patients with ALT $> 3$ times ULN data is provided. These should be consistent (should both be $\geq 3$ x ULN). In the adult section, use ALT rather than SGPT in the discussion of the larger premarketing database. In the adolescent section, I would recommend including the number of patients who discontinued due to elevations in LFTs.

Hyperprolactinemia: I would suggest including the % of patients with elevated prolactin levels for both adolescents and adults in the placebo-controlled acute trials.

Laboratory Tests: The information with regard to glucose monitoring should be included here.

ADVERSE REACTIONS
Other Adverse Events Observed During the Clinical Trial Evaluation of Oral Olanzapine

(b) (4)

Clinical Trials in Adolescent Patients
ECG Changes – correct spelling of Frederica to Fredericia

Postmarketing Experience
When was the last time the Sponsor updated this section? There have been some postmarketing reports of death due to diabetic ketoacidosis occurring in adolescents – should this data be included in this section?

## 9.4 Comments to Applicant

*Requests for information*

The Sponsor has responded to the following requests and the reviewer has reviewed the responses

1. In protocols HGIU and HGIN, height was obtained using "a measuring device supplied by the sponsor" that required calibration. Please provide a description of this measuring device.

2. The primary efficacy analysis in study HGIN excluded data from site 021 due to GCP issues at that site (it is noted that results are similar with and without this site). Please provide details regarding the GCP issues at this site or specify where this information may be found in the study report.

3. In protocol HGIN, it is noted that "The scoring of the anchored version of the BPRS-C is determined by interviews with both the patient and the parent/legal guardian at all visits. The reference score (as recorded in the CRFs) should be the higher of the two scores". Viewing the CRF, it does not appear that there is an area where the recorder could state the source of the ratings. Are both ratings, patient and parent/legal guardian, available for subjects in this study? If so, please provide these ratings and indicate the primary source for the ratings.

4. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF analysis (similar to table HGIN 14.20 for OC analysis) - with and without site 021.

5. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF and OC analysis for the US and Russia sites separately.

6. Provide patient baseline demographics and analysis for US vs. Russia sites (similar to HGIN.11.1 but comparing US vs. Russia).

7. It is noted that 50 patients were randomized at the 5 sites in Russia - 10 patients per site. Is it coincidental that 10 subjects were randomized at each of these sites? Were caps specified to the investigators such that each site could randomize no more than 10 patients?

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

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

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

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

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

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

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

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

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

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

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

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

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

21. It is unclear whether there was greater weight gain in patients with lower BMI at baseline (and visa versa). Please provide an analysis of weight gain based on the patient's baseline BMI to address this question.

22. Please provide the numbers of patients in both the placebo and olanzapine treatment groups who were obese (BMI > 30) at baseline and at end of study. Was there a statistical difference?

23. Please provide a subgroup analysis for laboratory data (similar to the summary in Table 2.7.4.33 in summary-clin-safety). Include all olanzapine patients who gained greater than 3.9 kg (mean weight gain from baseline) compared to all placebo patients.

The following questions were submitted to the Sponsor via email on 3/19/07. The Sponsor attempted to send an email response on 3/26/07 but encountered technical difficulties. The Sponsor faxed the response on 3/27/07 and was asked to also fax the response to this reviewer (working in another location). The Sponsor did not fax the response to this reviewer. This reviewer received the response on 4/2/07 (working in office) and had insufficient time to review the responses to meet the internal NDA deadline. Of note, request #30 was not addressed in this response and the Sponsor indicated that the response will be provided at a later date.

24. For the Acute Placebo Controlled Combined Database, please provide a subgroup analysis for age (< 15, >= 15) for the variable "weight in kg" similar to Table 2.7.4.70 in the summary-clin-safety document.

25. Please provide a subgroup analysis for age (< 15 and >=15) and gender for the variable "PCS weight change (> 7%)" for the Acute Placebo Controlled Combined Database.

26. It appears that the study report for HGIN includes all vital signs analyses for all subgroups (e.g. Table HGIN.14.47) while these analyses are only included in the study report for HGIU if the treatment by subgroups analysis was significant (e.g. HGIU.12.45). Please provide the subgroup analyses for HGIU similar to that provided in Table HGIN.14.47.

27. In section 2.7.4.7.5 of the summary-clin-safe-app document, analyses are provided for suicide-related adverse events. In reviewing Table APP.2.7.4.7.5.9 (patients with possible suicidal behavior or ideation - combined database), there appear to be 3 cases that do not have narratives listed in this document or in the Table of Significant and Notable Patients document. Please provide case narratives for the following cases: HGMF-008-0805, LOAY-401-4012 and LOAY-407-4077.

28. In the summary-clin-safe-app document, section 2.7.4.7.1.3.2.6 presents correlation coefficients between weight and a number of factors for the Overall Olanzapine Exposure Combined Database. Please provide these data for the Acute Placebo Controlled Database.

29. In the summary-clin-safe-app document, section 2.7.4.7.1.3.3 compares data between the adolescent and adult populations. For these population comparisons, the Overall Olanzapine Exposure Combined Database is used. Is a comparison of these populations including only the acute, double-blind trial data available?

30. In proposed labeling, (b) (4) from proposed product labeling.

Requests for additional information from the Sponsor – may be included in action letter:

31. Please provide narrative summaries for the following: 8 cases of gynecomastia, 1 case of opisthotonus, 1 case of "oculogyration", and two cases with high prolactin concentrations (HGIN 900-9009, HGIN 005-503) and the cases with CPK > 500 U/L.

32. Please review the MedWatch reports for fatalities and submit updates where possible for incomplete data. It was noted that these MedWatch reports had "DRAFT" at the top of the page and the date of the report was 7/27/06 - have all of these reports been previously filed with the Agency?

33. For MedWatch fatality case US_010158510, the narrative states "This is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in (b) (6). The reporter stated he has also notified the FDA...". The only MedWatch report included in this submission is

for US_010158510. Please provide the MedWatch reports for the additional 4 deaths indicated in this narrative.

34. Table APP.2.7.4.24 in summary-clin-safe-app provides prolactin data over time for the overall combined database. Please provide a similar table for only those patients who completed the 19-32 weeks in the study (n = 83 bipolar, n = 93 schizophrenia) - e.g. provide baseline, 1-6 week, 7-18 week and 19-32 week data for only those patients completing 19-32 weeks.

35. One of the exclusion criteria for HGIU was "patients who have been judged clinically to be at serious suicidal risk". However, a review of the CDRS-R individual item "suicidal ideation" noted a number of patients who were rated the maximum score of "7" at baseline (has made a suicide attempt within the last month or is actively suicidal". These patients include 012-1203, 012-1212, and 024-2402. Please provide more information regarding inclusion of these patients in this study.

36. Please provide an analysis of AIMs individual items and total score (change from baseline to endpoint) for the completers in the overall combined database.

37. For HGIU and HGIN, how was "treatment-emergent" parkinsonism, akathisia and dyskinesia defined by the respective rating scales?

38. For the acute phases of HGIU and HGIN, many patients had elevated prolactin at baseline, therefore the change from baseline to endpoint analyses can be difficult to interpret. Please provide additional analyses on the subset of patients with baseline prolactin within the normal range - please provide a separate analysis for gender and age.

39. For study HGIN, it is noted that 21/72 patients in the olanzapine group and 5/35 patients in the placebo group did not have any previous medications for schizophrenia (Table HGIN.14.4). How many of these patients were from the sites in Russia? How many were first-break schizophrenic patients?

40. The summary-clin-safe-app document includes comparisons of adult and adolescent data for metabolic parameters and prolactin but not for hepatic laboratory analytes. Please provide these comparisons for hepatic laboratory analytes.

41. Please provide an analysis of mean change to endpoint for prolactin by age (< 15, > 15) for HGIN + HGIU Acute Database, HGIN and HGIU.

# 10 APPENDICES

## 10.1 Investigators and Sites (HGIN)

| Site # | Principal Investigator | Site & Address | # Pts Randomized | # Pts Completing DB; OL |
|---|---|---|---|---|
| 3 | Bastani, Bijan | Northcoast Clinical Trials<br>3733 Park East Drive, Suite 100<br>Beachwood, OH 44122<br>USA | 2 | 2;1 |
| 4 | Kaplan, Stuart<br>Busner, Joan | Penn State University Milton S. Hershey Medical Center<br>500 University Drive<br>Dept. of Psychiatry, HO73, Rm H1141<br>Hershey, PA 17033<br>USA | 1 | 1;1 |
| 5 | Childress, Ann | Nevada Behavioral Health, Inc.<br>2055 W. Charlestone Blvd, Ste B<br>Las Vegas, NV 89102<br>USA | 2 | 1;1 |
| 6 | Cueva, Jeanette | Bioscience Research, Llc<br>222 W. 14th Street<br>New York, NY 10011<br>USA | 3 | 2;2 |
| 7 | DelBello, Melissa | University of Cincinnati Medical Center<br>231 Albert B. Sabin Way<br>Dept. of Psychiatry<br>Cincinnati, OH 45267<br>USA | 6 | 2;1 |
| 10 | Gracious, Barbara | Strong Memorial Hospital<br>300 Crittenden Blvd<br>Dept. of Psychiatry, Box PSYCH<br>Rochester, NY 14642<br>USA | 2 | 1;1 |
| 11 | Kaczenski, Gregory | Summit Research Group, Llc<br>1014 Autumn Rd, Suite 3<br>Little Rock, AR 72211<br>USA | 1 | 0;0 |
| 13 | Knutson, James | Eastside Therapeutic Resources<br>512 6th Street, Suite 101<br>Kirkland, WA 98033<br>USA | 2 | 2;0 |

| | | | | |
|---|---|---|---|---|
| 14 | Leventhal, Bennett | University of Chicago Pritzker School of Medicine<br>5841 S. Maryland Avenue<br>Dept. of Child & Adolescent, MC 3077<br>Chicago, IL 60637<br>USA | 3 | 1;1 |
| 16 | Mintz, Mark | Bancroft Neurohealth<br>201 King's Highway South<br>Cherry Hill, NJ 08034<br>USA | 1 | 1 ;1 |
| 17 | Plopper, Michael | Sharp Mesa Vist Hospital<br>7850 Vista Hill Avenue<br>San Diego, CA 92123<br>USA | 3 | 2;2 |
| 19 | Krishnasastry, Chandra | Tennessee Christian Medical Center<br>320 Hospital Drive<br>Madison, TN 37115<br>USA | 1 | 1;0 |
| 20 | Riesenberg, Robert | Atlanta Center of Medical Research<br>811 Juniper Street<br>Atlanta, GA 30308<br>USA | 5 | 3;3 |
| 21 | Robb, Adelaide | Children's National Medical Center<br>111 Michigan Ave, NW<br>Washington, DC 20010<br>USA | 3 | 1; 0 [1] |
| 25 | Soni, Poonam | University of Utah School of Medicine<br>Mood Disorder Clinic, Rm 5R218<br>Dept. of Psychiatry<br>30 N. 1900 East<br>Salt Lake City, UT 84132<br>USA | 4 | 1;0 |
| 26 | White, Tonya | University of Minnesota Medical School<br>2450 Riverside Avenue<br>Dept. of Psychiatry, F256/2B West<br>Minneapolis, MN 55454<br>USA | 2 | 2;0 |

| | | | | |
|---|---|---|---|---|
| 27 | Yadalam, Kashinath | Institute for Neuropsychiatry<br>2829 4th Avenue<br>Lake Charles, LA 70601<br>USA | 2 | 1;0 |
| 30 | Punjwani, Sohail | Segal Institute for Clinical Research<br>1065 NE 125th Street, Suite 417<br>North Miami, FL 33161<br>USA | 10 | 6;1 |
| 33 | Valencerina, Madeleine | BHC Alhambra Hospital<br>4619 N. Rosemead Blvd.<br>Rosemead, CA 91770<br>USA | 1 | 0;0 |
| 34 | Vogelfanger, Robert | Compass Intervention Center<br>7900 Lowrance Road<br>Memphis, TN 38125<br>USA | 3 | 2;2 |
| 900 | Smulevich, Anatoly | Moscow Clinical Psychiatric Hospital #1<br>N.A. Alexeyev<br>Zagorodnoye Shosse, 2<br>PKDO #2<br>Moscow, 117152<br>Russia | 10 | 8;7 |
| 910 | Bardenstein, Leonid | Moscow Medical University,<br>N.A. Semashko<br>Moskvorechye 7<br>City Psychiatric Hospital #15<br>Moscow, 115522<br>Russia | 10 | 6;9 |
| 920 | Alexandrovsky, Yuriy | Serbsky National Research Center<br>47 Volokolamskoye Shosse<br>Psychiatric Hospital #12, korp5, Rm 27<br>Moscow, 123367<br>Russia | 10 | 5;4 |
| 930 | Morozova, Margarita | National Mental Health Research Centre<br>Kashirskoye Shosse 34<br>Moscow, 115522<br>Russia | 10 | 6;7 |
| 940 | Krasnov, Valery | Moscow Research Institute of Psychiatry<br>UL. Poteshnaya 3<br>Moscow, 107076<br>Russia | 10 | 7;6 |

[1] Site was closed by sponsor due to protocol violations. Patients were discontinued.

10.2 Inclusion and Exclusion Criteria

Inclusion

1. Are male or female patients, 13 to 17 years of age, but must not yet have reached their 18th birthday prior to Visit 1, when informed consent is obtained.
2. Patient must have a diagnosis of schizophrenia according to DSM-IV-TR and confirmed by the K-SADS-PL. Patients must meet diagnostic criteria at Visit 1 and Visit 2.
3. Female patients of childbearing potential (not surgically sterilized) must test negative for pregnancy at the time of enrollment based on a serum pregnancy test. Furthermore, female patients must agree to abstain from sexual activity or to use a medically acceptable method of birth control during their participation in the study.
4. Each patient and the patient's parent/authorized legal representative must understand the nature of the study. The patient's parent/authorized legal representative must sign an informed consent document and the patient must sign an informed consent document/assent document as required by local regulations.
5. Each patient and the patient's parent/authorized legal representative must have a level of understanding sufficient to perform all tests and examinations required by the protocol.
6. Patient must obtain an Anchored BPRS-C total score of > 35 with a minimum score of 3 on at least one of the following items at Visit 1 and Visit 2: hallucinations, delusions, peculiar fantasies.
7. Patients must be capable of swallowing study medication whole (without crushing, dissolving, etc.).

Exclusion criteria

1. Are investigator site personnel directly affiliated with the study, or are immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted.
2. Are employed by Lilly (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical trials, but are not permitted to participate at a Lilly facility. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted.
3. Patients who have participated in a clinical trial of oral olanzapine or have received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry.
4. Patients who have a history of mental retardation, current comorbid autism or current comorbid pervasive developmental disorder.
5. Female patients who are either pregnant or nursing.
6. Patients with acute or unstable medical conditions, including (but not limited to) inadequately controlled diabetes, hepatic insufficiency (specifically any degree of jaundice), uncorrected hypothyroidism or hyperthyroidism, acute systemic infection, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic diseases (specifically current agranulocytosis with an absolute neutrophil count < 500 $mm^3$).

7. Patients with acute or unstable medical conditions, such that intensive care unit hospitalization for the disease is anticipated within 6 months.
8. Prolactin level at Visit 1 $\geq$ 200 ng/ml.
9. Patients who have been judged clinically to be at serious suicidal risk.
10. Patients who have experienced one or more seizures without a clear and resolved etiology.
11. Laboratory results, including serum chemistries, hematology, and urinalysis, must show no clinically significant abnormalities. In addition, there must be no clinical information that, in the judgment of a physician, should preclude a patient's participation at study entry.
12. Patients with a documented history of allergic reaction to olanzapine.
13. Patients who have undergone treatment with remoxipride within 6 months (180 days) prior to Visit 2.
14. Any concomitant medication with primarily central nervous system activity, including alternative medications, other than specified as permitted in Table HGIN.2 and HGIN.3 at Visit 2.
15. Use of any concomitant medication(s) at Visit 2 as specified in Section 5.7 or expected to need treatment with any medication during the study other than what is allowed.
16. Patients who have used monoamine oxidase inhibitors (MAOIs) within 14 days prior to Visit 2 or are expected to need treatment at any time during this study.
17. DSM-IV-TR substance (except nicotine and caffeine) dependence within the past 30 days.
18. Patients who have previously not responded to an adequate dose and/or duration of olanzapine treatment.
19. Patients, who, in the opinion of the investigator, are unsuitable in any other way to participate in this study including being unable to comply with the requirements of the study for any reason.
20. Treatment with an injectable neuroleptic $\leq$ 14 days before Visit 2.
21. Patients currently meeting DSM-IV-TR criteria for delusional disorder, psychotic disorder NOS, schizophreniform disorder, schizoaffective disorder, bipolar disorder, attention deficit/hyperactivity disorder or major depressive disorder.

## 10.3. Sponsor's Table. Schedule of Events HGIN

**Table HGIN.9.4. Schedule of Events for F1D-MC-HGIN (continued)**

| Description of the Data | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | Final SPII Visit[i] | Visit501 | V301 | V302 | V303 | V304 | V305 | V306 | V307 | V308 | V309 | Final SPIII Visit[i] | Visit 501 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AIMS, Barnes Akathisia Scale, Simpson-Angus Scale | X | X | X | X | X | X | X | X | X | | | X | X | X | X | X | X | X | X | X | | |
| LABORATORY TESTS[b] | | | | | | | | | | | | | | | | | | | | | | |
| Clinical chemistry/ electrolytes/lipids[e] | X | X | | X | X | X | X | X | X | X | | | X | | X | X | X | X | X | X | X | |
| Hematology | X | X | | X | X | X | X | X | X | X | | | X | | X | X | X | X | X | X | X | |
| Urinalysis | X | | | | | | | | | X | | | | | | | | | | | X | |
| Hepatitis screen[c], urine drug screen[d], serum pregnancy test[d], and TSH | X | | | | | | | | | | | | | | | | | | | | | |
| $HbgA1_c$[f] | X | | | | | | | | | X | | | | | | X | | | | | X | |
| Prolactin[g] | X | X | | | | | | | | X | | | | | | X | | | | | X | |
| EFFICACY ASSESSMENTS/Measurements | | | | | | | | | | | | | | | | | | | | | | |
| Anchored BPRS-C[j] | X | X | X | X | X | X | X | X | X | | | X | X | X | X | X | X | X | X | X | | |
| CGI Severity | | X | X | X | X | X | X | X | X | | | X | X | X | X | X | X | X | X | X | | |
| CGI-Improvement | | | X | X | X | X | X | X | X | | | X | X | X | X | X | X | X | X | X | | |
| PANSS | | X | | | | X | | | | X | | | | | | | | | | | X | |
| OAS | | X | | | | X | | | | X | | | | | | | | | | | X | |
| Child Health Questionnaire (CHQ)[k] | | X | | | | | | | | X | | | | | | | | | | | X | |
| Brief Assessment of Cognition for Schizophrenia (BACS)[k] | | X | | | | | | | | X | | | | | | | | | | | X | |

**Table HGIN.9.4. Schedule of Events for F1D-MC-HGIN (continued)**

| Description of the Data | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | Final SPII Visit[i] | Visit501 | V301 | V302 | V303 | V304 | V305 | V306 | V307 | V308 | V309 | Final SPIII Visit[i] | Visit 501 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AIMS, Barnes Akathisia Scale, Simpson-Angus Scale | X | X | X | X | X | X | X | X | X | | | X | X | X | X | X | X | X | X | X | | |
| LABORATORY TESTS[b] | | | | | | | | | | | | | | | | | | | | | | |
| Clinical chemistry/ electrolytes/lipids[e] | X | X | | X | X | X | X | X | X | X | | | X | | X | X | X | X | X | X | X | |
| Hematology | X | X | | X | X | X | X | X | X | X | | | X | | X | X | X | X | X | X | X | |
| Urinalysis | X | | | | | | | | | X | | | | | | | | | | | X | |
| Hepatitis screen[c], urine drug screen[d], serum pregnancy test[d], and TSH | X | | | | | | | | | | | | | | | | | | | | | |
| $HbgA1_c$[f] | X | | | | | | | | | X | | | | | | X | | | | | X | |
| Prolactin[g] | X | X | | | | | | | | X | | | | | | X | | | | | X | |
| EFFICACY ASSESSMENTS/Measurements | | | | | | | | | | | | | | | | | | | | | | |
| Anchored BPRS-C[j] | X | X | X | X | X | X | X | X | X | | | X | X | X | X | X | X | X | X | X | | |
| CGI Severity | | X | X | X | X | X | X | X | X | | | X | X | X | X | X | X | X | X | X | | |
| CGI-Improvement | | | X | X | X | X | X | X | X | | | X | X | X | X | X | X | X | X | X | | |
| PANSS | | X | | | | X | | | | X | | | | | | | | | | | X | |
| OAS | | X | | | | X | | | | X | | | | | | | | | | | X | |
| Child Health Questionnaire (CHQ)[k] | | X | | | | | | | | X | | | | | | | | | | | X | |
| Brief Assessment of Cognition for Schizophrenia (BACS)[k] | | X | | | | | | | | X | | | | | | | | | | | X | |

## 10.4 Severity of Illness: Russia vs. U.S. Sites

**Table 1. Illness Characteristics at Baseline by Country**
**All Randomized Patients**
**F1D-MC-HGIN, Acute Phase**

| Illness Characteristics | Statistics | Country: Russia (N=50) | Country: U.S. (N=57) | *P-value |
|---|---|---|---|---|
| Onset Age | No. of Patients | 50 | 57 | |
| | Mean | 13.02 | 12.65 | .536 |
| | Median | 14.00 | 13.00 | |
| | Std. Dev. | 2.64 | 3.43 | |
| | Minimum | 6.00 | 5.00 | |
| | Maximum | 17.00 | 17.00 | |
| No. of Prev. Schizophrenia episode | No. of Patients | 40 | 45 | |
| | Mean | 2.10 | 2.73 | .416 |
| | Median | 2.00 | 2.00 | |
| | Std. Dev. | 1.45 | 4.71 | |
| | Minimum | 0.00 | 0.00 | |
| | Maximum | 6.00 | 30.00 | |
| Total cum hospitalization in months | No. of Patients | 26 | 34 | |
| | Mean | 2.96 | 1.88 | .065 |
| | Median | 2.00 | 1.00 | |
| | Std. Dev. | 1.92 | 2.40 | |
| | Minimum | 1.00 | 0.10 | |
| | Maximum | 9.50 | 11.00 | |

* Means are analyzed using a Type III Sum of Squares analysis of variance(ANOVA); Model- Country

| Illness Characteristics | Statistics | Country: Russia (N=50) | Country: U.S. (N=57) | *P-value |
|---|---|---|---|---|
| Length of current episode in days | No. of Patients | 50 | 56 | |
| | Mean | 262.44 | 259.43 | .974 |
| | Median | 135.50 | 80.00 | |
| | Std. Dev. | 396.21 | 524.28 | |
| | Minimum | 7.00 | 0.00 | |
| | Maximum | 2139.00 | 2742.00 | |
| Days since the last hospitalization | No. of Patients | 37 | 40 | |
| | Mean | 476.95 | 149.58 | .012 |
| | Median | 163.00 | 7.00 | |
| | Std. Dev. | 632.51 | 477.26 | |
| | Minimum | 31.00 | 1.00 | |
| | Maximum | 2718.00 | 2889.00 | |

| Illness Characteristics | Category | Country: Russia (N=50) n (%) | Country: U.S. (N=57) n (%) | *P-value |
|---|---|---|---|---|
| Psychiatric hospitalization | Yes | 26(52.00) | 34(59.65) | .442 |
| | No | 24(48.00) | 23(40.35) | |

**Table 2. Severity of Illness at Baseline by Country**
**All Randomized Patients**
**F1D-MC-HGIN, Acute Phase**

| Illness Characteristics | Statistics | Country: Russia (N=50) | Country: U.S. (N=57) | *P-values |
|---|---|---|---|---|
| CGI Severity | No. of Patients | 50 | 57 | |
| | Mean | 4.86 | 4.88 | .904 |
| | Median | 5.00 | 5.00 | |
| | Std. Dev. | 0.70 | 0.76 | |
| | Minimum | 4.00 | 4.00 | |
| | Maximum | 6.00 | 7.00 | |
| BPRS-C Behavioral Problem(Sum 1-3) | No. of Patients | 50 | 57 | |
| | Mean | 5.46 | 7.77 | <.001 |
| | Median | 6.00 | 8.00 | |
| | Std. Dev. | 2.54 | 3.70 | |
| | Minimum | 0.00 | 0.00 | |
| | Maximum | 9.00 | 14.00 | |
| BPRS-C Depression(Sum 4-6) | No. of Patients | 50 | 57 | |
| | Mean | 5.30 | 6.47 | .044 |
| | Median | 5.50 | 6.00 | |
| | Std. Dev. | 2.61 | 3.25 | |
| | Minimum | 0.00 | 1.00 | |
| | Maximum | 11.00 | 16.00 | |

* Means are analyzed using a Type III Sum of Squares analysis of variance(ANOVA); Model= Country

| Illness Characteristics | Statistics | Country: Russia (N=50) | Country: U.S. (N=57) | *P-values |
|---|---|---|---|---|
| PANSS Total Score | No. of Patients | 50 | 57 | |
| | Mean | 97.62 | 93.35 | .116 |
| | Median | 96.00 | 95.00 | |
| | Std. Dev. | 13.09 | 14.60 | |
| | Minimum | 74.00 | 66.00 | |
| | Maximum | 122.00 | 123.00 | |

| Illness Characteristics | Statistics | Country: Russia (N=50) | Country: U.S. (N=57) | *P-values |
|---|---|---|---|---|
| BPRS-C Thinking Disturbance(Sum 7-9) | No. of Patients | 50 | 57 | |
| | Mean | 9.72 | 11.04 | .030 |
| | Median | 10.00 | 11.00 | |
| | Std. Dev. | 3.29 | 2.88 | |
| | Minimum | 4.00 | 5.00 | |
| | Maximum | 18.00 | 18.00 | |
| BPRS-C Psychomotor Excitation Subtotal(Sum 10-12) | No. of Patients | 50 | 57 | |
| | Mean | 6.08 | 7.32 | .038 |
| | Median | 5.00 | 7.00 | |
| | Std. Dev. | 2.84 | 3.12 | |
| | Minimum | 2.00 | 2.00 | |
| | Maximum | 13.00 | 14.00 | |
| BPRS-C Withdrawal Subtotal(Sum 13-15) | No. of Patients | 50 | 57 | |
| | Mean | 9.54 | 7.98 | .021 |
| | Median | 10.00 | 8.00 | |
| | Std. Dev. | 2.76 | 3.93 | |
| | Minimum | 4.00 | 1.00 | |
| | Maximum | 18.00 | 15.00 | |

| Illness Characteristics | Statistics | Country: Russia (N=50) | Country: U.S. (N=57) | *P-values |
|---|---|---|---|---|
| BPRS-C Anxiety Subtotal(Sum 16-18) | No. of Patients | 50 | 57 | |
| | Mean | 8.16 | 8.58 | .467 |
| | Median | 9.00 | 9.00 | |
| | Std. Dev. | 2.76 | 3.13 | |
| | Minimum | 2.00 | 1.00 | |
| | Maximum | 15.00 | 14.00 | |
| BPRS-C Organicity Subtotal(Sum 19-21) | No. of Patients | 50 | 57 | |
| | Mean | 3.22 | 3.44 | .708 |
| | Median | 2.50 | 3.00 | |
| | Std. Dev. | 3.29 | 2.74 | |
| | Minimum | 0.00 | 0.00 | |
| | Maximum | 12.00 | 10.00 | |
| BPRS-C Total Score | No. of Patients | 50 | 57 | |
| | Mean | 47.48 | 52.60 | .005 |
| | Median | 46.50 | 52.00 | |
| | Std. Dev. | 8.71 | 9.60 | |
| | Minimum | 36.00 | 35.00 | |
| | Maximum | 68.00 | 79.00 | |

| Illness Characteristics | Statistics | Country: Russia (N=50) | Country: U.S. (N=57) | *P-values |
|---|---|---|---|---|
| PANSS Positive Score | No. of Patients | 50 | 57 | |
| | Mean | 21.08 | 24.16 | <.001 |
| | Median | 21.00 | 25.00 | |
| | Std. Dev. | 4.29 | 4.95 | |
| | Minimum | 11.00 | 13.00 | |
| | Maximum | 32.00 | 36.00 | |
| PANSS Negative Score | No. of Patients | 50 | 57 | |
| | Mean | 26.92 | 23.02 | <.001 |
| | Median | 27.00 | 23.00 | |
| | Std. Dev. | 4.78 | 6.02 | |
| | Minimum | 18.00 | 11.00 | |
| | Maximum | 39.00 | 35.00 | |
| PANSS General Psychopathology Score | No. of Patients | 50 | 57 | |
| | Mean | 49.62 | 46.18 | .033 |
| | Median | 48.00 | 48.00 | |
| | Std. Dev. | 7.53 | 8.77 | |
| | Minimum | 36.00 | 25.00 | |
| | Maximum | 65.00 | 67.00 | |

## 10.5 BPRS-C Individual Items – Mean Change from Baseline to Endpoint

**Table HGIN.14.24. BPRS-C Individual Items**
**LOCF Mean Change from Baseline to Endpoint**
**Double-Blind Period**

| Efficacy Variable | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|
| Uncooperativeness | Olanzapine | 72 | 2.51 | 1.42 | -0.99 | 1.60 | -1.05 | -0.88 | .003 |
| | Placebo | 35 | 2.89 | 1.49 | -0.29 | 1.43 | -0.16 | | |
| Hostility | Olanzapine | 72 | 2.67 | 1.53 | -1.25 | 1.57 | -1.21 | -1.16 | <.001 |
| | Placebo | 35 | 2.43 | 1.48 | 0.03 | 1.74 | -0.06 | | |
| Manipulativeness | Olanzapine | 72 | 1.57 | 1.52 | -0.54 | 1.40 | -0.47 | -0.55 | .035 |
| | Placebo | 35 | 1.26 | 1.46 | 0.17 | 1.74 | 0.07 | | |
| Depressed Mood | Olanzapine | 72 | 2.83 | 1.28 | -1.00 | 1.42 | -1.01 | -0.20 | .460 |
| | Placebo | 35 | 2.86 | 1.40 | -0.80 | 1.39 | -0.81 | | |
| Feelings of Inferiority | Olanzapine | 72 | 2.46 | 1.46 | -1.03 | 1.41 | -1.05 | -0.44 | .104 |
| | Placebo | 35 | 2.60 | 1.58 | -0.66 | 1.57 | -0.61 | | |
| Suicidal Ideation | Olanzapine | 72 | 0.67 | 1.26 | -0.46 | 1.10 | -0.39 | -0.09 | .479 |
| | Placebo | 35 | 0.40 | 0.74 | -0.17 | 0.92 | -0.30 | | |
| Peculiar Fantasies | Olanzapine | 72 | 3.42 | 1.63 | -1.65 | 1.87 | -1.61 | -0.78 | .014 |
| | Placebo | 35 | 3.29 | 1.30 | -0.80 | 1.59 | -0.82 | | |
| Delusions | Olanzapine | 72 | 3.86 | 1.05 | -1.72 | 1.57 | -1.73 | -0.47 | .151 |
| | Placebo | 35 | 4.06 | 1.30 | -1.34 | 1.86 | -1.26 | | |
| Hallucinations | Olanzapine | 72 | 3.21 | 1.74 | -1.61 | 1.98 | -1.56 | -0.41 | .249 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Hallucinations | Placebo | 35 | 2.94 | 1.85 | -1.06 | 1.95 | -1.15 | | |
| Hyperactivity | Olanzapine | 72 | 1.81 | 1.76 | -0.78 | 1.59 | -0.77 | -0.82 | .004 |
| | Placebo | 35 | 1.77 | 1.55 | 0.06 | 1.66 | 0.04 | | |
| Distractibility | Olanzapine | 72 | 3.61 | 0.99 | -0.93 | 1.40 | -0.94 | -0.45 | .101 |
| | Placebo | 35 | 3.71 | 1.02 | -0.54 | 1.42 | -0.49 | | |
| Speech or Voice Pressure | Olanzapine | 72 | 1.14 | 1.42 | -0.53 | 1.20 | -0.61 | -0.42 | .068 |
| | Placebo | 35 | 1.63 | 1.52 | -0.37 | 1.59 | -0.19 | | |
| Underproductive Speech | Olanzapine | 72 | 2.39 | 1.47 | -0.61 | 1.34 | -0.56 | -0.37 | .164 |
| | Placebo | 35 | 2.03 | 1.81 | -0.09 | 1.62 | -0.20 | | |
| Emotional Withdrawal | Olanzapine | 72 | 3.40 | 1.11 | -0.86 | 1.59 | -0.81 | -0.17 | .528 |
| | Placebo | 35 | 3.26 | 1.24 | -0.57 | 1.72 | -0.64 | | |
| Blunted Affect | Olanzapine | 72 | 3.04 | 1.41 | -0.51 | 1.29 | -0.52 | -0.04 | .876 |
| | Placebo | 35 | 3.17 | 1.40 | -0.54 | 1.36 | -0.49 | | |
| Tension | Olanzapine | 72 | 2.97 | 0.92 | -1.07 | 1.33 | -1.07 | -0.44 | .120 |
| | Placebo | 35 | 2.97 | 1.25 | -0.63 | 1.63 | -0.62 | | |
| Anxiety | Olanzapine | 72 | 2.79 | 1.47 | -0.89 | 1.63 | -0.91 | -0.49 | .103 |
| | Placebo | 35 | 2.89 | 1.53 | -0.46 | 1.69 | -0.42 | | |

Table HGIN.11.17. BPRS-C Composite Factor Scores Mean Change from Baseline to Endpoint (LOCF) Double-Blind Period

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy Variable | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Diff. | *P-value |
| BPRS-C Behavioral Problem(Sum 1-3) | Olanzapine | 72 | 6.75 | 3.40 | -2.78 | 3.72 | -2.74 | -2.63 | <.001 |
| | Placebo | 35 | 6.57 | 3.45 | -0.09 | 3.81 | -0.11 | | |
| BPRS-C Depression(Sum 4-6) | Olanzapine | 72 | 5.96 | 3.15 | -2.49 | 2.85 | -2.47 | -0.81 | .129 |
| | Placebo | 35 | 5.86 | 2.76 | -1.63 | 2.95 | -1.66 | | |
| BPRS-C Thinking Disturbance(Sum 7-9) | Olanzapine | 72 | 10.49 | 3.16 | -4.99 | 4.53 | -4.91 | -1.70 | .050 |
| | Placebo | 35 | 10.29 | 3.12 | -3.20 | 4.62 | -3.21 | | |
| BPRS-C Psychomotor Excitation Subtotal(Sum 10-12) | Olanzapine | 72 | 6.56 | 2.99 | -2.24 | 3.15 | -2.33 | -1.68 | .006 |
| | Placebo | 35 | 7.11 | 3.28 | -0.86 | 3.63 | -0.65 | | |
| BPRS-C Withdrawal Subtotal(Sum 13-15) | Olanzapine | 72 | 8.83 | 3.39 | -1.99 | 3.40 | -1.91 | -0.61 | .357 |
| | Placebo | 35 | 8.46 | 3.76 | -1.20 | 3.95 | -1.30 | | |
| BPRS-C Anxiety Subtotal(Sum 16-18) | Olanzapine | 72 | 8.35 | 3.02 | -3.60 | 3.87 | -3.65 | -2.19 | .004 |
| | Placebo | 35 | 8.66 | 2.85 | -1.66 | 4.35 | -1.46 | | |
| BPRS-C Organicity Subtotal(Sum 19-21) | Olanzapine | 72 | 3.43 | 3.04 | -1.35 | 2.26 | -1.28 | -0.54 | .184 |
| | Placebo | 35 | 3.14 | 2.93 | -0.69 | 2.75 | -0.75 | | |

10.6 Patient Baseline Demographics – HGIN + HGIU Acute Database and Overall Combined Database

Table 10.6.1 Sponsor's Table

**Table 2.7.4.21. Patient Demographics at Baseline
All Randomized Patients
Acute Placebo-Controlled Combined Database**

| Demographic Variables | Statistics/ Category | Olanzapine (N=179) n (%) | Placebo (N=89) n (%) | *P-value |
|---|---|---|---|---|
| Gender | Male | 112(62.57) | 48(53.93) | .188 |
| | Female | 67(37.43) | 41(46.07) | |
| Age | No. of Patients | 179 | 89 | |
| | Mean | 15.54 | 15.74 | .200 |
| | Median | 15.54 | 15.62 | |
| | Std. Dev. | 1.36 | 1.42 | |
| | Minimum | 13.02 | 13.06 | |
| | Maximum | 17.99 | 18.00 | |
| Origin | African Descent | 30(16.76) | 9(10.11) | .359 |
| | Caucasian | 123(68.72) | 66(74.16) | |
| | East/Southeast Asian | 0(0.0) | 1(1.12) | |
| | Hispanic | 20(11.17) | 9(10.11) | |
| | Other | 6(3.35) | 4(4.49) | |
| Country | United States | 133(74.30) | 67(75.28) | 1.00 |
| | Puerto Rico | 12(6.70) | 6(6.74) | |
| | Russia | 34(18.99) | 16(17.98) | |

Table 10.6.2 Sponsor's Table. Age Distribution at Baseline (HGIN + HGIU)

**Table 2.7.4.22. Age Distribution at Baseline
All Randomized Patients
Acute Placebo-Controlled Combined Database**

| | HGIN | | HGIU | | Combined | |
|---|---|---|---|---|---|---|
| Age Group | n | % | n | % | n | % |
| 13 | 9 | 8.4% | 31 | 19.3% | 40 | 14.9% |
| 14 | 13 | 12.1% | 38 | 23.6% | 51 | 19.0% |
| 15 | 20 | 18.7% | 50 | 31.1% | 70 | 26.1% |
| 16 | 29 | 27.1% | 27 | 16.8% | 56 | 20.9% |
| 17 | 36 | 33.6% | 15 | 9.3% | 51 | 19.0% |
| Total | 107 | 100.0% | 161 | 100.0% | 268 | 100.0% |

Table 10.6.3 Sponsor's Table. Patient Demographics at Baseline – Overall Olanzapine Combined Database

**Table 2.7.4.24. Patient Demographics at Baseline**
**All Patients with Olanzapine Exposure**
**Overall Olanzapine Exposure Combined Database**

| Demographic Variables | Statistics/ Category | Bipolar (N=227) n (%) | Schizophrenia (N=227) n (%) | Overall (N=454) n (%) |
|---|---|---|---|---|
| Gender | Male | 124(54.63) | 162(71.37) | 286(63.00) |
| | Female | 103(45.37) | 65(28.63) | 168(37.00) |
| Age | No. of Patients | 227 | 227 | 454 |
| | Mean | 15.44 | 16.38 | 15.91 |
| | Median | 15.43 | 16.67 | 16.02 |
| | Std. Dev. | 1.33 | 1.27 | 1.38 |
| | Minimum | 13.02 | 13.03 | 13.02 |
| | Maximum | 18.00 | 18.00 | 18.00 |
| Origin | African Descent | 22(9.69) | 28(12.33) | 50(11.01) |
| | Caucasian | 166(73.13) | 189(83.26) | 355(78.19) |
| | East/Southeast Asian | 1(0.44) | 0(0.0) | 1(0.22) |
| | Hispanic | 31(13.66) | 6(2.64) | 37(8.15) |
| | Other | 7(3.08) | 4(1.76) | 11(2.42) |
| Country | United States | 205(90.31) | 58(25.55) | 263(57.93) |
| | Puerto Rico | 21(9.25) | 1(0.44) | 22(4.85) |
| | Russia | 1(0.44) | 79(34.80) | 80(17.62) |
| | Germany | 0(0.0) | 89(39.21) | 89(19.60) |

## 10.7 Weight Gain – Additional Analyses

Table 10.7.1. Weight Change by Visit (OC): Overall Combined Database

| | | | | Change to Maximum | | |
|---|---|---|---|---|---|---|
| | | Visit Week | N | Mean | Std | P-value |
| Weight (kg) | Bipolar | ≤ 1 | 224 | 1.27 | 1.55 | < 0.001 |
| | Schizophrenia | | 224 | 1.75 | 1.51 | < 0.001 |
| | Overall | | 448 | 1.51 | 1.55 | < 0.001 |
| | Bipolar | > 1 ≤ 2 | 221 | 2.29 | 2.04 | < 0.001 |
| | Schizophrenia | | 219 | 2.73 | 1.96 | < 0.001 |
| | Overall | | 440 | 2.51 | 2.01 | < 0.001 |
| | Bipolar | > 2 ≤ 3 | 183 | 3.07 | 2.62 | < 0.001 |
| | Schizophrenia | | 148 | 3.46 | 2.24 | < 0.001 |
| | Overall | | 331 | 3.25 | 2.46 | < 0.001 |
| | Bipolar | > 3 ≤ 4 | 199 | 3.74 | 2.84 | < 0.001 |
| | Schizophrenia | | 201 | 4.02 | 2.51 | < 0.001 |
| | Overall | | 400 | 3.88 | 2.68 | < 0.001 |
| | Bipolar | > 4 ≤ 5 | 167 | 4.05 | 3.31 | < 0.001 |
| | Schizophrenia | | 147 | 4.66 | 2.42 | < 0.001 |
| | Overall | | 314 | 4.34 | 2.94 | < 0.001 |
| | Bipolar | > 5 ≤ 9 | 157 | 6.03 | 3.80 | < 0.001 |
| | Schizophrenia | | 130 | 7.12 | 3.80 | < 0.001 |
| | Overall | | 287 | 6.52 | 3.83 | < 0.001 |
| | Bipolar | > 9 ≤ 13 | 121 | 7.59 | 4.95 | < 0.001 |
| | Schizophrenia | | 117 | 8.17 | 4.84 | < 0.001 |
| | Overall | | 238 | 7.87 | 4.89 | < 0.001 |
| | Bipolar | > 13 ≤ 17 | 114 | 8.84 | 5.87 | < 0.001 |
| | Schizophrenia | | 103 | 9.01 | 6.03 | < 0.001 |
| | Overall | | 217 | 8.92 | 5.93 | < 0.001 |
| | Bipolar | > 17 ≤ 21 | 102 | 9.69 | 6.43 | < 0.001 |
| | Schizophrenia | | 88 | 10.2 | 6.75 | < 0.001 |
| | Overall | | 190 | 9.93 | 6.56 | < 0.001 |
| | Bipolar | > 21 ≤ 25 | 93 | 10.19 | 6.98 | < 0.001 |
| | Schizophrenia | | 81 | 10.84 | 6.92 | < 0.001 |
| | Overall | | 174 | 10.49 | 6.94 | < 0.001 |
| | Bipolar | > 25 ≤ 32 | 53 | 9.60 | 7.12 | < 0.001 |
| | Schizophrenia | | 78 | 11.68 | 7.62 | < 0.001 |
| | Overall | | 131 | 10.84 | 7.46 | < 0.001 |

From Sponsor table APP.2.7.4.7.1.18 in summary-clin-safe-app document

Table 10.7.2. Adverse Event "Weight Increased" Gender Analysis: HGIU and HGIN Acute Phases

| | | | Olanzapine | | | Placebo | | | p-value | Homogeneity of Odds Ratio |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Gender | N | n | % | N | n | % | | |
| Weight Increased | HGIU | Female | 46 | 16 | 35% | 30 | 1 | 3% | 0.001 | |
| | | Male | 61 | 15 | 25% | 24 | 1 | 4% | 0.033 | 0.628 |
| | HGIN | Female | 21 | 6 | 29% | 11 | 2 | 18% | 0.681 | |
| | | Male | 51 | 16 | 31% | 24 | 1 | 4% | 0.008 | 0.186 |
| | | | | | | | | | | |
| Weight Increased | HGIU | < 15 yrs | 49 | 14 | 29% | 20 | 0 | 0 | 0.007 | |
| | | ≥ 15 yrs | 58 | 17 | 29% | 34 | 2 | 6% | 0.008 | 0.280 |
| | HGIN | < 15 yrs | 15 | 6 | 40% | 7 | 1 | 14% | 0.350 | |
| | | ≥ 15 yrs | 57 | 16 | 28% | 28 | 2 | 7% | 0.045 | 0.868 |

From Sponsor Tables HGIN.14.28 and HGIU.14.31

Table 10.7.3. Mean Change in Weight (kg) – Subgroup Analyses: HGIN

| | | | | Baseline | | Change to Endpoint | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Subgroup | Therapy | n | Mean | St.Dev | Mean | St. Dev | LS Mean | LSMean Diff | P-value | P-value |
| **HGIN** | | | | | | | | | | | |
| Weight (kg) | Female | Olanzapine | 21 | 64.0 | 16.6 | 3.8 | 3.7 | 3.4 | | | |
| | | Placebo | 10 | 61.0 | 12.5 | 0.8 | 3.5 | 0.7 | 2.73 | 0.063 | |
| | Male | Olanzapine | 51 | 68.3 | 11.6 | 4.5 | 3.2 | 4.6 | | | |
| | | Placebo | 24 | 72.2 | 17.6 | -0.2 | 2.5 | -0.2 | 4.76 | < 0.001 | 0.140 |
| | < 15 yrs | Olanzapine | 15 | 64.7 | 14.0 | 6.3 | 4.2 | 5.2 | | | |
| | | Placebo | 7 | 62.5 | 9.6 | 1.1 | 4.1 | -0.2 | 5.37 | 0.009 | |
| | | | | | | | | | | | |
| | ≥ 15 yrs | Olanzapine | 57 | 67.7 | 13.2 | 3.7 | 2.9 | 3.8 | | | |
| | | Placebo | 27 | 70.6 | 18.1 | -0.1 | 2.4 | -0.1 | 3.84 | < 0.001 | 0.370 |
| | | | | | | | | | | | |

From Sponsor Tables HGIN.14.47

Table 10.7.4. Mean Change from Baseline to Endpoint in Laboratory Values – Patients Who Gained > 3.9 kg vs. Placebo

*The LS Mean Change and p-value for the entire population is in parenthesis for comparison purposes*

| | | | Baseline | Change to Endpoint | | | |
|---|---|---|---|---|---|---|---|
| | Therapy | n | Mean | Mean | LS Mean Change | LSMean Diff | P-value |
| AST (U/L) | Olanzapine | 84 | 21.9 | 9.5 | 11.3 | | |
| | Placebo | 87 | 23.6 | -2.5 | -0.4 | 11.7 (8.91) | < 0.001 (0.002) |
| ALT (U/L) | Olanzapine | 84 | 20.8 | 25.8 | 29.6 | | |
| | Placebo | 87 | 20.4 | -3.1 | 1.0 | 28.5 (23.0) | < 0.001 (< 0.001) |
| CPK (U/L) | Olanzapine | 84 | 125 | 18.1 | 16.8 | | |
| | Placebo | 87 | 164 | -23.6 | -21.9 | 38.7 (16.1) | 0.037 (0.38) |
| Glucose, fasting (mg/dL)* | Olanzapine | 58 | 88.8 | 3.2 | 4.3 | | |
| | Placebo | 64 | 89.7 | -2.9 | -2.0 | 6.3 (5.6) | 0.001 (< 0.001) |
| Cholesterol (mg/dL)* | Olanzapine | 84 | 164.1 | 17.4 | 13.5 | | |
| | Placebo | 87 | 160.2 | -1.1 | -4.6 | 18.5 (14.3) | < 0.001 (< 0.001) |
| Triglycerides (mg/dL)* | Olanzapine | 84 | 97.3 | 51.3 | 46.9 | | |
| | Placebo | 87 | 110.6 | -4.4 | -7.1 | 54.0 (33.6) | < 0.001 (<0.001) |
| LDL (mg/dL)* | Olanzapine | 84 | 96.1 | 6.6 | 3.1 | | |
| | Placebo | 87 | 91.5 | -0.39 | -3.5 | 6.6 (6.6) | 0.038 (0.016) |
| Prolactin (ng/ml) | Olanzapine | 79 | 13.3 | 12.6 | 12.0 | | |
| | Placebo | 80 | 14.9 | -0.2 | -0.9 | 12.91 (11.7) | < 0.001 (< 0.001) |

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113, LDL = 0.0259

## 10.8 Patients with Possible Suicidal Behavior or Ideation Events
## HGIU + HGIN Acute Database

| Patient ID (Study-Inv-Patient) | Brief Description of Event | Code | Therapy | Days to Event | Fatal? |
|---|---|---|---|---|---|
| HGIU-001-0103 | THE PATIENT HAS REPORTEDLY BEEN HAVING DIFFICULTIES WITH DYSPHORIC MOOD. IN MID TO LATE APRIL, 2003, HE TRIED TO TIE A BELT AROUND HIS NECK RESULTING IN A RASH. | 5 | Placebo | 23 | No |
| HGIU-012-1206 | INTENTIONAL SELF-INJURY / SELF-INFLICTED CUT MARKS ON FOREARM | 5 | Olz | 22 | No |
| HGIU-012-1211 | SUICIDAL IDEATION / SUICIDAL IDEATION | 4 | Olz | 14 | No |

## Overall Combined Database

| Patient ID (Study-Inv-Patient) | Brief Description of Event | Code | Days to Event | Fatal? |
|---|---|---|---|---|
| HGIN-019-1901 | SUICIDAL IDEATION / SUICIDAL IDEATION | 4 | 167 | No |
| HGIN-026-2603 | SUICIDAL IDEATION / SUICIDAL IDEATION | 4 | 135 | No |
| HGIN-030-3001 | SUBJECT IS EXPERIENCING SYMPTOMS OF DELUSIONS, AUDITORY AND VISUAL HALLUCINATIONS, AND SUICIDAL IDEATIONS SUBJECT WILL BE HOSPITALIZED FOR STABILIZATION ON TRADITIONAL MEDICATION | 4 | 51 | No |
| HGIN-930-9307 | SUICIDE ATTEMPT / SUICIDE ATTEMPT | 2 | 59 | No |
| HGIU-001-0108 | ALCOHOL POISONING / ETOH INTOXICATION. LSS: ON (b) (6), NEARLY SIX MONTHS AFTER STARTING STUDY DRUG, THE PATIENT WAS ADMITTED TO THE HOSPITAL WITH ALCOHOL ("ETOH") POISONING. THE PATIENT WAS RECEIVING 15MG OLANZAPINE AT THE TIME OF THE EVENT. THIS WAS THE FIRST PSYCHIATRIC HOSPITALIZATION FOR THIS 14-YEAR OLD WHO WAS BROUGHT TO THE EMERGENCY ROOM (ER) BY POLICE AFTER THE PATIENT BECAME INTOXICATED, VOICED SUICIDAL IDEATION, AND PASSED OUT AT SCHOOL. APPROXIMATELY (b) (6) (A WEEK AND A HALF A GO), THE PATIENT TRIED TO JUMP OUT OF HER MOTHER'S MOVING VEHICLE AT 55 MILES PER HOUR, BUT THE MOTHER PREVENTED HER FROM FALLING OUT. | 3 | 157 | No |

| Patient ID (Study-Inv-Patient) | Brief Description of Event | Code | Days to Event | Fatal? |
|---|---|---|---|---|
| HGIU-012-1206 | INTENTIONAL SELF-INJURY / SELF-INFLICTED CUT MARKS ON FOREARM | 5 | 22 | No |
| HGIU-012-1211 | SUICIDAL IDEATION / SUICIDAL IDEATION | 4 | 14 | No |
| HGIU-012-1212 | THE PATIENT HAD BEEN DRAWING PICTURES OF HOW THE PATIENT COULD DIE . . . THE PATIENT COULD NOT ASSURE THE INVESTIGATOR THAT SHE WOULDN'T HARM HERSELF. | 4 | 34 | No |
| HGIU-013-1301 | SUICIDAL IDEATION / OCCASIONAL SUICIDAL THOUGHTS | 4 | 71 | No |
| HGIU-013-1310 | INTENTIONAL SELF-INJURY / SELF INJURY | 5 | 64 | No |
| HGIU-020-2016 | SUICIDE ATTEMPT / ATTEMPTED SUICIDE | 2 | 214 | No |
| HGIU-026-2604 | SELF INJURIOUS BEHAVIOUR / SELF-INJURIOUS BEHAVIOR. LSS: THE PATIENT REPORTED THAT HIS DEPRESSION WORSENED APPROXIMATELY ONE WEEK PRIOR ( (b) (6). ADDITIONALLY HE BEGAN FEELING SUICIDAL (WITHOUT PLAN) APPROXIMATELY THREE DAYS PRIOR ( (b) (6). THE PATIENT'S MOTHER CALLED THE SITE TO REPORT THAT THE PATIENT HAD CUT HIMSELF THE PRIOR EVENING AND DIDN'T FEEL SAFE. THE PATIENT WAS BROUGHT TO THE HOSPITAL FOR SAFETY AND STABILIZATION. | 4 | 59 | No |

| Patient ID (Study-Inv-Patient) | Brief Description of Event | Code | Days to Event | Fatal? |
|---|---|---|---|---|
| HGIU-026-2605 | THE PATIENT WAS BEHAVING INAPPROPRIATELY AND WAS ON THE ROOF OF HIS HOME REFUSING TO COME DOWN | 9 | 53 | No |
| HGIU-026-2606 | SUICIDAL IDEATION / SUICIDAL IDEATION | 4 | 35 | No |
| HGIU-027-2705 | INTENTIONAL SELF-INJURY / SELF-INFLICTED SUPERFICIAL LACERATIONS | 5 | 76 | No |
| HGIU-028-2805 | SUICIDAL IDEATION / SUICIDAL IDEATION. LSS: THE PATIENT'S MOTHER CALLED THE INVESTIGATOR'S SITE ON 14-MAY-2004 TO STATE THAT HER DAUGHTER HAD BECOME SUICIDAL WITH A PLAN TO OVERDOSE ON LORAZEPAM (ATIVAN) DURING THE LAST WEEK OF MAY 2004, BUT ENDED UP TELLING HER PARENTS THE EVENING OF 09-MAY-2004. | 3 | 108 | No |
| HGIU-730-7302 | SUICIDAL IDEATION / PASSIVE SUICIDAL IDEATION | 4 | 177 | No |
| HGMP-003-0304 | EXACERBATION OF BIPOLAR ILLNESS WITH POSITIVE SUICIDAL IDEATION | 4 | 29 | No |
| HGMP-008-0805 | INTENTIONAL SELF-INJURY, CUTTING LEFT ARM | 5 | 93 | No |
| LOAY-400-4001 | PATIENT IS IN A DEPRESSIVE MOOD AROUND 10-11.05.99 AND EXPRESSES SUICIDALTHOUGHTS, SIGNIFICANTLY SLOWED MOVEMENT. | 4 | 44 | No |
| LOAY-401-4012 | SELF-INJURIOUS BEHAVIOR, SELF-INJURY | 5 | 16 | No |
| LOAY-407-4077 | SELF INJURIOUS BEHAVIOR, SELF-INFLICTING TENDENCIES | 5 | 55 | No |

| Patient ID (Study-Inv-Patient) | Brief Description of Event | Code | Days to Event | Fatal? |
|---|---|---|---|---|
| LOAY-407-4078 | SUICIDAL IDEATION, ACUTE SUICIDAL TENDENCIES | 4 | 4 | No |
| LOAY-413-4150 | SUICIDAL IDEATION, SUICIDAL TENDENCY | 4 | 27 | No |

## 10.9 Laboratory Evaluations – Mean Change from Baseline to Endpoint

### Table 10.9.1 Sponsor's Table. Mean Change from Baseline to Endpoint: HGIN + HGIU Acute Database

Table 2.7.4.33. Laboratory Evaluations
Mean Change from Baseline to Endpoint
Acute Placebo-Controlled Combined Database

| Laboratory Evaluations | Unit | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| HEMATOCRIT | 1 | Olz | 174 | 0.43 | 0.03 | -0.01 | 0.03 | -0.01 | -0.01 | <.001 |
| | | Placebo | 87 | 0.43 | 0.04 | -0.00 | 0.03 | -0.00 | | |
| HEMOGLOBIN | mmol/L-F | Olz | 174 | 8.93 | 0.78 | -0.30 | 0.47 | -0.30 | -0.22 | <.001 |
| | | Placebo | 87 | 8.93 | 0.83 | -0.08 | 0.41 | -0.07 | | |
| ERYTHROCYTE COUNT | TI/L | Olz | 174 | 5.00 | 0.39 | -0.15 | 0.27 | -0.15 | -0.11 | .002 |
| | | Placebo | 87 | 4.99 | 0.49 | -0.04 | 0.26 | -0.04 | | |
| MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC) | mmol/L-F | Olz | 174 | 20.87 | 0.92 | -0.00 | 0.76 | 0.02 | 0.16 | .100 |
| | | Placebo | 87 | 21.00 | 0.79 | -0.17 | 0.73 | -0.14 | | |
| LEUKOCYTE COUNT | GI/L | Olz | 174 | 7.27 | 1.92 | -0.19 | 1.86 | -0.10 | -0.32 | .201 |
| | | Placebo | 87 | 7.18 | 1.91 | 0.14 | 1.99 | 0.21 | | |
| NEUTROPHILS, SEGMENTED | GI/L | Olz | 174 | 4.22 | 1.59 | -0.13 | 1.67 | -0.06 | -0.29 | .203 |
| | | Placebo | 87 | 4.29 | 1.48 | 0.17 | 1.79 | 0.23 | | |
| LYMPHOCYTES | GI/L | Olz | 174 | 2.38 | 0.66 | -0.09 | 0.49 | -0.06 | -0.07 | .297 |
| | | Placebo | 87 | 2.24 | 0.60 | -0.02 | 0.51 | 0.01 | | |
| MONOCYTES | GI/L | Olz | 174 | 0.43 | 0.14 | 0.02 | 0.17 | 0.01 | 0.01 | .544 |
| | | Placebo | 87 | 0.41 | 0.16 | 0.01 | 0.17 | 0.00 | | |

| Laboratory Evaluations | Unit | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| EOSINOPHILS | GI/L | Olz | 174 | 0.20 | 0.21 | 0.01 | 0.16 | 0.01 | 0.04 | .042 |
| | | Placebo | 87 | 0.19 | 0.14 | -0.02 | 0.10 | -0.03 | | |
| BASOPHILS | GI/L | Olz | 174 | 0.05 | 0.03 | -0.01 | 0.03 | -0.01 | -0.01 | .008 |
| | | Placebo | 87 | 0.05 | 0.03 | 0.00 | 0.03 | 0.00 | | |
| MEAN CELL VOLUME (MCV) | fL | Olz | 174 | 85.96 | 4.66 | -0.25 | 2.53 | -0.02 | -0.97 | .005 |
| | | Placebo | 87 | 85.76 | 4.59 | 0.72 | 2.78 | 0.95 | | |
| PLATELET COUNT | GI/L | Olz | 173 | 291.08 | 68.65 | 1.26 | 46.42 | 2.44 | 5.09 | .339 |
| | | Placebo | 87 | 286.54 | 63.84 | -4.68 | 52.18 | -3.66 | | |
| LYMPHOCYTES, ATYPICAL | GI/L | Olz | 1 | 0.06 | | 0.03 | | 0.03 | | |
| UA-SPECIFIC GRAVITY | NO UNIT | Olz | 156 | 1.02 | 0.01 | -0.00 | 0.01 | -0.00 | -0.00 | .292 |
| | | Placebo | 72 | 1.02 | 0.01 | -0.00 | 0.01 | -0.00 | | |
| AST/SGOT | U/L | Olz | 175 | 24.53 | 29.87 | 6.43 | 26.41 | 9.89 | 8.91 | .002 |
| | | Placebo | 87 | 23.63 | 8.46 | -2.47 | 7.51 | 0.98 | | |
| ALT/SGPT | U/L | Olz | 175 | 24.13 | 45.95 | 19.95 | 54.84 | 28.11 | 22.98 | <.001 |
| | | Placebo | 87 | 20.39 | 13.05 | -3.08 | 11.69 | 5.13 | | |
| CREATINE PHOSPHOKINASE | U/L | Olz | 175 | 141.28 | 138.78 | -7.31 | 131.11 | 2.81 | 16.06 | .376 |
| | | Placebo | 87 | 164.36 | 160.04 | -23.62 | 152.22 | -13.25 | | |

| Laboratory Evaluations | Unit | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| ALKALINE PHOSPHATASE | U/L | Olz | 175 | 152.33 | 82.35 | -1.35 | 25.61 | -2.74 | 2.57 | .396 |
| | | Placebo | 87 | 138.67 | 86.92 | -3.97 | 16.63 | -5.31 | | |
| GGT (GGPT/SGGT/YGGT) | U/L | Olz | 175 | 18.99 | 12.31 | 7.47 | 20.02 | 7.73 | 7.89 | <.001 |
| | | Placebo | 87 | 17.68 | 8.49 | -0.43 | 5.96 | -0.16 | | |
| THYROID STIMULATING HORMONE | mU/L | Olz | 6 | 2.73 | 2.32 | 0.11 | 1.02 | -0.12 | | |
| UREA NITROGEN | mmol/L | Olz | 175 | 4.40 | 1.18 | 0.22 | 1.18 | 0.14 | 0.39 | .010 |
| | | Placebo | 87 | 4.37 | 1.06 | -0.17 | 1.05 | -0.25 | | |
| CREATININE | umol/L | Olz | 175 | 93.29 | 14.47 | -2.90 | 9.85 | -2.07 | -1.80 | .147 |
| | | Placebo | 87 | 95.83 | 12.43 | -1.08 | 8.56 | -0.27 | | |
| CALCIUM | mmol/L | Olz | 175 | 2.48 | 0.08 | -0.03 | 0.09 | -0.03 | -0.02 | .215 |
| | | Placebo | 87 | 2.50 | 0.12 | -0.01 | 0.10 | -0.02 | | |
| SODIUM | mmol/L | Olz | 175 | 141.70 | 2.27 | -0.05 | 2.83 | -0.12 | 0.49 | .190 |
| | | Placebo | 87 | 141.78 | 2.44 | -0.53 | 2.94 | -0.61 | | |
| POTASSIUM | mmol/L | Olz | 175 | 4.32 | 0.33 | -0.04 | 0.36 | -0.07 | 0.04 | .462 |
| | | Placebo | 87 | 4.41 | 0.42 | -0.07 | 0.41 | -0.10 | | |
| ALBUMIN | g/L | Olz | 175 | 45.07 | 3.75 | -2.01 | 3.20 | -2.13 | -1.70 | <.001 |
| | | Placebo | 87 | 45.39 | 3.03 | -0.31 | 2.90 | -0.43 | | |

| Laboratory Evaluations | Unit | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| GLUCOSE, FASTING | mmol/L | Olz | 135 | 4.89 | 0.55 | 0.15 | 0.58 | 0.15 | 0.31 | <.001 |
| | | Placebo | 64 | 4.98 | 0.57 | -0.16 | 0.56 | -0.17 | | |
| GLUCOSE, NON-FASTING | mmol/L | Olz | 141 | 5.04 | 0.83 | 0.17 | 1.13 | 0.12 | 0.15 | .374 |
| | | Placebo | 73 | 5.01 | 0.79 | 0.03 | 1.23 | -0.03 | | |
| URIC ACID | umol/L | Olz | 175 | 331.18 | 74.27 | 25.21 | 51.54 | 30.87 | 26.95 | <.001 |
| | | Placebo | 87 | 329.40 | 84.01 | -1.86 | 53.02 | 3.92 | | |
| CHOLESTEROL | mmol/L | Olz | 175 | 4.17 | 0.83 | 0.34 | 0.59 | 0.33 | 0.37 | <.001 |
| | | Placebo | 87 | 4.15 | 0.85 | -0.03 | 0.63 | -0.04 | | |
| TRIGLYCERIDES | mmol/L | Olz | 175 | 1.18 | 0.66 | 0.33 | 0.91 | 0.30 | 0.38 | <.001 |
| | | Placebo | 87 | 1.25 | 0.73 | -0.05 | 0.62 | -0.07 | | |
| LDL CHOLESTEROL | mmol/L | Olz | 175 | 2.42 | 0.74 | 0.16 | 0.52 | 0.14 | 0.17 | .016 |
| | | Placebo | 87 | 2.37 | 0.76 | -0.01 | 0.53 | -0.02 | | |
| BILIRUBIN, TOTAL | umol/L | Olz | 175 | 7.84 | 5.27 | -1.73 | 3.82 | -2.21 | -2.52 | <.001 |
| | | Placebo | 87 | 8.56 | 5.33 | 0.78 | 5.96 | 0.31 | | |
| BILIRUBIN, DIRECT | umol/L | Olz | 175 | 1.84 | 1.07 | -0.33 | 1.07 | -0.36 | -0.38 | .005 |
| | | Placebo | 87 | 2.01 | 1.08 | 0.05 | 0.93 | 0.02 | | |
| HDL CHOLESTEROL-DEXTRAN PRECIP. | mmol/L | Olz | 175 | 1.22 | 0.31 | 0.03 | 0.23 | 0.02 | 0.03 | .331 |

| Laboratory Evaluations | Unit | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| HDL CHOLESTEROL-DEXTRAN PRECIP. | mmol/L | Placebo | 87 | 1.21 | 0.25 | -0.00 | 0.25 | -0.01 | | |
| PROLACTIN | ug/L | Olz | 163 | 14.06 | 9.92 | 11.44 | 14.52 | 10.51 | 11.66 | <.001 |
| | | Placebo | 80 | 14.95 | 11.86 | -0.16 | 10.69 | -1.15 | | |
| HEMOGLOBIN A1C | 1 | Olz | 6 | 0.05 | 0.00 | -0.00 | 0.00 | -0.00 | 0.00 | .741 |
| | | Placebo | 3 | 0.05 | 0.01 | -0.00 | 0.00 | -0.00 | | |

## 10.10 Prolactin Analysis by Gender

Table 10.10.1. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: HGIU + HGIN Acute Database.

| Laboratory Evaluations | Gender | Therapy | N | Baseline Mean | Baseline Std | Change to Endpoint Mean | Change to Endpoint Std | LSMean Change | LSMean Difference | *P-value | **P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PROLACTIN | Female | Olz | 63 | 15.87 | 10.06 | 15.63 | 16.86 | 14.26 | 14.25 | <.001 | .236 |
| | | Placebo | 37 | 15.25 | 7.59 | 1.35 | 9.20 | 0.00 | | | |
| | Male | Olz | 100 | 12.92 | 9.71 | 8.80 | 12.20 | 8.70 | 10.12 | <.001 | |
| | | Placebo | 43 | 14.70 | 14.67 | -1.46 | 11.78 | -1.42 | | | |

## 10.11 Vital Signs – Mean Change from Baseline to Endpoint

Table 10.11.1 Vital Signs, Weight, Height and BMI - Mean Change from Baseline to Endpoint (LOCF). HGIN + HGIU Acute Database

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Vital Signs | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Difference | *P-value |
| Systolic Blood Pressure - Supine | Olz | 177 | 111.52 | 10.95 | 2.94 | 10.57 | 1.73 | 3.66 | .009 |
| | Placebo | 89 | 112.79 | 13.18 | -0.71 | 10.90 | -1.93 | | |
| Systolic Blood Pressure - Standing | Olz | 177 | 113.33 | 12.25 | 3.14 | 12.06 | 2.16 | 1.94 | .225 |
| | Placebo | 89 | 112.18 | 13.25 | 1.22 | 12.51 | 0.23 | | |
| Systolic Blood Pressure - Orthostatic | Olz | 177 | -1.81 | 9.63 | -0.20 | 11.68 | -0.43 | 1.72 | .262 |
| | Placebo | 89 | 0.61 | 8.33 | -1.93 | 11.83 | -2.15 | | |
| Diastolic Blood Pressure - Supine | Olz | 177 | 67.71 | 9.27 | 1.24 | 9.74 | 1.56 | 2.17 | .095 |
| | Placebo | 89 | 68.19 | 8.53 | -0.92 | 10.27 | -0.61 | | |
| Diastolic Blood Pressure - Standing | Olz | 177 | 72.86 | 10.12 | 1.42 | 10.25 | -0.24 | 2.73 | .033 |
| | Placebo | 89 | 73.56 | 9.48 | -1.28 | 9.14 | -2.97 | | |
| Pulse - Supine | Olz | 177 | 73.88 | 11.40 | 7.07 | 13.99 | 7.55 | 7.71 | <.001 |
| | Placebo | 89 | 74.15 | 12.81 | -0.60 | 12.04 | -0.16 | | |
| Pulse - Standing | Olz | 177 | 83.77 | 12.73 | 6.97 | 14.83 | 6.55 | 7.90 | <.001 |
| | Placebo | 89 | 85.55 | 12.98 | -0.89 | 14.69 | -1.35 | | |
| Pulse - Orthostatic | Olz | 177 | 9.89 | 11.23 | -0.11 | 13.37 | -1.01 | 0.19 | .914 |
| | Placebo | 89 | 11.40 | 11.15 | -0.29 | 13.09 | -1.19 | | |

| | | | Baseline | | Change to Endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Vital Signs | Therapy | N | Mean | Std | Mean | Std | LSMean Change | LSMean Difference | *P-value |
| Temperature in Centigrade | Olz | 177 | 36.57 | 0.44 | -0.03 | 0.49 | -0.03 | -0.03 | .695 |
| | Placebo | 88 | 36.58 | 0.42 | -0.00 | 0.49 | -0.00 | | |
| Weight in Kg | Olz | 177 | 66.03 | 17.93 | 3.90 | 2.72 | 3.68 | 3.66 | <.001 |
| | Placebo | 88 | 67.63 | 17.24 | 0.24 | 2.16 | 0.01 | | |
| Height in cm | Olz | 177 | 165.84 | 10.13 | 0.48 | 1.22 | 0.46 | 0.18 | .235 |
| | Placebo | 88 | 167.59 | 9.67 | 0.31 | 1.01 | 0.28 | | |
| Body Mass Index | Olz | 177 | 23.91 | 6.01 | 1.22 | 1.01 | 1.11 | 1.17 | <.001 |
| | Placebo | 88 | 23.98 | 5.67 | 0.05 | 0.91 | -0.07 | | |

## 10.12 Potentially Clinically Significant Definitions for Safety Analyses

**Table 2.7.4.6. Criteria for Identifying Patients with Potentially Clinically Significant Changes in Vital Signs and Weight**

| Parameter | Low | High |
|---|---|---|
| Orthostatic hypotension (mm Hg) | ≥20 mm Hg decrease in systolic BP (supine to standing) and ≥10 bpm increase in pulse (supine to standing) | -- |
| Supine systolic BP (mm Hg) | ≤90 and decrease ≥20 | ≥180 and increase ≥20 |
| Standing systolic BP (mm Hg) | ≤90 and decrease ≥20 | ≥180 and increase ≥20 |
| Supine diastolic BP (mm Hg) | ≤50 and decrease ≥15 | ≥105 and increase ≥15 |
| Standing diastolic BP (mm Hg) | ≤50 and decrease ≥15 | ≥105 and increase ≥15 |
| Supine pulse (bpm) | <50 and decrease ≥15 | >120 and increase ≥15 |
| Standing pulse (bpm) | <50 and decrease ≥15 | >120 and increase ≥15 |
| Temperature (°F)[a] | -- | ≥101°F and increase ≥2 |
| Weight (kg) | decrease ≥7% | increase ≥7% |

## 10.13 Postmarketing Reports - Fatalities

Table 10.13.1. Postmarketing Reports – Fatalities

| Patient Identifier | Date of Death | Dose/Duration | Event | Concom Rx | Comments |
|---|---|---|---|---|---|
| BR200605002130<br>16 YOM | (b) (6) | 7.5 mg<br>10/05 - (b) (6) | Sudden death, cardiac arrest, prescribed overdose, suicide attempt, depression, psychosis | Alprazolam | Brazil<br>Autopsy done, result will be available by June 2006 (per summary) |
| BE200602002031<br>17 YOF | (b) (6) | Unknown<br>~6 years | Bilateral pneumonia, gastric hemorrhagia, fever, coma | Not reported | Belgium<br>(no autopsy) |
| US_0510123183<br>14 YO | (b) (6) | Unknown | Toxic exposure, completed suicide | Fluoxetine<br>Risperidone | Literature |
| JP_051007889<br>17 YOM | (b) (6) | 5 mg, 8/2005 –<br>(b) (6) | Completed suicide, suicidal ideation, apathy | Lorazepam | Japan<br>"Police told psychiatrist about patient's death, no details provided" [prior suicide attempt per hx] |
| CA_050708496<br>17 YOM | (b) (6) | 15 mg 11/03 –<br>(b) (6) | Completed suicide | Lorazepam<br>Flupentixol decanoate | Canada<br>5 days after discontinuing olanzapine, committed suicide (method unknown)<br>Not known whether autopsy performed. |
| US_0506118439<br>17 YOF | Unknown<br>(b) (6)<br>estimated | Unknown,<br>7/1999 - 2004 | Death, weight increased, diabetes mellitus, hyperglycemia, multiple drug overdose, triglycerides increased, cholesterol abnormal, musculoskeletal chest pain | | Reported by attorney via legal department |
| EWC050644285<br>17 YOF | (b) (6) | 5 mg 3/5/05 –<br>(b) (6) | Endotoxic shock, kidney infection, sepsis, acute abdomen, disseminated intravascular blood coagulation, myeloid hyperplasia of spleen, pancreatitis, gastric | | Russian Federation |

| | | | | | |
|---|---|---|---|---|---|
| | | | ulcer perforation, peritoneal infection | | |
| US_0506118189<br>15 YOM | Unknown<br>(b) (6)<br>estimated | ~ May 2003 - unknown | Death | | Reported by an attorney via the legal department<br>Cause of death not provided |
| CA_050207717<br>16 YOM | (b) (6) | Unknown | Completed suicide | Isotretinoin mepha | Canada<br>No details provided |
| US_0412108962<br>16 YOM | Unknown<br>(b) (6)<br>estimated | 1-2002 – unknown | Death, diabetes mellitus | | Reported by an attorney via the legal department<br>Cause of death not provided, not known if autopsy performed |
| JP_041105122<br>17 YOF | (b) (6) | 50 mg<br>11/10/2004 –<br>(b) (6) | Intentional overdose, completed suicide | Paroxetine, sulpiride, amoxapine, fluvoxamine, flunitrazepam | Japan<br>"Coroner refused to provide any information" |
| USA040979162<br>US_0402100550<br>15 YOM | (b) (6) | 10/29/2003? | Death, coma<br><br>Accidental overdose, drug toxicity, intentional drug misuse | Metronidazole, topiramate, clonazepam | Reported by an attorney via the legal department<br>Case reported in a newspaper<br>"Patient was sold olanzapine by another individual, not prescribed"<br>Olanzapine Cp = 490 ng/ml postmortem |
| US_0412109585<br>15 YOF | (b) (6) | 11/2000 - unk | Diabetic ketoacidosis, diabetic coma, diabetes mellitus, pain, anxiety, drug ineffective | Methylphenidate, sertraline | Reported to company by an attorney<br>No details provided about the event, unknown if an autopsy was performed |
| EWC031237179<br>16 YOM | (b) (6) | 5 mg,<br>11/24/2003 –<br>(b) (6) | Death, pulmonary infarction | | Greece<br>Pulmonary infarction per autopsy |
| USA030742307<br>13 YOF | (b) (6) | 5 mg<br>Unknown | Diabetic ketoacidosis, loss of consciousness, dizziness | | Diabetic ketoacidosis per autopsy. No labs provided. |
| USA030741953<br>17 YOM | (b) (6) | 8/2002 –<br>(b) (6) | Convulsion, heart rate increased | Mixed amphetamine salts, trazodone | Cause of death listed as idiopathic seizure disorder, toxicology screen |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | negative |
| GBS030413039<br>17 YOM | (b) (6) | 12.5 mg<br>10/2002 – unk | Completed suicide, sedation, eczema | Risperidone, biperiden | United Kingdom<br>Death by drowning, autopsy did not reveal other significant findings |
| US_020180581<br>15 YOM | (b) (6) | 20 mg<br>Unknown | Acute asthma | | Patient had been in blinded study 3/01 – 9/01 prior [F1D-US-X090]; did not receive olanzapine; taking marketed olanzapine at time of event. |
| US_010973481<br>17 YOM | Unknown (received by Sponsor (b) (6)) | 30 mg<br>Unknown | Prescribed overdose, drug toxicity | | No details provided, unknown if autopsy performed |
| EWC010928155<br>15 YOM | (b) (6) | 10 mg<br>8/1/2001 – (b) (6) | Death | Dextro-amphetamine | Switzerland<br>Asperger's syndrome<br>Patient drowned while swimming in lake; autopsy unremarkable |
| CA_010603921<br>17 YOF | Unknown (received by Sponsor (b) (6)) | Unknown | Death | Citalopram, valproate semisodium | Canada<br>Patient "died suddenly", autopsy was completed but not available. "Several attempts at follow-up unsuccessful". |
| CA_010603802<br>16 YOM | Unknown (received by Sponsor (b) (6)) | 10 mg<br>90 days | Diabetic coma | Valproate sodium<br>Topiramate | Canada<br>No personal history of diabetes. Weight at time of event unknown, labs not provided. "Numerous attempts to obtain follow-up unsuccessful". |
| US_010566315<br>16 YOM | (b) (6) | 5 mg<br>730 days | Drug interaction, death, hepatic steatosis | Mixed amphet-Amine salts | Patient found dead. Hepatic steatosis per autopsy, no cause of death provided. Autopsy never provided. |
| US_010158510<br>17 YOM | (b) (6) | 2.5 mg<br>Unknown | Accidental overdose | Citalopram, trazodone | Patient found dead by family member. Cause of death presumed |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | overdose. Olanzapine Cp = 158 ng/ml. |
| US_000542556<br>15 YOM | (b) (6) | Unknown<br>1998 x 120 days | Necrotizing pancreatitis, diabetes mellitus, increased cholesterol | Carbamazepine, paroxetine | Follow-up in the literature |
| US_000236591<br>17 YOM | (b) (6) | 22.5 mg<br>Unknown | Overdose, death | Fluoxetine, valproate semisodium, nortriptyline, buspirone, haloperidol, thioridazine | Patient died while being restrained by staff in group home. |
| US97121702A<br>14 YOM | (b) (6) | 12.5 mg<br>150 days | Asphyxia, agitation | Haloperidol, sertraline | Became agitated on school bus and was restrained and died. Per coroner, cause of death by mechanical asphyxia due to the restraining position. |

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/s/
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Cara Alfaro
4/6/2007 10:42:11 AM
PHARMACIST

Ni Aye Khin
4/18/2007 11:20:56 AM
MEDICAL OFFICER
I agree with Dr. Alfaro's recommendation that this application be considered for non-approval; see memo to file for additional comments.

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**020592 / S-035, 039, 040, 041, 049,053, 055**

**021086 / S-21, 031, 032, 034**

**021253 / S-037, 039, 043**

## 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

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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/s/
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Janice Brown
3/8/2007 11:18:32 AM
CHEMIST

Jim Vidra
3/9/2007 11:28:22 AM
CHEMIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
OFFICE OF NEW DRUG QUALITY ASSESSMENT

# POST-MARKETING EVALUATION
# CMC ASSESSMENT FORM

| APPLICANT: LILLY | NDA NUMBER: 020592 020592 | DOC TYPE: SE5 SE5 | SEQ NUMBER: 040 041 | SUBMISSION TYPE: ORIGINAL |
|---|---|---|---|---|

| PROPRIETARY NAME: ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ | ESTABLISHED NAME: OLANZAPINE |
|---|---|

| DOSAGE FORM: TAB | STRENGTH/POTENCY: 2.5; 5; 7.5; AND 10 MG | PHARMACOLOGICAL CATEGORY: |
|---|---|---|

| LETTER DATE: 10/30/2006 | STAMP DATE: 10/31/2006 | PDUFA GOAL DATE: 4/30/2007 | 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: fullfillment of FDA's request for pediatric studies. 11/15/06 amendment to includes the Environmental Assessment for both Zyprexa indications and request a waiver from the requirement in the new Physicians Labeling Rule that the Highlights section of labeling in the PLR format be limited to one-half page.

BUNDLED: No

CHANGE CATEGORY: Efficacy Supplement

| LABELING INVOLVED: Yes - PI only | PAT: No | COMPARABILITY PROTOCOL: No | PHASE 4 COMMITMENT: Np |
|---|---|---|---|

REVIEW PATH: 6 - OND Multi-Discipline Review

CONSULTS: NA

JUSTIFICATION/COMMENTS: 1/12/2007 - BROWNJA

1. The applicant has requested a categorical exclusion from submitting an environmental assessment for the use of Zyprexa in the treatment of schizophrenia. The active ingredient in Zyprexa is olanzapine and the expected concentration of olanzapine at the point of entry into the aquatic environment would be (b) (4) or less which is less than 1 part per billion ( 1μg/L) which qualifies for a categorical exclusion as described in 21 CFR 25.31(b). The applicant has also stated that there are no extraordinary circumstances known to exist for this proposed action. The applicant's request for a categorical exclusion is granted.

2. There are no CMC labeling changes.

3. From a CMC standpoint, this supplement can be approved.

PAL ACTION: Recommend Approval

BRANCH CHIEF: James Vidra

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/s/

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Janice Brown
1/17/2007 02:49:46 PM
CHEMIST

Jim Vidra
1/17/2007 03:50:48 PM
CHEMIST

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**020592 / S-035, 039, 040, 041, 049,053, 055**

**021086 / S-21, 031, 032, 034**

**021253 / S-037, 039, 043**

# STATISTICAL REVIEW(S)

# Addendum

| | |
|---|---|
| **NDA/Serial Number:** | 20-592 |
| **Drug Name:** | Olanzapine |
| **Indication(s):** | Schizophrenia for Adolescents |
| **Applicant:** | Eli Lilly and Company |
| **Date(s):** | December 29, 2006 |
| **Review Priority:** | Priority |
| | |
| **Biometrics Division:** | Division of Biometrics I |
| **Statistical Reviewer:** | Fanhui Kong, PhD |
| **Concurring Reviewers:** | Peiling Yang, H. M. James Hung |
| | |
| **Medical Division:** | Division of Psychiatry Products |
| **Clinical Team:** | Cara Alfaro, Mitchell Mathis, Thomas Laughren |
| **Project Manager:** | Doris J. Bates |

## 1. BACKGROUND

Reference is made to Statistical Review of NDA 20592 submitted to DFS on April 6, 2007.

In this NDA submission, the sponsor conducted 2 pivotal short-term olanzapine studies HGIN and HGIU on adolescent patients, one (HGIU) for the treatment of Mania in Bipolar I Disorder and the other (HGIN) is for the treatment of schizophrenia. These studies were reviewed in the Statistical Review. The primary efficacy endpoint for Study HGIN was the change from baseline to Endpoint of BRPS-C total score and the primary statistical analysis was the ANCOVA procedure using LOCF for missing data. The sponsor provided the efficacy analysis results for LOCF, along with that of OC and MMRM.

In the statistical review that I submitted, with the data sets provided by the sponsor, the corresponding analysis results were also given. They are given in Table 1.

**Table 1.1: Treatment Effects on the Change from Baseline of Primary Efficacy Measures at the Endpoint in Studies HGIN --- ITT Population**

| | Placebo | Olanzapine |
|---|---|---|
| **Study HGIN** | (N=35) | (N=72) |
| **N (Analysis population)** | 35 | 72 |
| **N (BPRS-C Total Score)** | 35 | 72 |
| Baseline Mean | 50.1 | 50.3 |
| Median change from baseline | -9.3 | -19.4 |
| **ANCOVA Analysis (LOCF)** | | |
| LS Mean change from baseline (SE) [a] | -9.1 (2.73) | -19.3 (1.91) |
| Difference between LS Means and C.I.[a] | -10.1 (-16.7, -3.5) | |
| P-value [a] | 0.003 | |
| **MMRM Analysis** | | |
| LS Mean change from baseline (SE) [b] | -23.5 (3.06) | -24.7 (1.70) |
| Difference between LS Means and C.I.[b] | -1.25 (-8.11, 5.61) | |
| P-value [b] | 0.72 | |
| **OC Analysis** | | |
| **N (BPRS-C Total Score)** | 15 | 50 |
| LS Mean change from baseline (SE) [c] | -24.1 (3.35) | -24.4 (1.82) |
| Difference between LS Means and C.I.[c] | -0.25 (-7.9, 7.4) | |
| P-value [b] | 0.95 | |

a: Test for no difference between treatments at the endpoint from ANCOVA model with treatment and country as factors and baseline efficacy measure as covariate.
b: Test for no difference between treatments at the endpoint from MMRM model with treatment, country, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.
c: Test for no difference between treatments at the endpoint from OC model with treatment and country as factors and baseline efficacy measure as covariate.
Note: Negative change in score indicates improvement.

Source: Table 3.7 in Statistical Review

Due to the contradictory results between LOCF, MMRM and OC, I suggested that this study did not support the claim of the effectiveness of Olanzapine on the adolescents with schizophrenia.

## 2. CORRECTIONS

The MMRM analysis was conducted based on the default variance-covariance structure of Variance Components in SAS software package, which requires the independence between the repeated observations for any subject. In fact, the choice of the variance-covariance structure affects the estimate of treatment effect as well as its significance levels dramatically. Usually, the Unstructured variance-covariance matrix is used for MMRM analysis. In order to see which variance-covariance structure gives a better fit for the data, I applied the MMRM procedure using several different variance-covariance structures and gave the corresponding results along with the AIC values. The AIC values are generally used as a goodness-of-fit criterion of the model. The smaller the AIC value is, the better the model seems to fit the data. These results are depicted in Table 2.1

**Table 2.1 MMRM Analysis Results Using Different Variance-Covariance Structure in Study HGIN**

| Variance-covariance Structure | Placebo | Olanzapine | AIC |
|---|---|---|---|
| **Variance Components** | | | |
| LS Mean change from baseline (SE) | -24.1 (3.13) | -24.5 (1.73) | |
| Difference between LS Means and C.I. | -0.43 (-6.6,7.5) | | |
| P-value | 0.90 | | 4691 |
| **Unstructured** | | | |
| LS Mean change from baseline (SE) | -12.6 (2.99) | -21.5 (1.97) | |
| Difference between LS Means and C.I. | -8.9 (-16.0, -1.9) | | |
| P-value | 0.015 | | 4055.2 |
| **Compound Symmetry** | | | |
| LS Mean change from baseline (SE) | -17.8 (2.61) | -22.9 (1.60) | |
| Difference between LS Means and C.I. | -5.1 (-11.1, 0.9) | | |
| P-value | 0.10 | | 4353.0 |
| **Toeplitz** | | | |
| LS Mean change from baseline (SE) | -14.3 (2.68) | -21.9 (1.65) | |
| Difference between LS Means and C.I. | -7.67 (-13.8, -1.5) | | |
| P-value | 0.015 | | 4129.0 |
| **Toeplitz with Two Bands** | | | |
| LS Mean change from baseline (SE) | -21.7 (2.70) | -24.4 (1.53) | |
| Difference between LS Means and C.I. | -2.68 (-8.8, 3.4) | | |
| P-value | 0.39 | | 4356.0 |
| **First Order Auto-regression** | | | |
| LS Mean change from baseline (SE) | -15.4 (2.71) | -22.3 (1.64) | |
| Difference between LS Means and C.I. | -7.0 (-13.8, -0.8) | | |
| P-value | 0.029 | | 4129.0 |

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

Source: Reviewer

In this analysis, country is not used as a factor in the statistical models since it was not prespecified in the protocol. These results indicate that the Unstructured variance-covariance structure in the statistical model seems to give a better fitting. The significance results derived seem to support the claim that Olanzapine improves placebo in treating the adolescents with schizophrenia. Another important observation is that treatment effect estimates and the corresponding p-values are dramatically different for different choices of variance-covariance structure of the repeated observations. This suggests that the efficacy results derived from this model may not be as stable as we expect. Extra care should be exercised in doing such analyses.

**Efficacy analysis for each country.** The subgroup analysis with respect to country is considered as exploratory. In Table 2.2, the nominal p-values for the treatment effects at Endpoint using MMRM procedure are provided for each country using the Unstructured variance-covariance structure model.

**Table 2.2 Treatment Effect by Country by MMRM Analysis**

| Country | Placebo | Olanzapine |
|---|---|---|
| **Russia** | | |
| **N (Number of patients)** | 16 | 34 |
| LS Mean change from baseline (SE) | -5.3 (4.46) | -19.0 (2.73) |
| Difference between LS Means and C.I. | -13.7 (-23.9,3.3) | |
| P-value | 0.012 | |
| **US** | | |
| **N (Number of patients)** | 19 | 35 |
| LS Mean change from baseline (SE) | -18.7 (4.13) | -23.5 (2.89) |
| Difference between LS Means and C.I. | -4.8 (-14.7, -5.1) | |
| P-value | 0.35 | |

Recourse: Reviewer

Based on the above results, treatment effects seem to be more evident in Russia than in US. Given similar number of subjects in these two countries, the estimated treatment effect in Russia is 13.7 US while that of US is only 4.8. The data suggests that the there was a very small placebo effect in Russia while there was a certain placebo effect in US. Careful investigations might be needed to find why this is the case.

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/s/
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Fanhui Kong
4/27/2007 11:50:29 AM
BIOMETRICS

Peiling Yang
4/27/2007 12:04:43 PM
BIOMETRICS

James Hung
4/27/2007 01:54:45 PM
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/Serial Number:** | 20-592 |
| **Drug Name:** | Olanzapine |
| **Indication(s):** | Schizophrenia for Adolescents |
| **Applicant:** | Eli Lilly and Company |
| **Date(s):** | December 29, 2006 |
| **Review Priority:** | Priority |
| | |
| **Biometrics Division:** | Biometrics I (HFD-710) |
| **Statistical Reviewer:** | Fanhui Kong |
| **Concurring Reviewers:** | Peiling Yang, H. M. James Hung |
| | |
| **Medical Division:** | Division of Psychiatry Products |
| **Clinical Team:** | Cara Alfaro, Mitchell Mathis, Thomas Laughrem |
| **Project Manager:** | Doris J. Bates |

**Keywords:** Olanzapine, Adolescent, Schizophrenia, ANCOVA, LOCF, MMRM

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

In this submission, the sponsor conducted 2 pivotal short-term olanzapine studies between November 2002 and May 2005 in the United States, Russia and Puerto Rico. The primary objectives of the studies were to evaluate the efficacy and safety of olanzapine compared with placebo in the treatment of the adolescents (ages 13 to 17) with schizophrenia (Study HGIN) and in the treatment of the adolescents with Mania in Bipolar I Disorder (Study HGIU). The primary efficacy measures were the change from baseline to Endpoint of the BPRS-C total score (Study HGIN) and the change from baseline to Endpoint of the YMRS total score (Study HGIU).

In the two studies, only Study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Study HGIN, however, does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents with schizophrenia. Indeed, the difference between treatment groups only occurred in the patients who dropped out of Period II of the study.

## 1.2 Brief Overview of Clinical Studies

Two pivotal studies were submitted for the evaluation of the efficacy of olanzapine (2.5 to 20mg/day) in the treatment of adolescents (ages 13 to 17) with Schizophrenia (Study HGIN) and adolescents with Mania in Bipolar I Disorder (Study HGIU). The studies were conducted between November 2002 and May 2005 (26 November 2002 to 29 April 2005 for Study HGIN and 18 November 2002 to 9 May 2005 for Study HGIU) in the United States, Russia and Puerto Rico.

Study HGIN was a Phase IV, multicenter, randomized, double-blind, placebo-controlled, flexible dose study in adolescent with schizophrenia, with a 6-week acute period conducted in the Unites States and Russia. The primary objective of this study was to assess the efficacy of olanzapine (2.5 to 20 mg/day) compared to placebo in the treatment of adolescents (ages 13 to 17) with schizophrenia. The primary efficacy measure was the change from baseline to endpoint (up to 6 weeks double-blind treatment) in the anchored version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score.

Study HGIU was a Phase IV, multicenter, randomized, double-blind, placebo-controlled, flexible dose study in adolescents with Mania in Bipolar I Disorder, with an acute double-blind treatment period of 3 weeks in the Unites States and Puerto Rico. The primary objective was to evaluate the efficacy and safety of olanzapine (2.5 to 20mg/day) compared with placebo in adolescents with Mania in Bipolar I Disorder. The primary efficacy measure was the change from baseline to Endpoint of the Adolescent Structured Young-Mania Rating Scale (YMRS) total score.

In Study HGIN, 99 subjects were planned in a 2:1 ratio to have 80% power at the Type I error rate of 0.05 to test a treatment group difference of 7.93, a common standard deviation estimate of 12.15. One hundred and fifteen subjects entered the study. Of these, 107 (72 to olanzapine and 35 to placebo) were randomized and 64 subjects (49 to olanzapine and 15 to placebo) completed the acute phase of the study. Seventy two percent (72%) of the patients were Caucasian and 22% were Africa-Americans. Seventy percent (70%) were male and 30% were female. All the patients were between 13 and 17 years of age (inclusive).

In Study HGIU, 130 to 200 subjects were planned in a 2:1 ratio to have 80% power at the Type I error rate of 0.05 to detect an anticipated treatment group difference of 7.00, a common standard deviation estimate of 12.50. Two hundred and three subjects entered the study. Of these, 161 (107 to olanzapine and 54 to placebo) were randomized and 120 subjects (85 in olanzapine and 35 in placebo) completed the acute phase of the study. Seventy percent (70%) of the patients were Caucasian, 16% Hispanics and 9% were Africa-Americans. More than half were male. All the patients were between 13 and 17 years of age (inclusive).

After the screening and washout period (2 days to 2 weeks for screening and washout), subjects in Study HGIN were treated for 6 weeks, and subjects in Study HGIU were treated for 3 weeks, during a double-blind phase.

### 1.3 Statistical Issues and Findings

In this submission, the sponsor conducted 2 pivotal short-term olanzapine studies. In Study HGIN, the primary efficacy measure was the change from baseline to Endpoint of the BPRS-C total score. In Study HGIU, the primary efficacy measure was the change from baseline to Endpoint of the YMRS total score. The treatment efficacy was analyzed using ANCOVA with LOCF data.

In Study HGIU, the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder is supported by both the primary efficacy results using LOCF, and the results using OC and MMRM. In Study HGIN, however, the efficacy results using OC and MMRM strongly contradict that of the LOCF result. Both the OC and MMRM results are highly nonsignificant. Although LOCF yields highly significant efficacy result, this procedure is reliable only when efficacy measures are stable over the study period. This is not the case in this study. On the other hand, MMRM yields quite reliable result if patient dropout mechanism depends only on the observed data, not on unobserved ones. This seems to be a more reasonable assumption. Indeed, the individual outcome profile plots indicate that most dropouts happened when there were no obvious improvements. On the other hand, both the population mean profile plot and individual profile plot suggest that the difference between treatment groups only occurred in the patients who dropped out before the Endpoint. Together, Study HGIN does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents (ages 13 to 17) with schizophrenia.

## 2. INTRODUCTION

### 2.1 Overview

In this submission, two efficacy studies were submitted for the evaluation of the efficacy and safety of olanzapine in doses from 2.5 to 20 mg/day in the treatment of adolescents (ages 13 to 17) with Schizophrenia (Study HGIN) and adolescents with Mania in Bipolar I Disorder (Study HGIU) (Table 2.1). In the pooled pivotal Studies HGIN and HGIU, a total of 268 subjects were randomized. Of those, 179 subjects were in the olanzapine group (2.5 to 20mg/day) and 89 subjects were in the placebo group. The numbers of subjects in these studies are given in Table 2.1.

**Table 2.1: Studies Supporting the Efficacy of Olanzapine**

| Protocol | Study Description | Study Treatment | No. of Subjects[a] |
|---|---|---|---|
| **Study HGIN** | 6-week, randomized, double-blind, placebo-controlled, multicenter, flexible dose study | Placebo | 35 |
| | | Olanzapine (flexible doses) | 72 |
| **Study HGIU** | 3-week, randomized, double-blind, placebo-controlled, multicenter, flexible dose study | Placebo | 54 |
| | | Olanzapine (flexible dose) | 107 |

a: Includes all subjects who were randomized.
Source: FDA analysis.

## 2.2 Data Sources

The Clinical Study Reports and SAS transport data sets for the studies were provided in electronic form in \\CDSESUB1\N20592\S_040\2006-10-30.

# 3. STATISTICAL EVALUATION

## 3.1 Evaluation of Efficacy

Efficacy studies were designed to evaluate the efficacy and safety of olanzapine compared with placebo in adolescents (ages 13 to 17) with Schizophrenia (Study HGIN) and adolescents with Mania in Bipolar I Disorder (Study HGIU). In both studies, eligible subjects were randomly assigned to receive olanzapine or placebo in a 2:1 ratio (Table 2.1). The subjects received a screening or washout period of 2 to 14 days before randomization. Following randomization, all subjects went through a 6-week (3-week for Study HGIU) double-blind acute period starting with 2.5 or 5mg/day of olanzapine or placebo given once daily. The dose was increased by 2.5 or 5 mg/day dose increments at the investigator's discretion to the maximum tolerable dose, not to exceed 20 mg/day.

In Study HGIN, the primary efficacy measure was the change from baseline to Endpoint of the BPRS-C total score. The secondary measures included CGI-I, CGI-S, PANSS total score and Overt Aggressive Scale (OAS), ECGs, AIMS, CHQ and BACS. In Study HGIU, the primary efficacy measure was the change from baseline to Endpoint of the Y-MRS total score. The secondary measures included Y-MRS individual scores, CGI scale Bipolar Version Severity of Illness, CDRS-R, OAS, EPS, AIMS, CHQ and CGI-S.

Eligible subjects were from 13 to 17 years of age. Patient must have a diagnosis of schizophrenia according to DSM-IV-TR and confirmed by the K-SADS-PL in Study HGIN. Patients were diagnosed as bipolar I disorder and currently displayed an acute manic or mixed episode according to DSM-IV-TR in Study HGIU.

### 3.1.1 Baseline Demographic Characteristics

The patient baseline demographic characteristics are summarized in Tables 3.1 to 3.2 for these two studies. In Study HGIN, the majority of patients were male, Caucasian, and from the United States. The mean age of patients in the study was 16.1 years in the olanzapine treatment group and 16.3 years in the placebo group. There were 71% males and 29% females in the olanzapine group, 69% males and 31% females in the placebo group. In Study HGIU, the majority of patients were Caucasian and from the United States, with a mean age of 15.1 years in the olanzapine group and 15.4 years in the placebo group. There were 57% males and 43% females in the olanzapine group, 44% males and 56% females in the placebo group. Patient demographic characteristics were not significantly different between treatment groups at baseline.

**Table 3.1 Demographic Characteristics for Study HGIN at Baseline of Period II**

| | | Therapy | | |
|---|---|---|---|---|
| | | Olanzapine (N=72) | Placebo (N=35) | |
| Demographic Variables | Statistics/ Category | n (%) | n (%) | *P-value |
| Gender | Male | 51(70.83) | 24(68.57) | .825 |
| | Female | 21(29.17) | 11(31.43) | |
| Age | No. of Patients | 72 | 35 | |
| | Mean | 16.14 | 16.30 | .536 |
| | Median | 16.31 | 17.00 | |
| | Std. Dev. | 1.25 | 1.55 | |
| | Minimum | 13.03 | 13.06 | |
| | Maximum | 17.99 | 18.00 | |
| Origin | African Descent | 17(23.61) | 7(20.00) | .656 |
| | Caucasian | 52(72.22) | 25(71.43) | |
| | Hispanic | 2(2.78) | 1(2.86) | |
| | Other | 1(1.39) | 2(5.71) | |
| Country | America | 38(52.78) | 19(54.29) | 1.00 |
| | Russia | 34(47.22) | 16(45.71) | |

* Frequencies are analyzed using the Fisher's Exact Test

Means are analyzed using a Type III Sum of Squares analysis of variance(ANOVA); Model= Country Therapy

Source: Table HGIN.11.1 of sponsor's HGIN Study Report.

**Table 3.2 Demographic Characteristics for Study HGIU at Baseline Period II**

| Demographic Variables | Statistics/ Category | Olanzapine (N=107) n (%) | Placebo (N=54) n (%) | *P-value |
|---|---|---|---|---|
| Gender | Male | 61(57.01) | 24(44.44) | .137 |
| | Female | 46(42.99) | 30(55.56) | |
| Age | No. of Patients | 107 | 54 | |
| | Mean | 15.14 | 15.38 | .250 |
| | Median | 15.12 | 15.41 | |
| | Std. Dev. | 1.28 | 1.20 | |
| | Minimum | 13.02 | 13.07 | |
| | Maximum | 17.89 | 17.68 | |
| Origin | African Descent | 13(12.15) | 2(3.70) | .247 |
| | Caucasian | 71(66.36) | 41(75.93) | |
| | East/Southeast Asian | 0(0.0) | 1(1.85) | |
| | Hispanic | 18(16.82) | 8(14.81) | |
| | Other | 5(4.67) | 2(3.70) | |
| Country | America | 95(88.79) | 48(88.89) | 1.00 |
| | Puerto Rico | 12(11.21) | 6(11.11) | |

* Frequencies are analyzed using a Fisher's Exact Test

Means are analyzed using a Type III Sum of Squares analysis of variance(ANOVA), Model= Country Therapy

Source: Table HGIU.11.1 of sponsor's HGIN Study Report.

### 3.1.2 Baseline Disease Characteristics

Across the individual studies, the baseline disease characteristics between the treatment and placebo groups were compared.

In Study HGIN, there were no statistically significant differences between the two treatment groups on the age of onset, the number of previous schizophrenia episode, the total cumulative hospitalization in months, the length of current episode in days, the BPRS-C total score and corresponding subtotal scores.

In Study HGIU, The treatment groups differed considerably at baseline on several illness characteristics. Patients in the placebo group had greater numbers of previous manic, depressive, and mixed episodes. Patients in the olanzapine treatment group had much higher baseline scores on the CGI Severity of Depression scale. In addition, the treatment groups differed on several subscales of the CHQ at baseline. Finally, considerably more patients in the olanzapine treatment group reported a paternal history of psychosis and a history of psychiatric hospitalization at baseline. These are depicted in Table 3.3. The different Quality-of-Life scores at baseline in CHQ are given by the sponsor in Table HGIU.11.9 in the Clinical Study Report. A more specific assessment of these differences will be made by the medical officer.

**Table 3.3 Patient Differences in Illness Characteristics and Family History at Baseline in Study HGIU**

| Illness Characteristics | Placebo | Olanzapine | P-value |
|---|---|---|---|
| | (N=54) | (N=106) | |
| **No. Prev. Mania Episode** | 4.43 (8.95)* | 2.07 (4.97) | 0.048 |
| | (N=46) | (N=92) | |
| **No. Prev. Depression Episodes** | 3.98 (8.26) | 1.60 (2.84) | 0.014 |
| | (N=50) | (N=92) | |
| **No. of Prev. Mixed Episodes** | 3.85 (9.40) | 1.19 (3.65) | 0.027 |
| | (N=46) | (N=81) | |
| **CGI Severity Depression** | 2.65 (1.60) | 3.14 (1.57) | 0.043 |
| | N=54 | (N=107) | |
| **Paternal History of Psychosis-Fahter** | 0/51/3† | 8/78/20 | 0.025 |
| | (N=54) | (N=106) | |
| **Paternal History of Hospitalization** | 9/45‡ | 34/72 | 0.040 |
| | (N=54) | (N=106) | |

*Standard Deviation. †Yes/No/Unknown. ‡Yes/No.

Source: Tables HGIU.11.2, HGIU.11.6 in Clinical Study Report.

### 3.1.3 Patient Discontinuation

In Study HGIN, 107 subjects were randomized and 63 (60%) subjects completed the 3-week double-blind phase of the study (Table 3.4), including 49 (32%) subjects from the olanzapine group and 15 (43%) from the placebo group. Lack of efficacy was the most common reason for early termination in both groups. But there was a dramatic difference, which was also statistically significant in nominal sense, between the two treatment groups. In the placebo group, eighteen (51%) patients dropped because of lack of efficacy and the corresponding number for the olanzapine group was 10 (14%).

In Study HGIU, 161 subjects were randomized and 120 (74.5%) completed the 3-week double-blind phase, as shown in Table 3.4. The most common reason for the early withdrawal in both treatment groups was the Lack of Efficacy which had a total of 28 subjects (17.4%). Sixteen (30%) patients dropped out of study because of lack of efficacy in the placebo group and the corresponding number in the olanzapine group was 12 (12%). The difference between the two treatment groups is highly statistically significant in nominal sense (p-value = 0.007).

**Table 3.4 Number (%) of Subjects Who Discontinued Treatment During the Double-Blind Period by Primary Reason for Withdrawal in Studies HGIN and HGIU**

| | Placebo | Olanzapine | Overall |
|---|---|---|---|
| **Study HGIN** | (N=35) | (N=72) | (N=107) |
| **Total withdrawal** | 20 (57.1%) | 23 (31.9%) | 43 (40.2%) |
| **Reason for Withdrawal** | | | |
| Adverse event | 0 | 5 (6.9) | 5 (4.7) |
| Lack of efficacy | 18 (51.4) | 10 (13.9) | 28 (26.2) |
| Patient decision/ Personal conflict | 1 (2.9) | 4 (5.6) | 5 (4.7) |
| Noncompliance | 1 (2.9) | 2 (2.8) | 3 (2.8) |
| Sponsor decision | 0 | 1 (1.4) | 1 (0.9) |
| Lost to follow-up | 0 | 1 (1.4) | 1 (0.9) |
| **Study HGIU** | (N=54) | (N=107) | (N=161) |
| **Total withdrawal** | 19 (35.2%) | 22 (20.1%) | 41 (25.5%) |
| **Reason for Withdrawal** | | | |
| Adverse event | 1 (1.9) | 3 (2.8) | 4 (2.5) |
| Lack of efficacy | 16 (29.6) | 12 (11.2) | 28 (17.4) |
| Patient decision/Personal conflict | 1 (1.9) | 4 (3.7) | 5 (3.1) |
| Non-compliance | 1 (1.9) | 0 | 1 (0.6) |
| Physician decision | 0 | 1 (0.9) | 1 (0.6) |
| Other | 0 | 2 (1.9) | 2 (1.2) |

Source: Tables HGIN.10.1 and HGIU.10.1 – Results in Clinical Study Report.

### 3.1.4 Statistical Issues and Results

According to the protocol, efficacy analyses were performed on an intent-to-treat (ITT) basis. An ITT analysis defines the treatment groups as those to which patients were assigned by random allocation, even if a patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. For each efficacy variable, the analysis included all randomized patients with baseline and post baseline observations. Using LOCF for missing observations, only patients with a baseline and a post baseline measure were to be included in the analysis. 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.

According to the protocol, the null hypothesis for primary analysis was that there was no difference between treatment groups in the mean change from baseline to Endpoint in the BPRS-C total score for Study HGIN (the YMRS total score for Study HGIU). For efficacy analyses, baseline was defined as the

last observation prior to the end of Study Period II of the study (the period for efficacy study) and Endpoint was defined as the last observation within the period. This was analyzed using the ANCOVA model which included baseline score as covariate, treatment and country as factors.

**Interim Analyses:** According to the protocol, an interim analysis might be conducted after approximately half of the required patients finished the double-blind acute therapy phase of the study, regardless of whether they completed the 6-week double-blind therapy or discontinued from the double-blind therapy. This interim analysis was planned with the intent to terminate the double-blind phase if overwhelming efficacy of olanzapine was shown. If enrollment was faster than initially anticipated, the sponsor might elect not to conduct the interim analysis. Statistical evidence of overwhelming efficacy was defined to be a statistically significant difference between the placebo and olanzapine group in the change from baseline to Endpoint of the BPRS-C total score, consistent with the primary efficacy analysis, at the $\alpha$=.0294 level. In the final analysis, the treatment comparison on the BPRS-C total score would also be tested at $\alpha$=.0294 level. This adjustment followed the methodology described in Pocock (1977).

## STUDY HGIN

The protocol for this study was approved by the sponsor on 15 July 2002 and was amended on: 17 October 2002; 03 February 2004; and 08 July 2004. According to the sponsor, the statistical analysis plan (SAP), which supersedes the statistical plans described in the protocol, was approved on 10 June 2005, the same day the reporting database was validated and subsequently locked for analysis. The sponsor made substantial changes on Version C of the protocol. The SAP was not submitted to FDA for review until 21 March 2006, upon the request of the agency. Some changes were made to the planned analyses outlined in the Final SAP after the unblinding of the database. These additional analyses did not alter the interpretation of the primary efficacy analysis of this study (See 9.8.2.2.1 of the Clinical Study Report).

Based on the data set of Study HGIN, the normality test for the primary endpoint gives a p-value of 0.76 using the Shapiro-Wilk test, density plot also shows a symmetric and single mode distribution so the normality assumption is not seriously violated in my opinion. Therefore, no nonparametric method is used on the efficacy test. The analysis results are presented in Table 3.7.

According to the sponsor, the interim analysis was not conducted.

Using the data sets provided by the sponsor, the reviewer confirmed the efficacy results on LOCF data set. The ANCOVA with the primary efficacy measure gave similar significance results as reported in the Clinical Study Report. The homoscedasticity was assessed through the plot of residuals against the predicted values from ANCOVA model on the primary efficacy measure. No heteroscedasticity was found from the plots.

Given the high percentages of patient dropout as indicated in Table 3.4, the reliability and interpretability of the efficacy results becomes an issue. In general, LOCF procedure is reliable only when the mean outcome measure is stable over the whole study period. This is obviously not the case as the mean BPRS-C total score decreased 24.5 points from a baseline mean of 56 for those stayed to the Endpoint of Study Period II. Alternatively, the MMRM method gives reliable efficacy results if the patient dropouts were non-informative, with dropouts only depending on the observed outcome values, not on the unobserved values. This seems to be a reasonable assumption in this study.

**Table 3.7: Treatment Effects on the Change from Baseline of Primary Efficacy Measures at the Endpoint in Studies HGIN --- ITT Population**

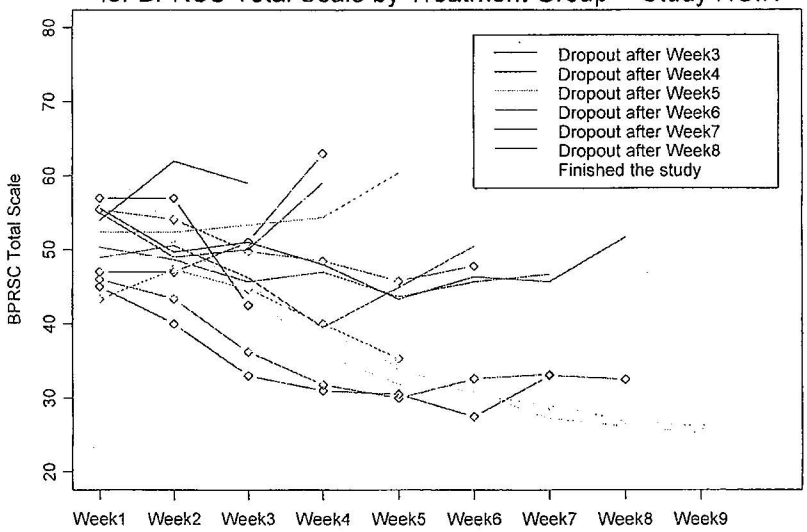
| | Placebo | Olanzapine |
|---|---|---|
| **Study HGIN** | (N=35) | (N=72) |
| **N (Analysis population)** | 35 | 72 |
| **N (BPRS-C Total Score)** | 35 | 72 |
| Baseline Mean | 50.1 | 50.3 |
| Median change from baseline | -9.3 | -19.4 |
| **ANCOVA Analysis (LOCF)** | | |
| LS Mean change from baseline (SE) [a] | -9.1 (2.73) | -19.3 (1.91) |
| Difference between LS Means and C.I.[a] | -10.1 (-16.7, -3.5) | |
| P-value [a] | 0.003 | |
| **MMRM Analysis** | | |
| LS Mean change from baseline (SE) [b] | -23.5 (3.06) | -24.7 (1.70) |
| Difference between LS Means and C.I.[b] | -1.25 (-8.11, 5.61) | |
| P-value [b] | 0.72 | |
| **OC Analysis** | | |
| **N (BPRS-C Total Score)** | 15 | 50 |
| LS Mean change from baseline (SE) [c] | -24.1 (3.35) | -24.4 (1.82) |
| Difference between LS Means and C.I.[c] | -0.25 (-7.9, 7.4) | |
| P-value [b] | 0.95 | |

a: Test for no difference between treatments at the endpoint from ANCOVA model with treatment and country as factors and baseline efficacy measure as covariate.
b: Test for no difference between treatments at the endpoint from MMRM model with treatment, country, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.
c: Test for no difference between treatments at the endpoint from OC model with treatment and country as factors and baseline efficacy measure as covariate.
Note: Negative change in score indicates improvement.

Source: Reviewer.

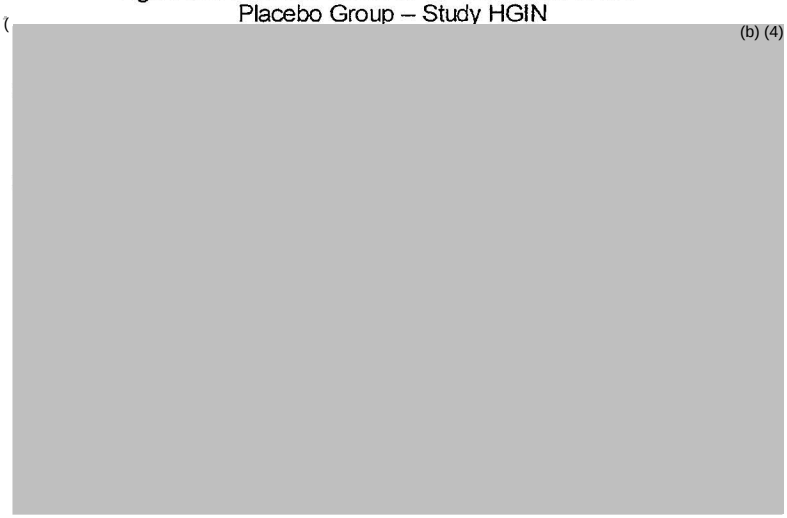
Using the data sets provided by the sponsor, the OC and MMRM analyses yield statistically **very non-significant** efficacy results for the primary outcomes. OC analysis yields **a p-value of 0.95** while MMRM analysis yields **a p-value of 0.72.** These results contradict that of the LOCF analysis on the effectiveness of olanzapine in the treatment of adolescents with schizophrenia. To see why this is the case, this reviewer plotted both the population mean profiles and individual profiles for both treatment groups. These are depicted in Figures 3.1 to 3.3.

Figure 3.1: Population Mean Profiles by Dropout Time
for BPRSC Total Scale by Treatment Group -- Study HGIN



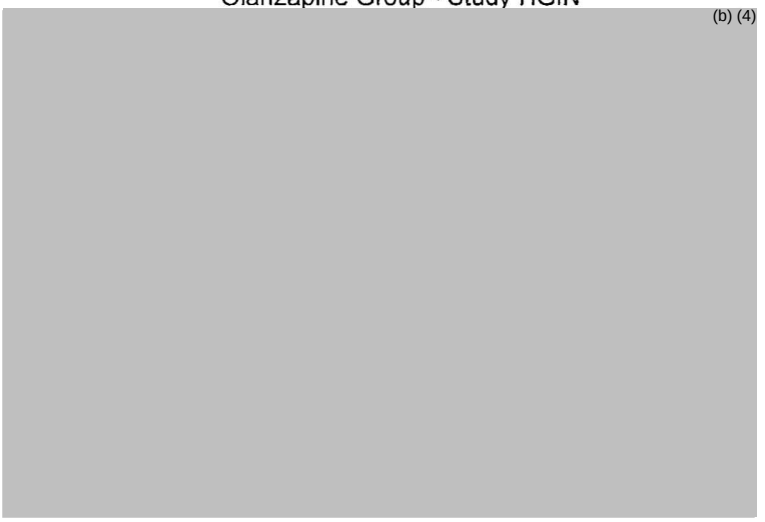

Source: Reviewer

Figure 3.2: Patient Profiles of BPRSC Total Score
Placebo Group – Study HGIN




Source: Reviewer

Figure 3.3: Patient Profiles of BPRSC Total Score
Olanzapine Group - Study HGIN




Source: Reviewer

These figures clearly indicate that there appears to be no difference between the treatment groups among those who stayed to the end of Period II of the study. The difference appears only among those who dropped out before the end of Period II. Among those patients, olanzapine seems to have improved patient BPRS-C total score over placebo. In fact, Figures 3.2 and 3.3 seem to indicate that olanzapine reduced the BPRS-C total score in both the dropout group and the non-dropouts group while placebo reduced the score only in the non-dropouts group, not in the dropouts group.

This phenomenon was observed in both US and Russia.

## STUDY HGIU:

The protocol for this study was approved by the sponsor on 15 July 2002. According to the sponsor, the statistical analysis plan (SAP) addressed the planned statistical analyses prior to unblinding, and was approved prior to the unblinding of the reporting database. The sponsor stated that the SAP was approved on 21 June 2005. The reporting database was validated and subsequently locked for analysis on 24 June 2005. It was not submitted to the Agency for review until 26 March 2006.

Of the 161 randomized patients, 159 were analyzed for the primary efficacy measure. Two of the patients randomized to receive olanzapine did not have a post baseline observation that could be used for the primary efficacy analysis. In addition, the primary analysis, LOCF mean change from baseline to endpoint in the YMRS total score, was conducted without data from patients in Site 021. The efficacy result in Table 3.8 was derived using the data set provided by the sponsor with Site 021 included. Similar results were obtained when Site 021 was excluded.

**Table 3.8: Treatment Effects on the Change from Baseline of Primary Efficacy Measures at the Endpoint in Study HGIU --- ITT Population**

| | Placebo | Olanzapine |
|---|---|---|
| **Study HGIU** | (N=54) | (N=107) |
| **N (Analysis population)** | 54 | 107 |
| **N (YMS-R Total Score) ITT** | 54 | 105 |
| Baseline Mean | 32.0 | 33.1 |
| Median change from baseline | -6.5 | -15.0 |
| **ANCOVA Analysis (LOCF)** | | |
| LS Mean change from baseline (SE) [a] | -10.0 (1.53) | -17.7 (1.27) |
| Difference between LS Means and C.I.[a] | -7.7 (-10.7, -4.6) | |
| P-value [a] | <0.0001 | |
| **MMRM Analysis** | | |
| LS Mean change from baseline (SE) [b] | -12.6 (1.28) | -17.8 (0.87) |
| Difference between LS Means and C.I.[b] | -5.6 (-8.7, -2.5) | |
| P-value [b] | 0.0004 | |
| **OC Analysis** | | |
| **N (BPRS-C Total Score)** | 37 | 88 |
| LS Mean change from baseline (SE) [c] | -13.4 (1.70) | -19.1 (1.31) |
| Difference between LS Means and C.I.[c] | -5.7 (-9.2, -2.3) | |
| P-value [b] | 0.0013 | |

a: Test for no difference between treatments at the endpoint from ANCOVA model with treatment and country as factors and baseline efficacy measure as covariate.
b: Test for no difference between treatments at the endpoint from MMRM model with treatment, country, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.
c: Test for no difference between treatments at the endpoint from OC model with treatment and country as factors and baseline efficacy measure as covariate.
Note: Negative change in score indicates improvement.

Source: Reviewer.

Using the data sets provided by the sponsor, the reviewer confirmed the efficacy results in the Clinical Study Report. The efficacy result in the primary analysis was highly statistically significant. The OC and MMRM analyses were conducted by the reviewer and they yielded similar results as that of ANCOVA. These efficacy results are depicted in Table 3.8. These results all support the effectiveness of olanzapine in reducing the YMRS total score in adolescents with schizophrenia compared to placebo.

The treatment-by-country interaction for the primary efficacy measure was explored using the ANCOVA model, including baseline, country, treatment, and treatment-by-country interaction. The corresponding estimated treatment effect was -6.8, which was close to that in Table 3.8. But the p-value for treatment difference became 0.006. The interaction was not statistically significant. There were a total of 143 patients in US and 18 patients in Puerto Rico. In addition to including country as a factor in the efficacy model, statistical comparisons were made between treatment groups on the primary efficacy parameter in US alone and it yielded similar result.

In conclusion, the primary efficacy results using LOCF data set in both Studies HGIN and HGIU support the effectiveness of olanzapine in the treatment of schizophrenia in adolescent patients. However, only the

results in Study HGIU were supported by the results using OC data and MMRM procedure. The efficacy results using OC data set and MMRM strongly contradicted that using LOCF data set in Study HGIN. The OC and MMRM results were both highly nonsignificant. The population mean profiles and individual profiles suggest that the difference of the treatment effect only occurred among the patients who dropped out of the Period II of the study.

### 3.2 Evaluation of Safety

See medical review for detail.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

Using LOCF data, subgroup analyses were performed on the primary efficacy measure, for age (younger than 15 years versus 15 years and older), gender and origin (Caucasian versus non-Caucasian) provided there were at least 10 patients in each treatment group. All subgroup analyses were considered exploratory. The treatment-by-subgroup interaction was tested using an ANCOVA model including the terms for baseline, treatment, country, subgroup, and the treatment-by-subgroup interaction. The treatment-by-subgroup interaction was tested to find out whether treatment differences in the mean primary efficacy measure were similar for each subgroup. In addition, the primary measure was analyzed for each country using the ANCOVA model including terms for baseline and treatment.

In both Studies HGIN and HGIU, neither sex nor the interaction between sex and treatment group was statistically significant at the nominal significance level of 0.05 in the ANCOVA analysis. The treatment effects and their significance levels stayed similar whether sex or the interaction between sex and treatment group was adjusted. However, Table 4.1 shows that the improvement on the primary endpoint was numerically larger for male than for female patients.

In both Studies HGIN and HGIU, neither age group (younger than 15 years versus 15 years and older) nor the interaction between age group and treatment was statistically significant at the nominal significance level of 0.05 in the ANCOVA analysis. The treatment effects and their significance levels were similar whether age group or the interaction between age group and treatment was adjusted. However, Table 4.2 shows that the improvement on the primary endpoint was numerically larger for older patients (15 years and older) than for younger ones.

**Table 4.1 Treatment Effect by Sex on the effect size in Studies HGIN and HGIU (LOCF Analysis)**

| Study | Placebo | Olanzapine |
|---|---|---|
| **Study HGIN** | | |
| **Male** | N=24 | N=51 |
| **Mean Change From Baseline of BPRS-C Total (SD)** | -8.8 (17.5) | -19.7 (16.6) |
| **Female** | N=11 | N=21 |
| **Mean Change From Baseline of BPRS-C Total (SD)** | -10.5 (21.9) | -18.7 (12.8) |
| **Study HGIU** | | |
| **Male** | 24 | 60 |
| **Mean Change From Baseline of YMRS Total (SD)** | -5.8 (9.35) | -16.8 (10.0) |
| **Female** | 30 | 45 |
| **Mean Change From Baseline of YMRS Total (SD)** | -9.3 (9.3) | -14.7 (10.1) |

Source: FDA analysis.

**Table 4.2 Treatment Effect by Age Group on the effect size in Studies HGIN and HGIU (LOCF Analysis)**

| Study | Placebo | Olanzapine |
|---|---|---|
| **Study HGIN** | | |
| **Age below 15** | N=7 | N=15 |
| **Mean Change From Baseline of BPRS-C Total (SD)** | -12.6 (20.4) | -17.3 (17.8) |
| **Age 15 and Above** | N=28 | N=57 |
| **Mean Change From Baseline of BPRS-C Total (SD)** | -8.5 (18.6) | -20.0 (15.0) |
| **Study HGIU** | | |
| **Age below 15** | 20 | 49 |
| **Mean Change From Baseline of YMRS Total (SD)** | -9.5 (11.0) | -14.6 (10.2) |
| **Age 15 and Above** | 34 | 56 |
| **Mean Change From Baseline of YMRS Total (SD)** | -6.7 (8.4) | -17.0 (9.9) |

Source: FDA analysis.

**Table 4.3 Treatment Effect by Country on the effect size in Study HGIN (LOCF Analysis)**

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

Source: FDA analysis.

To explore the treatment effect in different countries, we noted that there were about 89% patients in US and only 11% patients in Puerto Rico in Study HGIU, so efficacy analysis was considered in US alone. In Study HGIN, country was not statistically significant at the nominal level of 0.05 but the interaction between country and treatment group yielded a p-value of 0.15 in the ANCOVA analysis. However, Table 4.3 suggests that treatment effect of olanzapine over placebo occurred mainly in Russian rather than in US patients. From Figure 4.1, it appears that the Russian patients in placebo group received very little improvement. Of the 16 patients in the placebo group, 10 dropout patients hardly received any

improvement by the time when they dropped out. The remaining 6 received very limited improvement. Of the 34 patients in the olanzapine group, only 8 dropped out. The improvement in this group appeared to be in line with that of the US patients.

Figure 4.1 Patient Profiles for BPRSC Total Score, by Country

Placebo Group - Study HGIN, Russia

Olanzapine Group - Study HGIN, Russia

Placebo Group - Study HGIN, US

Olanzapine Group - Study HGIN, US

Source: Reviewer.

## 4.2 Other Special/Subgroup Populations

Not available.

# 5. SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

Studies HGIN and HGIU were 6-week (Study HGIU was 3-week), Phase IV, multicenter, randomized, double blind, placebo-controlled, flexible-dose studies with treatment arms of olanzapine and placebo for adolescent outpatients in the United States, Russia and Puerto Rico. The primary objective for Study

HGIN was to assess the efficacy and safety of olanzapine (2.5 to 20 mg/day) in the treatment of adolescents (ages 13 to 17) with schizophrenia. The primary efficacy measure was the change from baseline to Endpoint of the BPRS-C total score. In Study HGIU, the primary objective was to evaluate the efficacy and safety of olanzapine (2.5 to 20mg/day) in the treatment of adolescents with Mania in Bipolar I Disorder. The primary efficacy for the study was the YMRS total score. In both studies, the primary efficacy analyses were performed on the primary efficacy measure using the ANCOVA procedure with LOCF data.

In Study HGIU, the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder is supported by both the primary efficacy results using LOCF, and the sensitivity analysis results using OC and MMRM. In Study HGIN, however, the efficacy results using OC and MMRM strongly contradict that of the LOCF result. Both the OC and MMRM results are highly nonsignificant. Although LOCF yields highly significant efficacy result, this procedure is reliable only when efficacy measures are stable over the study period. This does not seem to be the case in this study. On the other hand, MMRM gives quite reliable result if patient dropout mechanism depends only on the observed data, not on unobserved ones. This seems to be a more reasonable assumption in this study. Indeed, the individual outcome profile plots suggest that most dropouts happened when there were no obvious improvements. On the other hand, both the population mean profile plot and individual profile plot suggest that the difference between treatment groups only occurred in the patients who dropped out before the Endpoint. Together, Study HGIN does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents (ages 13 to 17) with schizophrenia.

## 5.2 Conclusions and Recommendations

In this submission, the sponsor conducted 2 pivotal short-term olanzapine studies between November 2002 and May 2005 in the United States, Russia and Puerto Rico. The primary objective of Study HGIN was to evaluate the efficacy and safety of olanzapine in the treatment of the adolescents (ages 13 to 17) with schizophrenia. The primary objective of Study HGIU was to evaluate the efficacy and safety of olanzapine in the adolescents with Mania in Bipolar I Disorder. The primary efficacy measure for Study HGIN was the change from baseline to Endpoint of the BPRS-C total score and the primary efficacy measure for Study HGIU was the change from baseline to Endpoint of the YMRS total score.

In the two studies, only Study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Study HGIN, however, does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents with schizophrenia. Indeed, the difference between treatment groups only occurred in the patients who dropped out of Period II of the study.

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James Hung
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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**020592 / S-035, 039, 040, 041, 049,053, 055**

**021086 / S-21, 031, 032, 034**

**021253 / S-037, 039, 043**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Clinical Pharmacology/Biopharmaceutics Review
# BPCA Summary Review

| | |
|---|---|
| PRODUCT (Generic Name): | Olanzapine |
| PRODUCT (Brand Name): | Zyprexa |
| DOSAGE FORM: | Tablets |
| DOSAGE STRENGTHS: | 2.5, 5,7.5, 10 and 20 mg |
| NDA: | 20-592/040,041(SE5) |
| NDA TYPE: | Supplement for **Schizophrenia** and Bipolar disorder in adolescents in response to FDA Pediatric Written Request Letter |
| SUBMISSION DATE: | October 30, 2006 |
| SPONSOR: | Eli Lilly |
| OND DIVISION: | HFD |

## EXECUTIVE SUMMARY

Olanzapine is currently indicated in the treatment of schizophrenia or bipolar I in adults. Previous studies in children and adolescents have shown a progressive increase in olanzapine concentrations with corresponding increases in dose. The data also suggested that pediatric patients generally have olanzapine plasma concentrations similar to those for adults for a given weight-adjusted dose. This sNDA provides information on the clearance of olanzapine in adolescents age 13-17 years with varying doses of 2.5 to 20 mg/day.

This sNDA includes a population pharmacokinetic study done in adolescents using flexible doses between 2.5mg/day to 20 mg/day.

The population pharmacokinetic study was done in 105 patients (Study F1D-MC-HGMF). Study duration was 4 and ½ weeks and the study population consisted of 64 males and 41 females.

The overall conclusions from the pharmacokinetic study in adolescents were:

- The exposure at steady-state in adolescents was 30-63% higher than in adults.
- Clearance in female adolescents was found to be 28% lower than in male adolescents.

## RECOMMENDATION

From a Clinical Pharmacology/Biopharmaceutics perspective this sNDA is acceptable with the labeling changes suggested by the reviewer.

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# Office of Clinical Pharmacology and Biopharmaceutics/ Pharmacometrics Review

| | |
|---|---|
| NDA: | 20-592-SE5/040, 041 |
| Compound: | Olanzapine |
| Submission Dates: | October 30, 2006 |
| Sponsor: | Eli Lilly |
| Reviewer: | Andre Jackson |


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## Executive Summary

A study was done combining data from several centers in adolescents ages 13-17 to determine if the pharmacokinetics were similar or different from that previously observed in adults. The study data from 4 study sites were analyzed by mixed effects modeling to identify any important covariates which impacted Olanzapine pharmacokinetics in adolescents. The study results indicated that weight and gender were the significant covariates which influenced the clearance of Olanzapine in the subject population. Clearance/F in females was found to be 13.6 L/hr whereas that for males was 17.5 L/hr. Exposure in adolescents was higher due to their lower average body weights.

## Introduction

Study F1D-MC-HGMF (Study HGMF) was performed to address the request by the United States (US) Food and Drug Administration (FDA) to provide pharmacokinetic information in a population of adolescent patients with schizophrenia or bipolar I disorder. Previous studies in children and adolescents have shown a progressive increase in olanzapine concentrations with corresponding increases in dose. The data also suggested that pediatric patients generally have olanzapine plasma concentrations similar to those for adults for a given weight-adjusted dose (Studies F1D-MC-HGCS, F1D-MCHGGC).

In this report, the pharmacokinetic data from Study HGMF was combined with other existing adolescent pharmacokinetic data (Studies F1D-MC-HGCS, F1D-MCHGCR, F1D-MC-HGGC, and F1D-SB-LOAY) to characterize olanzapine pharmacokinetics in adolescents and to address pharmacokinetic aspects of the FDA Pediatric Written Request for olanzapine.

## Summary

The goal of this study was to collect data for Olanzapine in a pediatric population to determine if the levels were similar or different from those observed in adult schizophrenia or bipolar I disorder subjects. Previous studies in adults showed that the CL/F was 13.6 L/hr with smoking and gender being important covariates. In the current analysis the sponsor has used a 1 compartment model similar to that used in adults and analyzed the data obtained following a 4.5 week study in adolescents ages 13-17 following the administration of doses ranging from 2.5 to 20 mg/day. Body weight and gender were identified as important covariates. The label claim from this analysis was (b) (4) . However this was not accepted by OCP since the result was not consistent with the experimental data.

### *COMMENTS TO MEDICAL REVIEWER*

OCP has revised the following portion of the label based upon the completed Pediatric Written Request:

The firm (b) (4) . This statement was deleted.
The firm also wanted to include a statement (b) (4) .
However due to the poor quality of the prediction of the true steady-state values with the model, only the observed range of steady-state values was used.

**OCP REVISED LABEL**
Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents had a lower average body weight compared to adults, resulting in an average range of olanzapine exposure that was approximately 30-63% higher in adolescents than adult patients.

## Objective of the analysis

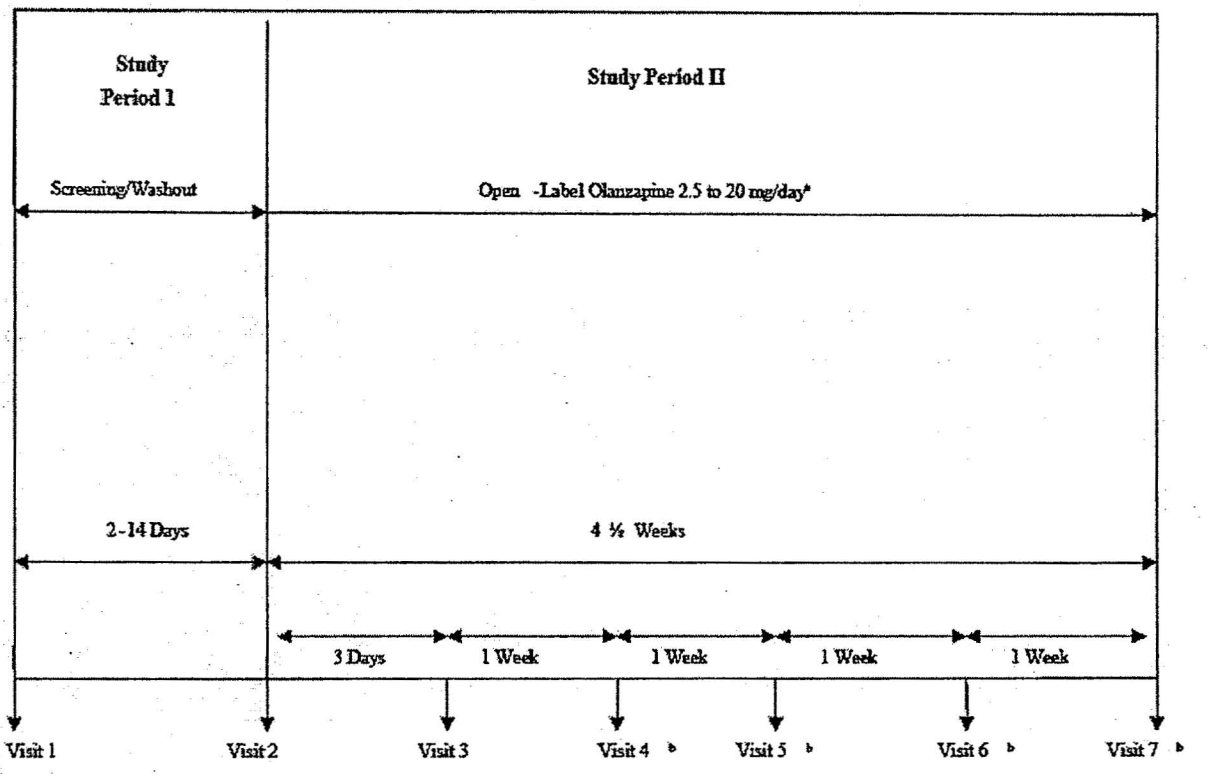
The primary objective of this study was to characterize olanzapine pharmacokinetics (CL/F and V/F); the inter- and intra-subject variabilities of olanzapine pharmacokinetics; and the potential influence of patient factors such as age, weight, gender, ethnic origin, and smoking status on olanzapine pharmacokinetics in adolescents 13 to 17 years of age that have been diagnosed with schizophrenia or bipolar I disorder.

# Methods

## Design

***Study#1:***

Study HGMF was a multicenter, openlabel, single arm trial in adolescent patients (13 to 17 years) meeting diagnostic criteria for schizophrenia or bipolar I disorder as defined by the DSM-IV-TR . The study design consisted of two study periods:
Study Period I was a 2- to 14-day Screening and Washout Period, and Study Period II was a 4 and ½ -week Open-Label Treatment Period. In order to protect patient well-being, this study employed as short a washout period as practical and was consistent with washout periods typical of real-world clinical practice. Since the elimination half-life of most orally administered antipsychotics ranges from 20 to 40 hours and the half-life of decanoate depot preparations (for example, fluphenazine) ranges from 7 to 10 days , the washout period was appropriate for this patient population. Patients already taking olanzapine continued on their previous dosage (between 2.5 to 20 mg/day) unless a dose adjustment was deemed necessary by the investigator, while patients new to olanzapine therapy started on an initial dose of 2.5 to 5.0 mg/day, as determined by the investigator.




[a]The starting dose for olanzapine-naïve patients was 2.5 to 5 mg/day. For patients entering the study already on olanzapine treatment, the maximum initial dose was 20 mg/day.
[b]PK sampling at Visits 4, 5, 6, and 7.

Table 1. **Summary of Olanzapine Studies Included in the Adolescent Population Pharmacokinetic Evaluation**

| Study | Patient Population | Dose (mg) [a] | Sample Collection [b] | Patients and Observations |
|---|---|---|---|---|
| HGMF | • 80-100 adolescents<br>• 13-17 years old<br>• Diagnosed with schizophrenia or bipolar I disorder | • 2.5 - 20 | • 4 blood samples per patient | • To be determined after database lock |
| LOAY | • 88 adolescents and young adults<br>• 12-20 years old<br>• Diagnosed with schizophrenia, shizoaffective or schizophreniform disorders | • 5 - 20 | • 1 to 8 blood samples per patient | • 80 adolescents<br>• 293 observations |
| HGCR/S | • 9 children and adolescents<br>• 10-18 years old<br>• Diagnosed with schizophrenia | • 2.5 - 20 | • 9 to 15 blood samples per patient | • 6 adolescents<br>• 84 observations |
| HGGC | • 23 children and adolescents<br>• 5-14 years old<br>• Diagnosed with bipolar disorder | • 2.5 - 20 | • 1 to 4 blood samples per patient | • 5 adolescents<br>• 15 observations |

[a] Olanzapine was administered as a once-daily (QD) oral dose
[b] All samples were collected at steady-state. Steady-state is defined as a patient being on a fixed olanzapine dose for at least 5 consecutive days.

## Analytical

Assay Validation - Zyprexa

| Parameter | Zyprexa |
|---|---|
| Method | Olanzapine was assayed by liquid chromatography with electrochemical detection (LCEC), using extracts based on its acid-base behavior. |
| Extract Stability | 6 days |
| Number of Freeze-thaw | 2 Cycles<br>QC's 80, 40, and 0.64 ng/ml<br>Diff=0.1%, -0.4% and --2.8% |

| | |
|---|---|
| Benchtop Stability at RT | 4 hrs |
| Long term at<br>–20° C<br>-60C<br>-80C | 378 days<br>1017 days<br>8.5 months |
| Extraction Recovery | (b) (4) ng/ml<br>ng/ml<br>ng/ml<br>Internal standard (b) (4) % |

All samples stored at -80C

1.F1D-MC-HGGC

Date of first sample analysis: 13 April 1999

Date of last sample analysis: 20 April 1999

Date for 1st sample draw 2/27/98
Total storage time= 425 days

**Table 2** **Back Calculated Calibration Standard Concentration Data for HPLC Assay for Olanzapine in Human Plasma**

**Summary Statistics:**

| | Concentration (ng/mL) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Nominal | 100 | 50.0 | 25.0 | 10.0 | 5.00 | 2.50 | 1.00 | 0.500 | 0.250 |
| Average | 99.7 | 50.8 | 24.8 | 9.87 | 4.81 | 2.44 | 1.02 | 0.521 | 0.252 |
| % Error | -0.3 | 1.7 | -0.9 | -1.3 | -3.8 | -2.5 | 2.1 | 4.2 | 0.8 |
| N | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

**Individual Results:**

| Batch | |
|---|---|
| S031 | (b) (4) |
| S041 | |

**Table 3** **Control Results from the HPLC Assay for Olanzapine in Human Plasma**

**Summary Statistics:**

| | Concentration (ng/mL) | | | | |
|---|---|---|---|---|---|
| Nominal | 80.0 | 40.0 | 0.640 | 80.0 | (DFAC of 6.67) |
| Average | 84.9 | 42.9 | 0.703 | 82.4 | |
| Std. Dev. | 1.80 | 1.17 | 0.0343 | | |
| Precision (%) | | | (b) (4) | | |
| % Error | 6.2 | 7.3 | 9.9 | | |
| N | 4 | 4 | 4 | 2 | |

**Individual Results:**

2.F1D-MC-HGCS

Date of First Sample Analysis: 18/11/96 (d/m/y)

Date of Last Sample Analysis: 23/04/97 (d/m/y)

Date for 1st sample draw 10/25/95
Total storage time= 545 days

**Table 2** **Back-Calculated Calibration Standard Concentrations**

| | nominal olanzapine concentration (ng/mL) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **batch** | **100** | **50.0** | **25.0** | **10.0** | **5.00** | **2.50** | **1.00** | **0.500** | **0.250** |
| **O00F** | 98.7 | 49.8 | 26.6 | 9.97 | 4.95 | 2.52 | 0.984 | 0.544 | 0.222 |
| **O01F** | 99.8 | 50.2 | 24.4 | 9.64 | 6.13 | 2.39 | 1.00 | 0.436 | note 1 |
| **O02F** | 101 | 51.8 | 23.8 | 8.24 | 4.83 | 2.65 | 0.995 | 0.533 | 0.272 |
| **O03F** | 99.3 | 50.3 | 25.5 | 9.92 | 4.96 | 2.52 | 1.01 | note 2 | 0.244 |
| **O04F** | 100 | 50.2 | 24.8 | 9.82 | 4.99 | 2.33 | 1.02 | 0.489 | 0.273 |
| **n** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 | 4 |
| **mean** | 99.9 | 50.5 | 25.0 | 9.52 | 5.17 | 2.48 | 1.00 | 0.500 | 0.253 |
| **std dev** | 0.943 | 0.793 | 1.08 | 0.724 | 0.538 | 0.126 | 0.0140 | 0.0491 | 0.0245 |
| **%rsd** | 0.9% | 1.6% | 4.3% | 7.6% | 10.4% | 5.1% | 1.4% | 9.8% | 9.7% |
| **% error** | -0.1% | 0.9% | 0.0% | -4.8% | 3.4% | -0.7% | 0.3% | 0.1% | 1.1% |

**Table 4** **Assay Accuracy Data - QC Samples**

| | nominal Olanzapine concentration (ng/mL) | | | | | |
|---|---|---|---|---|---|---|
| batch | 80.0 | 80.0 | 40.0 | 40.0 | 0.640 | 0.640 |
| O00F | (b) (4) | | | | | |
| O01F | | | | | | |
| O02F | | | | | | |
| O03F | | | | | | |
| O04f | | | | | | |
| n | 10 | | 10 | | 9 | |
| mean | 82.7 | | 39.9 | | 0.638 | |
| std dev | 2.53 | | 1.92 | | 0.0971 | |
| % rsd | 3.1% | | 4.8% | | 15.2% | |
| % error | 3.3% | | -0.2% | | -0.3% | |

3.F1D-MC-HGMF

Date for 1st sample draw 6/1/05
Total storage time=

Analytical Performance: Back-Calculated Concentrations (ng/mL) of LY170053 Calibration Standard in (Human) (Plasma - hep) in (Protocol 0062-05167)

| Assay Date | Analytical Run Number | STD 0.250 0.250 ng/mL | STD 0.500 0.500 ng/mL | STD 1.00 1.00 ng/mL | STD 2.50 2.50 ng/mL | STD 5.00 5.00 ng/mL | STD 10.0 10.0 ng/mL | STD 25.0 25.0 ng/mL | STD 50.0 50.0 ng/mL | STD 100 100 ng/mL |
|---|---|---|---|---|---|---|---|---|---|---|
| 11-Jan-2006 | 1 | 0.26 | 0.539 | 1 | 2.37 | 5.02 | 10.2 | 23.6 | 51.4 | 98.2 |
| | | 0.244 | 0.507 | 0.997 | 2.44 | 5.02 | 9.74 | 24.6 | 51.2 | 101 |
| 12-Jan-2006 | 2 | 0.251 | 0.523 | 1.11 | 2.43 | 5.15 | 9.65 | 24 | 50.1 | 101 |
| | | 0.269 | *0.363 | 0.954 | 2.27 | 4.86 | 10 | 24.6 | 49.9 | 101 |
| 26-Jan-2006 | 4 | 0.256 | 0.477 | 0.874 | 2.24 | 4.77 | 9.72 | 22.9 | 48.3 | 97.4 |
| | | 0.285 | 0.571 | 1.05 | 2.44 | 5.27 | 10.2 | 25.2 | 52.1 | 104 |
| 07-Mar-2006 | 5 | 0.262 | 0.557 | 1.02 | 2.41 | 4.96 | 9.55 | 23.3 | 49.7 | 102 |
| | | *0.347 | 0.528 | *1.21 | 2.36 | 4.92 | 10.1 | 23.3 | 51 | 101 |
| 15-Mar-2006 | 6 | 0.244 | 0.488 | 0.98 | 2.4 | 5.05 | 9.82 | 24.3 | 50.8 | 100 |
| | | *0.165 | 0.473 | 1.01 | 2.76 | 4.95 | 10.7 | 25.4 | 51.1 | 97.7 |
| 22-Mar-2006 | 7 | 0.268 | 0.518 | 1.02 | 2.4 | 4.97 | 9.75 | 23.4 | 50.3 | 100 |
| | | 0.213 | 0.535 | 0.995 | 2.47 | 5.52 | 9.99 | 24.2 | 51.1 | 101 |
| 27-Mar-2006 | 8 | 0.254 | 0.543 | 1.01 | 2.35 | 4.93 | 9.6 | 25.1 | 49.1 | 95.9 |
| | | 0.22 | 0.545 | 1.07 | 2.38 | 5.17 | 9.23 | 25.2 | 55.1 | 101 |
| Mean | | 0.252 | 0.523 | 1.01 | 2.41 | 5.04 | 9.88 | 24.2 | 50.8 | 100 |
| S.D. | | 0.0202 | 0.0301 | 0.0565 | 0.119 | 0.189 | 0.36 | 0.829 | 1.59 | 2.11 |
| %CV | | 8 | 5.8 | 5.6 | 4.9 | 3.8 | 3.6 | 3.4 | 3.1 | 2.1 |
| %Bias | | 0.8 | 4.6 | 1 | -3.6 | 0.8 | -1.2 | -3.2 | 1.6 | 0 |
| n | | 12 | 13 | 13 | 14 | 14 | 14 | 14 | 14 | 14 |

Reason Deactivated
* F Calibration standard deactivated due to unacceptable % deviation

Analytical Performance of LY170053 Quality Control Samples in Human Plasma - hep (Protocol 0062-05167)

| Run Date | Curve Number | QC 0.640 0.640 ng/mL | QC 40.0 40.0 ng/mL | QC 80.0 80.0 ng/mL | QC 180 180 ng/mL |
|---|---|---|---|---|---|
| 11-Jan-2006 | 1 | 0.652 | 38.2 | 77.6 | 188 |
| | | 0.663 | 39.6 | 76 | 183 |
| 12-Jan-2006 | 2 | 0.678 | 37.9 | 79.2 | |
| | | 0.483 | 38.5 | 78.1 | |
| 26-Jan-2006 | 4 | 0.598 | 36.6 | 75.9 | 176 |
| | | 0.693 | 41.4 | 79.9 | 195 |
| 07-Mar-2006 | 5 | 0.748 | 38.4 | 75.9 | 189 |
| | | 0.707 | 37.3 | 75.5 | 276 |
| 15-Mar-2006 | 6 | 0.618 | 37.6 | 77.2 | 178 |
| | | 0.566 | 39.2 | 77.2 | 166 |
| 22-Mar-2006 | 7 | 0.691 | 40.3 | 78.1 | 173 |
| | | 0.672 | 43.8 | 76.2 | 176 |
| 27-Mar-2006 | 8 | 0.678 | 38.5 | 73.7 | 169 |
| | | 0.664 | 42.1 | 70.2 | 176 |
| Mean | | 0.651 | 39.2 | 76.5 | 187 |
| S.D. | | 0.0665 | 2.02 | 2.41 | 29.2 |
| %CV | | 10.2 | 5.2 | 3.2 | 15.6 |
| %Theoretical | | 101.7 | 98 | 95.6 | 103.9 |
| %Bias | | 1.7 | -2 | -4.4 | 3.9 |
| n | | 14 | 14 | 14 | 12 |
| Overall %CV | | 8.6 | | | |

## *Data:*

*Studies:*

Pharmacokinetics

No dosing or sampling times were recorded during study LOAY. Each of the ten LOAY study sites provided a window of approximate sampling and dosing times. The firm did an analysis including and excluding the LOAY study however the FDA analysis only verified the analysis without the LOAY data set.

The times from dose for the concentrations were unknown because both actual time of last dose and the actual time of the blood sample were not collected in Study LOAY. Smoking status and ethnic origin information were not documented in Study LOAY.

Smoking status in Study HGMF was determined from the results of the cotinine test. Any concentrations reported as below quantification limit (BQL) were treated as missing values for the analyses.

Pharmacodynamics

N/A.

*Data Checking*

The data was checked by: perusing entered data to see if it was correct for units and definitions were consistent with entries. Data entry was consistent with the control stream. Scatter plots of the raw data were investigated to determine if the data contained a lot of outliers.

## *Models*

*Pharmacokinetics*

Structural Model

Base Model Development

Pharmacokinetics of oral olanzapine in an adult population has been previously

characterized by a one compartment model (original NDA submission NDA (b) (4) . Therefore, a one compartment pharmacokinetic model with parameters such as absorption rate constant (Ka), oral clearance (CL/F), and oral volume of distribution (V/F) was initially tested to evaluate the adolescent pharmacokinetic data. The available data in adolescent patients did not allow reliable estimation of Ka, therefore, Ka was fixed to the adult population value. The base model was able to determine the inter-patient variability in CL/F and V/F with covariance using the omega block.

Three inter-patient variability models (Equation 1) were tested: $\eta$ on CL/F, $\eta$ on V/F and $\eta$ on CL/F and V/F with covariance (omega block).

$$P = \Theta 1 \cdot \exp(\eta) \qquad \text{Equation 1}$$

where P is the individual parameter estimate (CL/F or V/F), $\Theta_1$ represents the typical or population value of the parameter and $\eta$ is a random variable with a mean of zero and variance of $\omega 2$.

The difference between model predicted olanzapine plasma concentration and the observed olanzapine concentration was modeled using the residual error model. The two residual error models evaluated were proportional (Equation 2) and combined additive and proportional.

Parameter sensitivity analyses were performed on various base models and a final base model was selected for identification of potential significant covariates.

Final Model Development

All potentially significant covariates identified were added in combination to the base model to establish a full model. Each covariate was removed (one covariate at a time) from the full model. When the removal of a covariate from the full model resulted in a significant increase of the minimal objective function ($\geq$10.828, $p<.001$), that covariate was retained in the final model. In case of physiologically related, therefore highly correlated factors, such as age and weight, the covariate that best explained the data was selected for inclusion in the final model.

## Covariate Models

Patient factors such as body weight, age, gender, ethnic origin, smoking status, and dose were tested for their influence on CL/F and V/F. Equations 3 to 5 were applied to test continuous covariates (body weight, age) and equation 6 to test categorical covariates (gender, ethnic origin, smoking status, and dose).

$P = \Theta 1 \cdot [1 \div \Theta 2 \cdot (COV\text{-}MED)]$ Equation 3

$P = \Theta 1 \cdot EXP[\Theta 2 \cdot (COV\text{-}MED)]$ Equation 4

$P = \Theta 1 \cdot (COV/MED)\ \Theta 2$ Equation 5

$P = \Theta 1 \cdot (1 \div \Theta 2 \cdot IND)$ Equation 6

where P is the individual parameter estimate, $\Theta 1$ represents the typical value of a parameter, $\Theta 2$ represents the effect of a covariate, COV is the value of a covariate, and MED is the median value of a covariate. IND is an indicator variable with a value of either 0 or 1 assigned for values of a categorical covariate (for example, smoker=0 and nonsmoker=1).

Each covariate was individually added to the base model and tested. When the objective function of the base model with a covariate was reduced by 6.635 ($p<0.01$), the covariate was considered to be potentially significant.

## Random Variance Models

Two residual error models evaluated were proportional (Equation 7) and combined additive and proportional.

$Cij = IPRED \cdot (1 + ERR)$ Equation 7

where Cij is the predicted jth olanzapine concentration in the ith patient, IPRED is the model predicted olanzapine concentration in the individual and ERR is a random variable with a mean of zero and variance of $\sigma 2$.

### *Pharmacodynamics*

N/A

### ***Model Selection***

Final Model Evaluation

Parameter sensitivity analysis and leverage analysis were applied to evaluate the robustness of the final model. Posterior predictive check was conducted to examine if the final model reliably predicts the data that was used to develop it.

Parameter Sensitivity Analysis

This analysis examined the parameter space, confirms the absence of local minima, and identifies the 95% confidence interval (CI) of the parameter using a process developed at Eli Lilly and Company (Allerheilgen et al. 1994, O'Brien et al. 1998). The analysis was

performed by fixing the parameter of interest to ±5, 10, 15, 20, 30, 40% of the population estimate and estimating all other parameters. The effect of modifying the parameter value on the overall fit of the data was examined. If needed, the parameter of interest was fixed to additional values up to ±100%. The relationship between change in objective function and the parameter value was described using polynomial regression to obtain a 95% CI of the parameter. Assuming a chi-square distribution, the parameter values which produce a change in objective function of 3.841 represent the 95% confidence limits.

Leverage Analysis

The leverage analysis was performed to evaluate the contribution of subsets of patients on the final model . Ten datasets were created with 10% of the patients randomly omitted such that each patient was omitted only once. The final model was run with each dataset containing only 90% of the patients. The parameter estimates from all 10 runs were compared with the 95% confidence limits determined from the parameter sensitivity analysis.

Posterior Predictive Check

The final model parameter estimates, variance covariance matrix, and inter-patient variability estimates were used to perform simulations that predicted olanzapine concentrations at various olanzapine doses. The distributions of the predicted olanzapine concentrations were compared to the observed concentrations for each study.

Comparison of Adolescent and Adult Olanzapine Pharmacokinetics

Individual estimates of the pharmacokinetic parameters in adolescent patients were obtained from the final model post-hoc estimates. The pharmacokinetic model for oral olanzapine in adult patients from Study F1D-MC-HGAJ (original NDA 20-592, 21 September 1995) was developed in NONMEM, Version 4 using first order (FO) method of estimation. In an effort to be consistent with the software version and method of estimation used for adolescent pharmacokinetic modeling, the individual pharmacokinetic parameters in the adult patients were obtained by rerunning the final pharmacokinetic model for adult patients in NONMEM, Version V and using FOCE with interaction method.

### *Initial Model Selection*

The basis of rejecting and/or accepting a particular model (e.g.: additive versus proportional, with or without weight, sex, etc.,) should be described. The estimation method and the alpha level of the chi-square test should be included. Further, the type of model selection should also be presented (forward, backward, stepwise, etc.,).

*Final Model Selection*

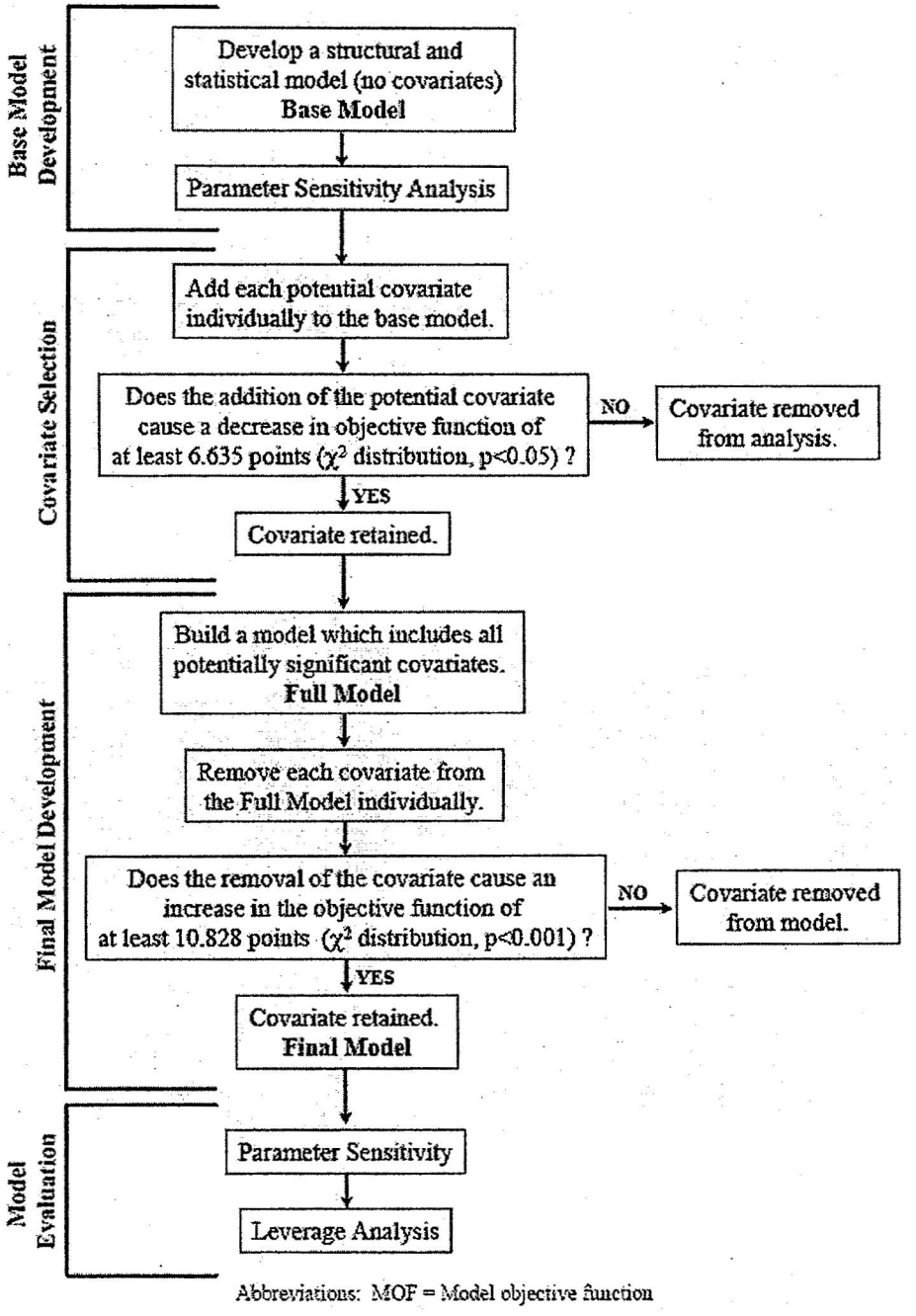



Figure HGMF.5.2. General process for pharmacokinetic model development

### *Software*

The software used for the data formatting, modeling, simulation, graphing, and statistical tests should be included (e.g.; EXCEL, SAS, , S-PLUS, NONMEM version V,,).

## Results and Discussion

### *Design Adequacy*

**Table HGMF.7.1. Baseline Demographics for Patients Included in the Pharmacokinetic Modeling (Studies HGCS, HGCR, HGGC, HGMF)**

| Demographic | HGCR | HGCS | HGGC | HGMF | Total |
|---|---|---|---|---|---|
| n | 9 | 75 | 15 | 363 | 462 |
| N | 1 | 5 | 5 | 105 | 116 |
| **Age (years)** | | | | | |
| Mean±SD | 16 | 16.0±1.41 | 14.3±0.593 | 16.1±1.37 | 16.0±1.38 |
| (Min, Max) | | (14,17) | (13.3,14.7) | (13.43,17.99) | (13.3,17.99) |
| **Body weight (kg)** | | | | | |
| Mean±SD | 78.9 | 65.6±15.8 | 65.3±10.4 | 72.9±20.9 [a] | 72.3±20.3 [b] |
| (Min, Max) | | (48.2,85.8) | (56.7,77.1) | (41.1,147.7) [a] | (41.1,147.7) [b] |
| **Gender (N)** | | | | | |
| Male | 1 | 2 | 0 | 64 | 67 |
| Female | 0 | 3 | 5 | 41 | 49 |
| **Smoking status (N)** | | | | | |
| Smoker | NA | NA | NA | 20 | 20 |
| Non-smoker | NA | NA | NA | 73 | 73 |
| **Origin (N)** | | | | | |
| Caucasian | NA | NA | 4 | 90 | 94 |
| African American | NA | NA | 0 | 8 | 8 |
| Hispanics | NA | NA | 1 | 7 | 8 |

Abbreviations: n = number of observations; N = number of patients; Max = maximum; Min = minimum; SD = standard deviation; NA = not available.

[a] n = 103

[b] n = 114

The number of subjects appears adequate although it may have been better for them to have more subjects at age 13-14 to replace those in study LOAY.

### *Data Integrity*

The data base contained subjects below 13 and above 17 who were excluded.

***Model and Model Selection:***

*Base Model*

Model description

Parameter estimation results

**Table HGMF.7.3. Pharmacokinetic Parameters for the Base Population Model (Studies HGCS, HGCR, HGGC, HGMF)**

| | Units | Estimate | %SEE |
|---|---|---|---|
| **Pharmacokinetic Model** | | | |
| Absorption rate constant, $K_a$ | $hr^{-1}$ | 0.543 (Fixed) | - |
| Oral clearance, CL/F | L/hr | 16.3 | 4.61 |
| Oral Volume of Distribution, V/F | L | 879 | 17.1 |
| **Interpatient Variability** | | | |
| CL/F | % | 45.9 | 15.9 |
| V/F | % | 68.8 | 42.3 |
| Covariance between CL/F and V/F | - | 0.258 | 22.5 |
| **Residual Error** | | | |
| Proportional | % | 27.0 | 13.7 |

Abbreviations: SEE = standard error of the estimate.

Goodness of fit

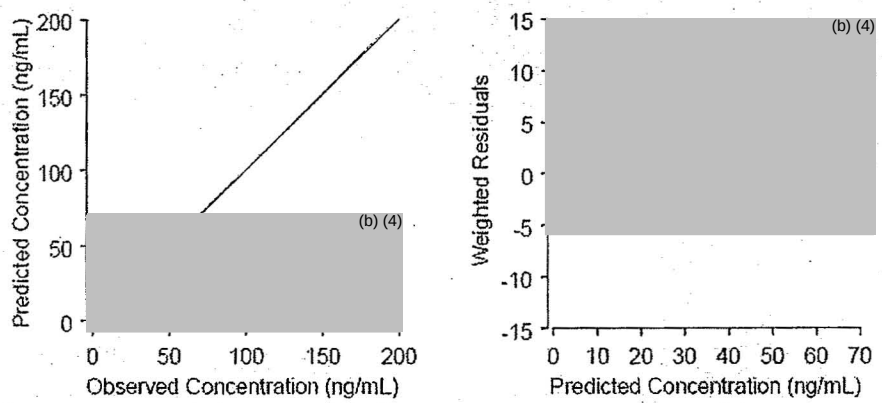



**Figure HGMF.7.4. Goodness-of-fit plots for the base pharmacokinetic model. Data from Studies HGCS, HGCR, HGGC and HGMF.**

*Model Selection*

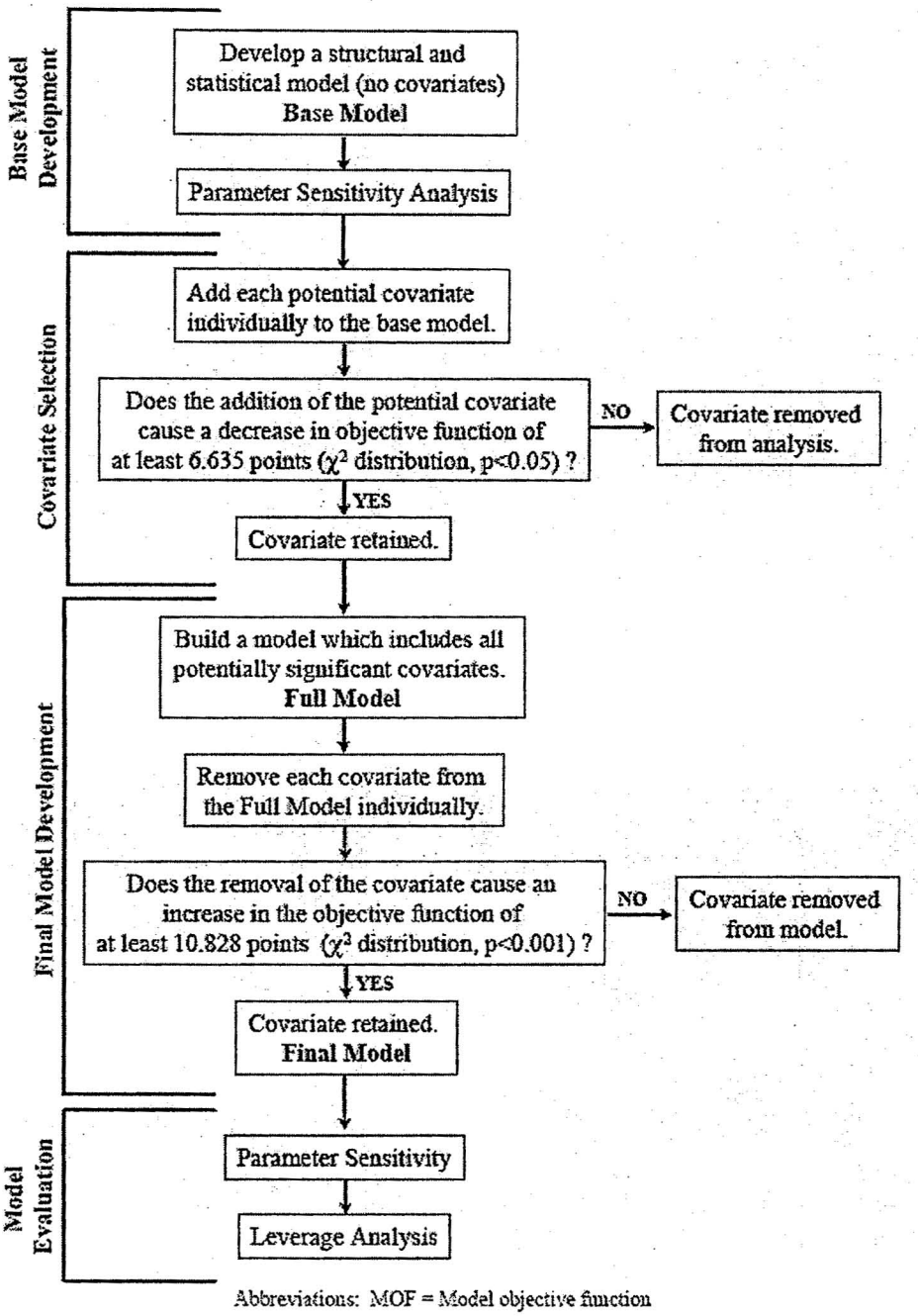



Figure HGMF.5.2. General process for pharmacokinetic model development

*Final Model*

Model description

Final Model Development

All potentially significant covariates identified were added in combination to the base model to establish a full model. Each covariate was removed (one covariate at a time) from the full model. When the removal of a covariate from the full model resulted in a significant increase of the minimal objective function (≥10.828, $p<.001$), that covariate was retained in the final model. In case of physiologically related, therefore highly correlated factors, such as age and weight, the covariate that best explained the data was selected for inclusion in the final model.

Final Model Evaluation
Parameter sensitivity analysis and leverage analysis were applied to evaluate the robustness of the final model. Posterior predictive check was conducted to examine if the final model reliably predicts the data that was used to develop it.

Parameter Sensitivity Analysis

This analysis examines the parameter space, confirms the absence of local minima, and identifies the 95% confidence interval (CI) of the parameter using a process developed at Eli Lilly and Company (Allerheilgen et al. 1994, O'Brien et al. 1998). The analysis was performed by fixing the parameter of interest to ±5, 10, 15, 20, 30, 40% of the population estimate and estimating all other parameters. The effect of modifying the parameter value on the overall fit of the data was examined. If needed, the parameter of interest was fixed to additional values up to ±100%. The relationship between change in objective function and the parameter value was described using polynomial regression to obtain a 95% CI of the parameter. Assuming a chi-square distribution, the parameter values which produce a change in objective function of 3.841 represent the 95% confidence limits.

Leverage Analysis
The leverage analysis was performed to evaluate the contribution of subsets of patients on the final model (Mandema et al. 1992). Ten datasets were created with 10% of the patients randomly omitted such that each patient was omitted only once. The final model was run with each dataset containing only 90% of the patients. The parameter estimates from all 10 runs were compared with the 95% confidence limits determined from the parameter sensitivity analysis.

Posterior Predictive Check

The final model parameter estimates, variance covariance matrix, and inter-patient variability estimates were used to perform simulations that predicted olanzapine concentrations at various olanzapine doses. The distributions of the predicted olanzapine

concentrations were compared to the observed concentrations for each study.

Final Pharmacokinetic Model

Two covariates, gender and body weight had a statistically significant influence on olanzapine pharmacokinetics and were retained in the final model. The effects of gender and body weight were on CL/F. Other patient specific factors such as age, race and smoking status did not have a significant influence on olanzapine pharmacokinetics although the Cl/F difference in adolescents due to smoking may have been confounded due to weight..

The following mean concentrations were observed in adolescents.

| | Olanzapine Concentration (ng/mL) | | | |
|---|---|---|---|---|
| Dose (mg) | N | n | Mean ± SD | (Minimum, Maximum) |
| 2.5 | 20 | 47 | 5.11±2.33 | (0.290, 9.65) |
| 3.0 | 1 | 3 | 14.5±1.82 | (13.11, 16.57) |
| 5.0 | 47 | 104 | 13.8±7.52 | (0.890, 70.17) |
| 7.5 | 28 | 46 | 20.6±9.75 | (4.41, 52.46) |
| 10.0 | 47 | 101 | 30.9±17.9 | (3.18, 101.98) |
| 12.5 | 10 | 17 | 50.3±21.4 | (23.86, 118.78) |
| 15.0 | 26 | 65 | 36.6±18.7 | (2.56, 97.17) |
| 17.5 | 7 | 9 | 78.2±40.7 | (37.14, 145.37) |
| 20.0 | 16 | 70 | 76.5±32.8 | (11.36, 160.36) |

Abbreviations: N = number of patients, n = number of observations, SD = standard deviation.

Based upon the mean concentrations it appears that dose has no impact on the kinetics of Olanzapine in adolescents. The lack of a dose effect on pharmacokinetics was also observed in adults.

## Parameter estimation results Final Model

**Table HGMF.7.4. Pharmacokinetic Parameters for the Final Population Model**

| | Units | Estimate | %SEE | 95 % CI |
|---|---|---|---|---|
| **Pharmacokinetic model** | | | | |
| Absorption rate constant, $K_a$ | $hr^{-1}$ | 0.543 (Fixed) | - | - |
| Oral Clearance (CL/F) [a] | L/hr | 13.6 | 6.16 | (12.2 – 15.3) |
| Effect of gender on CL/F (Θ3) [b] | - | 0.288 | 31.1 | (0.127 – 0.477) |
| Effect of weight on CL/F (Θ4) [c,d] | 1/kg | 0.00585 | 34.4 | (0.00248 – 0.00907) |
| Oral Volume of Distribution (V/F) | L | 899 | 16.2 | (687 – 1150) |
| **Interpatient variability** | | | | |
| CL/F | % | 40.5 | 19.7 | - |
| V/F | % | 65.4 | 47.2 | - |
| Covariance between CL/F and V/F | - | 0.232 | 31.8 | - |
| **Residual Error** | | | | |
| Proportional | % | 27.1 | 14.2 | - |

Abbreviations: CI = confidence interval; SEE = standard error of the estimate.

[a] $CL_{,female} = 13.6$ L/hr.

[b] $CL_{,male} = CL_{,female} \cdot (1 + \Theta 3) = 17.5$ L/hr.

[c] $CL_{,female\ at\ weight(n)} = 13.6\ L/hr \cdot e^{[\Theta 4 (n-70.1)]}$; where 70.1 is the median.

[d] $CL_{,male\ at\ weight(n)} = 17.5\ L/hr \cdot e^{[\Theta 4 (n-70.1)]}$; where 70.1 is the median.

## Goodness of fit

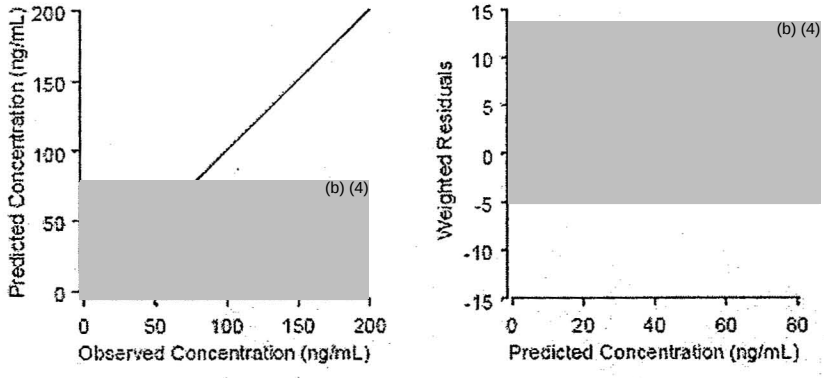
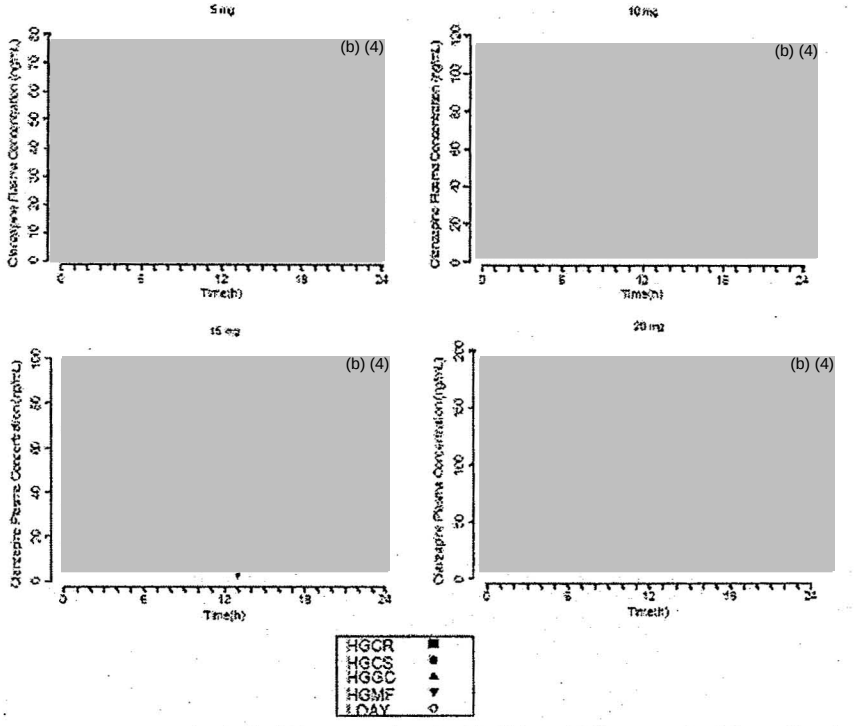



**Figure HGMF.7.5. Goodness of fit plots for final model. Data from Studies HGCS, HGCR, HGGC, and HGMF.**

---

*Model Qualification*

Posterior predictive check allowed for the comparison of the model predicted olanzapine concentrations with the observed olanzapine concentrations for each study. Most of the observed concentrations are within the model predicted concentration range (5th to 95th percentile) (Figure HGMF.7.7).



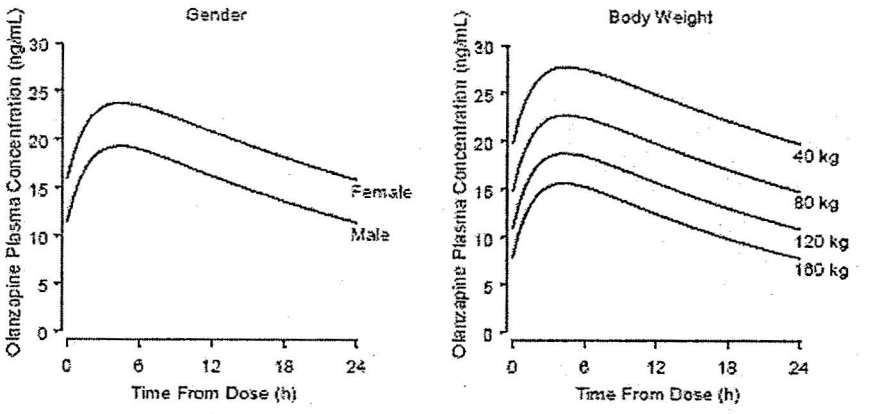

Note: Solid lines represent the 5th, 50th, and 95th percentile of the predicted olanzapine concentration-time profiles obtained simulating 1000 patients. Symbols represent observed olanzapine concentration.

Figure HGMF.7.7. **Comparison of model predicted olanzapine concentration and observed olanzapine concentration by dose.**

## Overall Conclusions

Effects of Gender

Gender had a significant influence on CL/F. Inclusion of gender as a covariate reduced inter-patient variability from 45.9% to 40.5%. The CL/F of olanzapine in male patients is approximately 29% higher as compared with the female patients. Thus, on average, female patients receiving the same olanzapine dose as male patients are predicted to have approximately 29% higher steady state olanzapine concentrations. The predicted effect of gender on olanzapine concentrations for typical population is shown in(Figure HGMF.7.6).




Note: Gender: Predictions shown at the median body weight.
Body weight: Predictions show the effect of body weight on a female patient.

**Figure HGMF.7.6. Final population pharmacokinetic model. Predicted effect of covariates on plasma olanzapine concentrations at 10-mg olanzapine dose.**

Variability in Olanzapine Pharmacokinetics

Variability in the final population pharmacokinetic model reflects the combination of inter-patient variability in pharmacokinetic parameters and intra-patient variability characterized by residual error. The interpatient variability in CL/F and V/F is 41% and 65%, respectively and the residual error is 27% (Table HGMF.7.4). The model predicted olanzapine concentrations at various doses of olanzapine are summarized in (Table HGMF.7.5). The maximal olanzapine concentration at steady state (Cmax,ss) ranged from 7.81 ng/mL to 146 ng/mL (5th percentile after 5 mg to 95th percentile after 20 mg) in the dose range of 5 to 20 mg. The mean time of Cmax,ss was 6.6 hours. The minimal olanzapine concentration at steady state (Cmin,ss) ranged from 5.51 ng/mL to 86.2 ng/mL (5th percentile after 5 mg to 95th percentile after 20 mg).

Table HGMF.7.5. **Summary of Predicted Steady-state Olanzapine Concentrations Following Simulated Once-Daily Dosing**

| | $C_{max,ss}$ (ng/mL) | $C_{min,ss}$ (ng/mL) | $t_{max,ss}$ (h) |
|---|---|---|---|
| 5-mg | | | |
| Geometric Mean | 16.6 | 10.8 | 6.55 |
| Geometric CV% | 49.7 | 43.1 | 7.38 |
| 5th Percentile | 7.81 | 5.51 | 5.79 |
| 50th Percentile | 16.7 | 10.8 | 6.56 |
| 95th Percentile | 36.4 | 21.5 | 7.37 |
| 10-mg | | | |
| Geometric Mean | 33.3 | 21.7 | 6.55 |
| Geometric CV% | 49.7 | 43.1 | 7.38 |
| 5th Percentile | 15.6 | 11.0 | 5.79 |
| 50th Percentile | 33.5 | 21.6 | 6.56 |
| 95th Percentile | 72.8 | 43.1 | 7.37 |
| 15-mg | | | |
| Geometric Mean | 49.9 | 32.5 | 6.55 |
| Geometric CV% | 49.7 | 43.1 | 7.38 |
| 5th Percentile | 23.4 | 16.5 | 5.79 |
| 50th Percentile | 50.2 | 32.4 | 6.56 |
| 95th Percentile | 109 | 64.6 | 7.37 |
| 20-mg | | | |
| Geometric Mean | 66.6 | 43.3 | 6.55 |
| Geometric CV% | 49.7 | 43.1 | 7.38 |
| 5th Percentile | 31.2 | 22.0 | 5.79 |
| 50th Percentile | 66.9 | 43.2 | 6.56 |
| 95th Percentile | 146 | 86.2 | 7.37 |

Abbreviations: CV = coefficient of variation

**Comparison of Adolescent and Adult Olanzapine Pharmacokinetics**

(Study HGAJ, 912 patients) which was a study comparing Olanzapine and Haloperidol in the treatment of Schizophrenia.

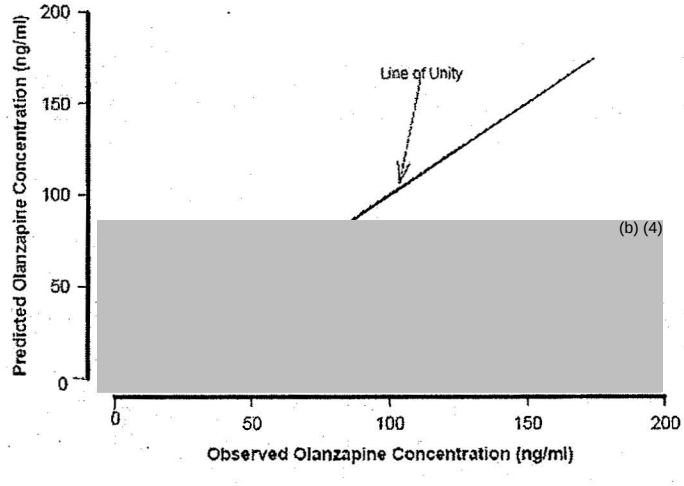
The results from study HGAJ is presented in the following Table: HGMF7.6

Table HGMF 7.6 Population pharmacokinetic parameters and 90% CI from adult study HGAJ

| NONMEM Parameter Estimates | | |
|---|---|---|
| Parameter | Parameter Value | 95% Confidence Interval[d] |
| $Cl_1$[a] (L/hr) | 13.50 | 12.61 - 14.39 |
| $Cl_2$_Male_Smoker[b](L/hr) | 28.40 | 27.28 - 29.52 |
| $Cl_2$_Female_Smoker[b] (L/hr) | 23.06 | 22.15 - 23.97 |
| $Cl_2$_Male_Nonsmoker[b] (L/hr) | 18.01 | 16.86 - 19.15 |
| $Cl_2$_Female_Nonsmoker[b] (L/hr) | 12.01 | 11.35 - 12.68 |
| V_Male_Smoker (L) | 1360.0 | 1196.13 - 1523.87 |
| V_Female_Smoker (L) | 961.52 | 792.24 - 1130.80 |
| V_Male_Nonsmoker (L) | 918.00 | 801.92 - 1034.08 |
| V_Female_Nonsmoker (L) | 788.80 | 688.67 - 888.93 |
| pc | 0.731 | 0.679 - 0.783 |

a= Low clearance population
b = High clearance population
c = Fraction of patients in high clearance population
d = Determined from objective function mapping

Predicted vs Observed Olanzapine Concentrations Including The Extreme Outliers In The Final Model (Study HGAJ)




The firm compared the distributions of CL/F and V/F statistically using the Kolmogorov-Smirnov test, a nonparametric method. The test showed that were significantly different in adolescent and adult population ($p<.001$). The common area under the two distributions (adolescent and adult) of Figure HGMF.7.8 represents the proportion of patients having comparable values. Approximately 77% of the adolescent and adult patients had comparable CL/F estimates and approximately 69% of the patients had comparable V/F. The typical values (for example, geometric mean) of CL/F and V/F in adolescent patients are 21% and 17% lower than in adults. It should be noted that in adults, gender and smoking had a significant effect on CL/F and V/F while in

adolescents, gender and body weight had a significant effect. Thus, the effect of body weight on CL/F in adolescent patients and the high proportion of nonsmokers in adolescent patients (78%in adolescents versus 40% in adults) may explain the differences in oral olanzapine pharmacokinetics observed in these populations.

The observed steady state olanzapine concentrations in adolescent patients were also compared with those observed in adults (Study HGAJ). As noted above, the median steady state olanzapine concentrations in adolescent patients were slightly higher than those in adults at each dose (Figure HGMF.7.9). However, there is considerable overlap in the olanzapine concentration distribution in adolescents and adults. At 20 mg dose, olanzapine concentrations in a few adolescent patients exceeded the maximum concentration observed at 20 mg in adults. Steady state olanzapine concentrations in adolescent patients up to doses of 15 mg were encompassed within the range of olanzapine concentration ($10_{th}$ percentile after 5 mg and $90_{th}$ percentile after 20 mg) reported in adults.

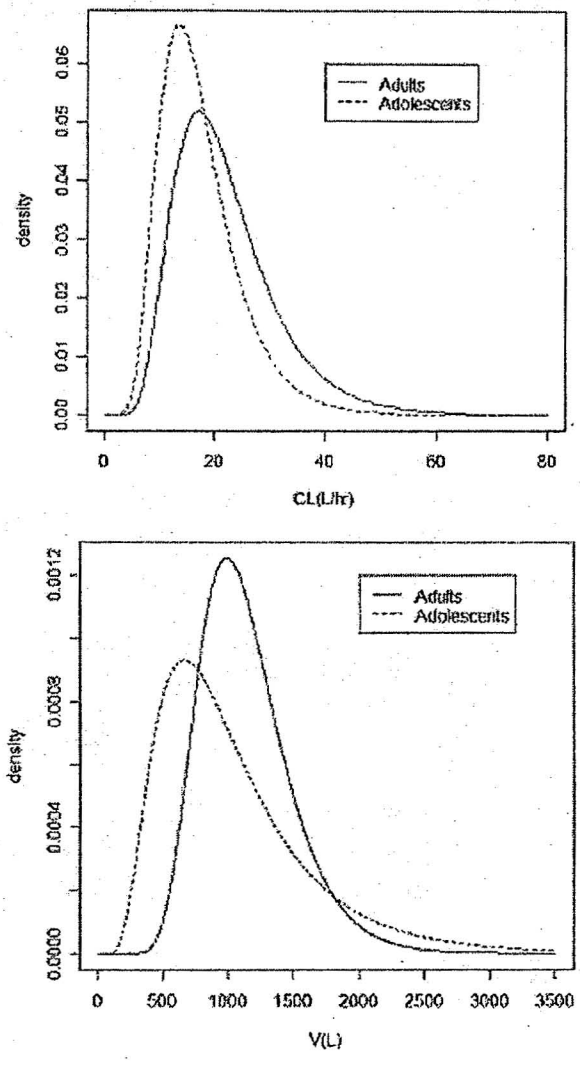
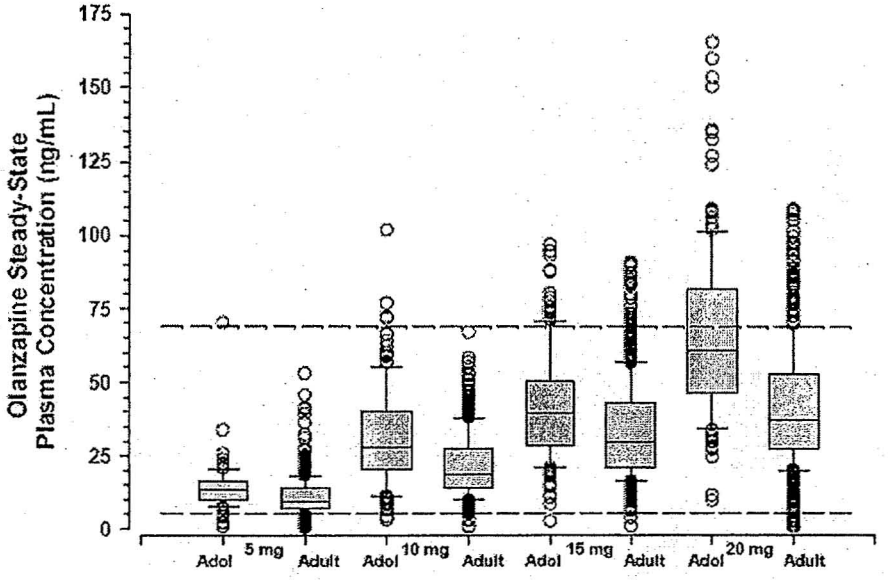



Figure HGMF.7.8. **Distribution of individual olanzapine pharmacokinetic parameters (oral clearance and oral volume of distribution) in adult and adolescent patients.**




Abbreviations: Adol = Adolescent

Note:

The middle line in each box plot represents the median; the top and bottom margins represent the 75th and 25th percentiles; the whiskers extend to the 90th and 10th percentiles; data points beyond the whiskers represent data in the tails of the distribution.

The dashed lines represent the 10th percentile of olanzapine concentration following 5-mg olanzapine daily and the 90th percentile of olanzapine concentration following oral 20-mg olanzapine daily in adults.

Figure HGMF.7.9. **Steady-state olanzapine plasma concentrations in adolescent and adult patients following oral olanzapine administration.**

## *FDA RESULTS*

BASE MODEL

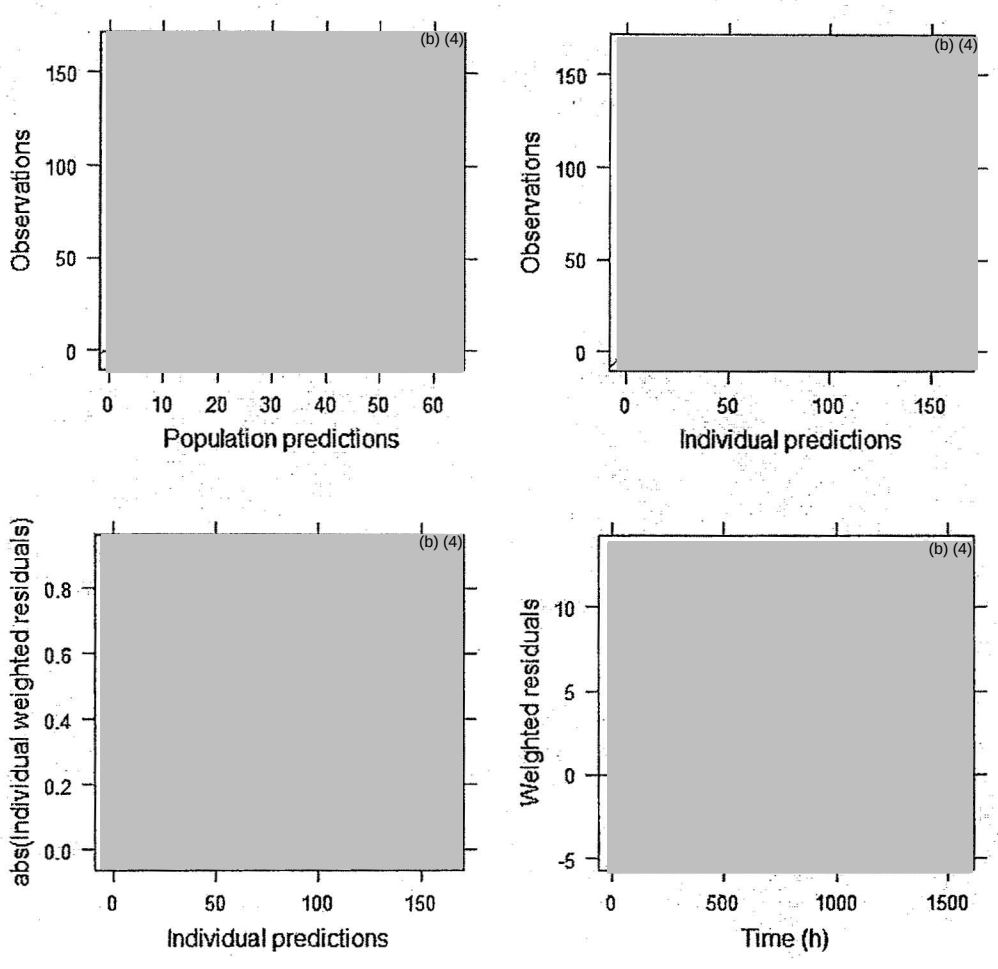



**Table Summary of FDA Pharmacokinetic Parameters for the Base Population Model (Studies HGCS, HGCR, HGGC, HGMF)**

| Units Estimate | | %SEE |
|---|---|---|
| **Pharmacokinetic Model** | | |
| Absorption rate constant, Ka hr-1 | 0.543 (Fixed) | - |
| Oral clearance, CL/F L/hr | 16.3 | 4.61 |
| Oral Volume of Distribution, V/F L | 879 | 17.1 |
| **Interpatient Variability** | | |
| CL/F % | 43.7 | 15.9 |
| V/F % | 62.2 | 42.3 |
| Covariance between CL/F and V/F - | 0.258 | 22.5 |
| **Residual Error** | | |
| Proportional % | 27.0 | 13.7 |

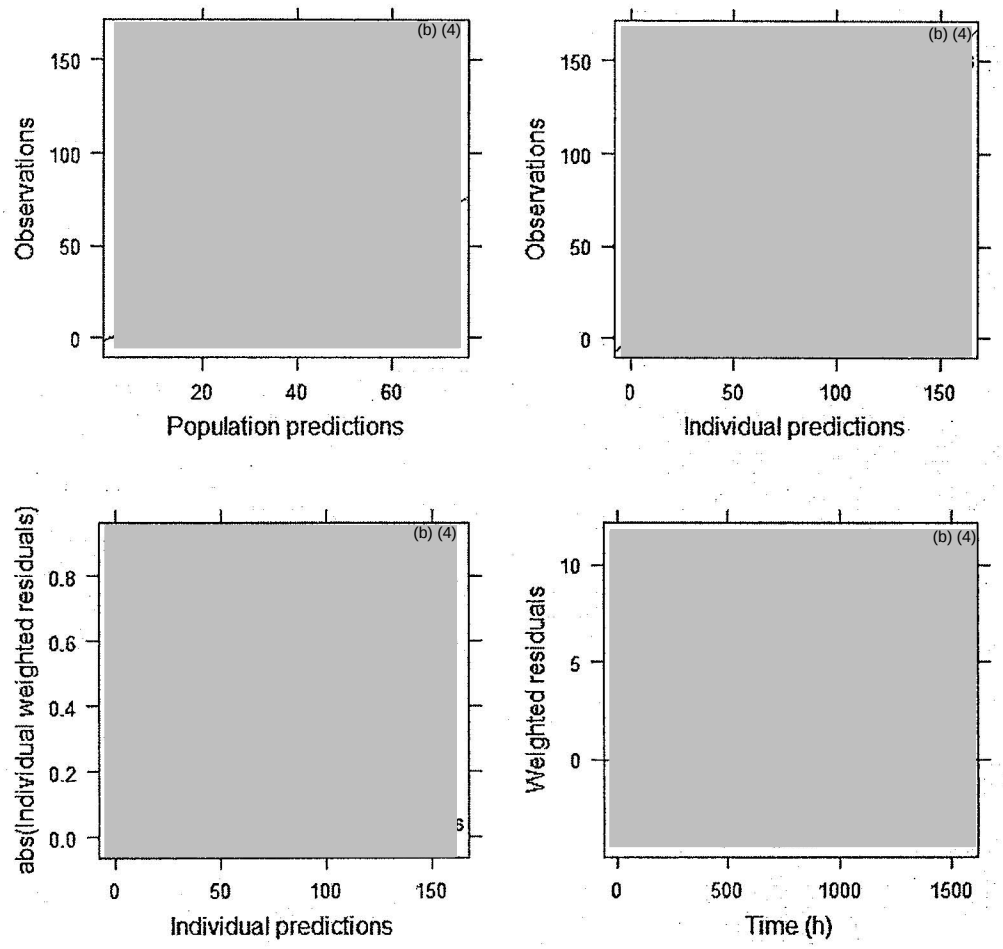
Abbreviations: SEE = standard error of the estimate.

FDA Values all agree with sponsor for the Base model

**Table Summary of FDA Pharmacokinetic Parameters for the Final Population Model (Studies HGCS, HGCR, HGGC, HGMF)**

| Units Estimate | | %SEE |
|---|---|---|
| **Pharmacokinetic Model** | | |
| Absorption rate constant, Ka hr-1 | 0.543 (Fixed) | - |
| Oral clearance, CL/F L/hr | 13.66 | 456 |
| Effect of Gender on CL/F | 0.288 | 1191 |
| Effect of Weight on CL/F | 0.00585 | 80.7 |
| Oral Volume of Distribution, L | 899 | 993 |
| **Interpatient Variability** | | |
| CL/F % | 38 | 401 |
| V/F % | 60 | 1291 |
| Covariance between CL/F and V/F - | 0.27 | |
| **Residual Error** | | |
| Proportional % | 27 | 599 |

Abbreviations: SEE = standard error of the estimate.



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## FDA's PROPOSED LABEL CHANGES

794 12.3 Pharmacokinetics

Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents had a lower average body weight compared to adults, resulting in average olanzapine exposure that was approximately 30-63% higher in adolescents than adult patients.

Comments:

1The base model results were consistent with those from the firm, however for the final model only the mean parameter values were in agreement. The variability of the data was much less with the firm's results. When OCP ran the control stream with WINGS OCP obtained a var/cov matrix file but when it was run under NMFE5 it terminated prior to the var/cov step. OCP was informed by the Pharmacometrics Division Director that computational differences were sometimes observed between different compilers and further resolution of the reason for the differences was not necessary.

2.Based upon visual comparison of the observed vs fitted graphs for studies HGAJ in adults and the current study, the graphical results indicate higher olanzapine levels in adolescents than in adults.

## SIGNATURES

Andre Jackson_____
Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D._____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 20592, HFD-860(Mehta, Baweja, Jackson)
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### *References*

Allerheiligen S, Cerimele B, Milosevich S, Johnson R, Nelson R, Tarassoff P. 1994. A population pharmacokinetic analysis of gemcitabine following variable length infusions. Pharmaceutical Res 11(10):S-377. Abstract 8178.

O'Brien L, Hewitt R, Heathman M, Ni L, Allerheiligen S. 1998. Challenging the robustness of a population pharmacokinetic model obtained from a phase III raloxifene study. In: AAPS Pharm Sci 1(1). Abstract 3548

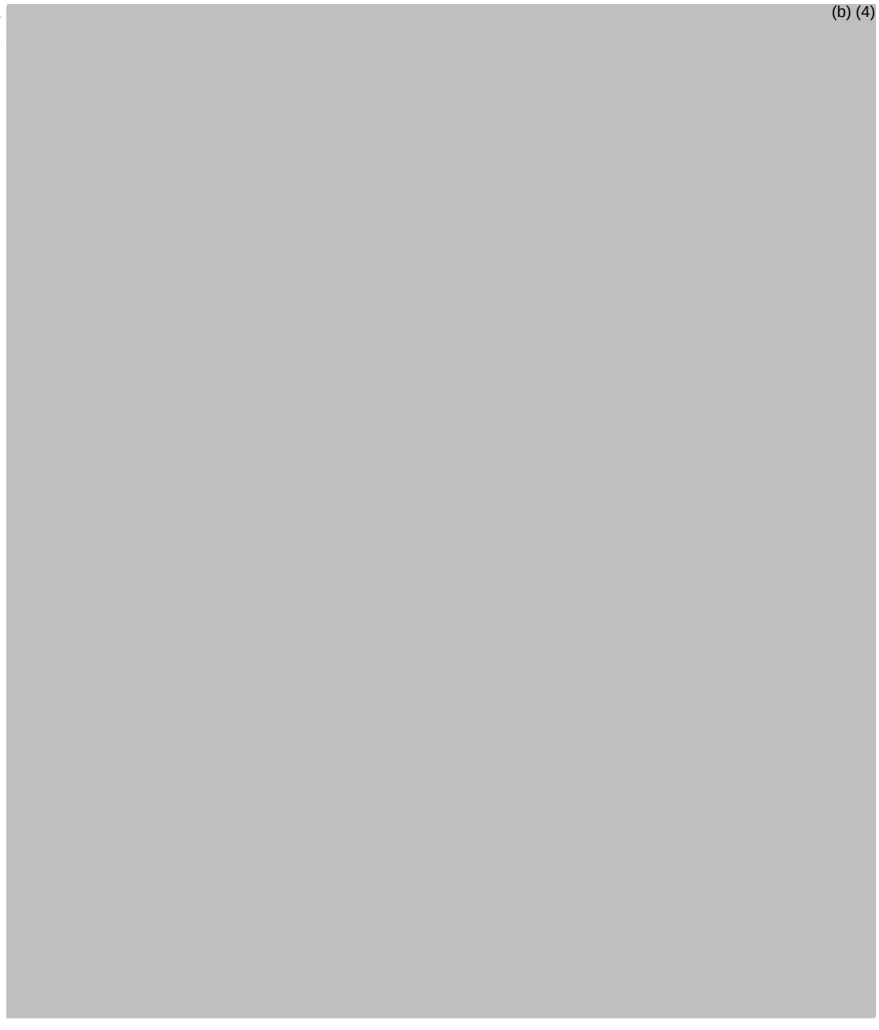
Mandema JW, Verotta D, Sheiner LB. 1992. Building population pharmacokineticpharmacodynamic models. I. Models for covariate effects. J Pharmacokinet Biopharm 20(5):511-528.

## Appendix I

(b) (4)

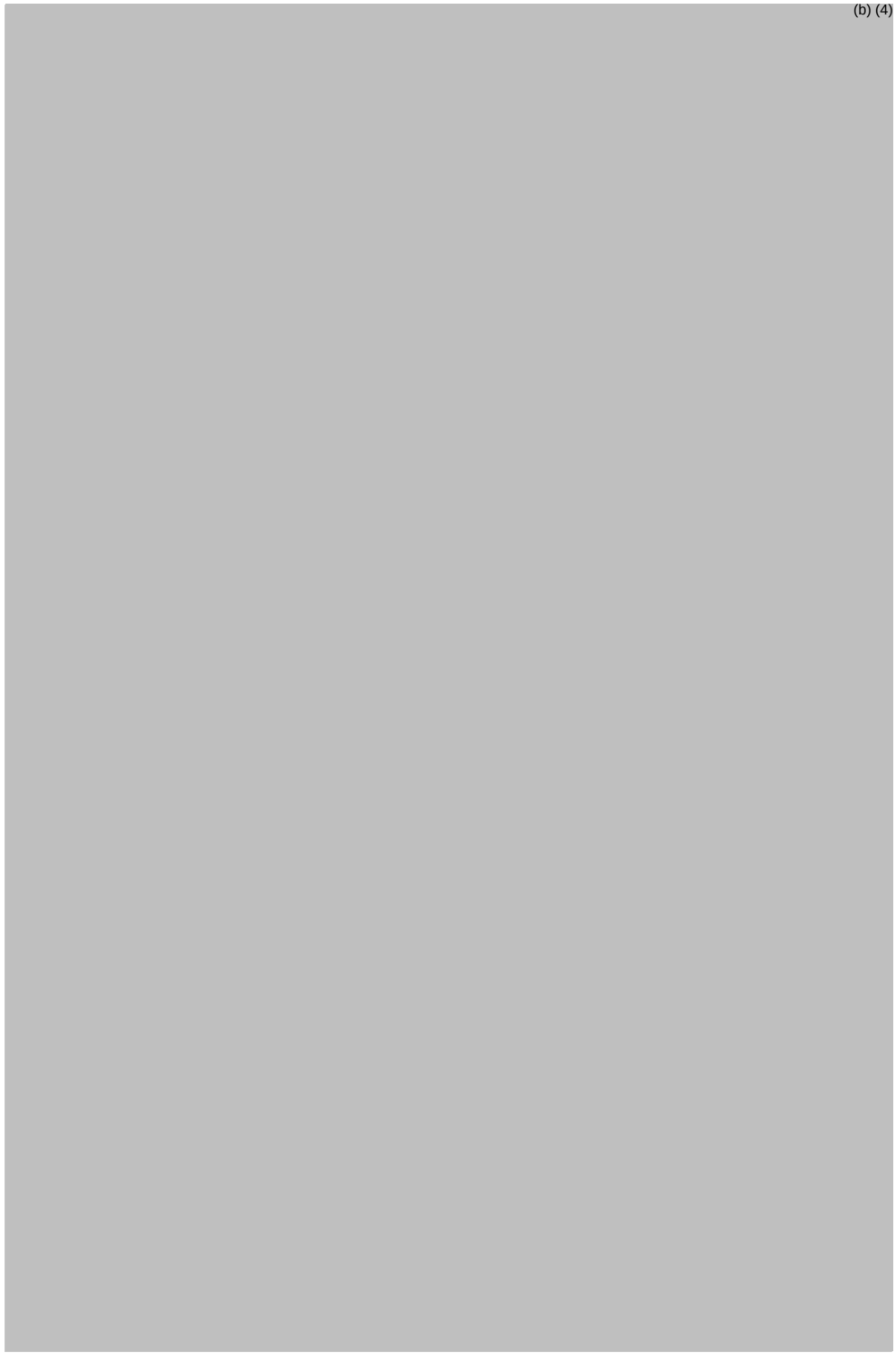
I. BASE MODEL CONTROL STREAM

(b) (4)




II. FINAL MODEL CONTROL STREAM

41



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

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/s/
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Andre Jackson
3/27/2007 08:35:38 AM
BIOPHARMACEUTICS

Raman Baweja
3/27/2007 12:16:22 PM
BIOPHARMACEUTICS

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**020592 / S-035, 039, 040, 041, 049,053, 055**

**021086 / S-21, 031, 032, 034**

**021253 / S-037, 039, 043**

## OTHER REVIEW(S)

**REGULATORY PROJECT MANAGER**
**LABELING REVIEW**

Date: May 11, 2010
DRUG/NDA: Zyprexa (olanzapine) Tablets (NDA 20592), Zydis ODT (NDA 021086), injection (NDA 021253)
Sponsor: Eli Lilly
Indications: Zyprexa Tablets, ODT, IM injection - Schizophrenia and Bipolar

Supplements:

| | | | | | |
|---|---|---|---|---|---|
| 21-253 | S-039 | PA | Zyprexa (olanzapine) Inj. | Revisions to laboratory and clinical findings | SDN 184, letter date 10/23/09 |
| 21-086 | S-032 | PA | Zyprexa Zydis (olanzapine) ODT | Revisions to laboratory and clinical findings | SDN 176, letter date 10/23/09 |
| 20-592 | S-053 | PA | Zyprexa (olanzapine) Oral Tablets | Revisions to laboratory and clinical findings | SDN 418, letter date 10/23/09 |

## REVIEW

**Reviewed by Medical Officer: Yes.**

The supplements listed above provide for revisions to section 6.2, Vital Signs and Laboratory Studies, of the label. The previously approved label, approved 1/27/10 (NDA 20592 S-052, NDA 21086 S-031, and NDA 21253 S-037), provided for changes to section 5.15, Hyperprolactinemia - these supplements add nothing more than the proposed changes listed below. The medical officer's review concurs with all changes as proposed by the sponsor.

These supplemental applications provide for the following changes to product labeling:

**6.2 Vital Signs and Laboratory Studies**

Vital Sign Changes — Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials *[see Warnings and Precautions (5)]*.

(b) (4)

[redacted]

(b) (4)

*{See appended electronic signature page}*

Keith Kiedrow, Pharm.D., Team Leader, Senior Regulatory Project Manager

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-20592 | SUPPL-53 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |
| NDA-21253 | SUPPL-39 | ELI LILLY AND CO | ZYPREXA IM (OLANZAPINE) 10MG VIALS INJ |
| NDA-21086 | SUPPL-32 | ELI LILLY AND CO | ZYPREXA ZYDIS(OLANZAPINE)5/10/15/20/ MGTS |

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

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/s/

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KEITH J KIEDROW
05/27/2010

**REGULATORY PROJECT MANAGER**
**LABELING REVIEW**

Date: January 26, 2010
Drug/NDA: Zyprexa (olanzapine) & Symbyax (olanzapine/fluoxetine)
Sponsor: Lilly
Indication: Schizophrenia; Treatment Resistant Depression
Supplements:

| NDA | Supplement | Dated | Action |
|---|---|---|---|
| **Symbyax (olanzapine/fluoxetine) ; NDA 21-520** | | | |
| 21-520 | S-022 | 8-3-09 | Approved 8-31-09 |
| 21-520 | S-023 | 9-1-09, and amended on 9-18-09 | Open |
| **Zyprexa (olanzapine) Tablets ; NDA 20-592** | | | |
| 20-592 | S-040/S-041 | 8-3-09 | Approved 12-4-09 |
| 20-592 | S-052 | 9-1-09, and amended on 9-18-09, 10-6-09, and 12-16-09 | Open |
| **Zyprexa (olanzapine) ODT ; NDA 21-086** | | | |
| 21-086 | S-030 | 8-3-09 | Approved 8-31-09 |
| 21-086 | S-031 | 9-1-09, and amended on 9-18-09, 10-6-09, and 12-16-09 | Open |
| **Zyprexa (olanzapine) Injection ; NDA 21-253** | | | |
| 21-253 | S-036 | 8-3-09 | Approved 8-31-09 |
| 21-253 | S-037 | 9-1-09, and amended on 9-18-09, 10-6-09, and 12-16-09 | Open |

**Materials Reviewed**

1. Last approved labelings attached to approval letters dated 8-31-09, and 12-4-09.
2. Medical officer review of supplements.
3. Correspondence to sponsor regarding labeling negotiations.

**Zyprexa Labeling Changes**

- Revisions to Section 5.14 (Hyperprolactinemia)

**Symbyax Labeling Changes**

- Revisions to Section 5.20 (Hyperprolactinemia)

- Revisions to Section 6.2 (Vital Signs and Laboratory Studies) regarding an increase in creatinine phosphokinase.

**Review**

- Both the Zyprexa and Symbyax labeling supplements, submitted as "Prior Approval" applications were amended to provide for updated language secondary to Agency approval actions on separate applications. For Symbyax, the labeling was amended to include the leukopenia class labeling language (approved on 8-31-09). For Zyprexa, the labeling was updated to include both the leukopenia class labeling language as well as the pediatric approval (Agency action letters dated 8-31-09, and 12-4-09, respectively).
- The clinical team requested revisions to the sponsors' proposed labeling in order to secure labeling agreement at the team leader level, and this was conveyed to the sponsor in an e-mail dated 1-12-10. Lilly submitted a counterproposal in an e-mail dated 1-14-10 which was found to be acceptable to the clinical team.

**CONCLUSIONS**

1. The supplement only provides for changes when compared to the last approved labeling (see attached labeling comparing proposed labeling to last approved labeling).
2. The clinical team concurs with the sponsor's counterproposal.
3. I recommend that an approval letter issue for these supplemental applications.

*{See appended electronic signature page}*

Paul David, CPMS

Attachment

1) 1-12-10 e-mail
2) 1-14-10-e-mail
3) Annotated labeling denoting revisions when compared to the last approved labeling

## David, Paul A

**From:** David, Paul A
**Sent:** Tuesday, January 12, 2010 2:32 PM
**To:** 'phillipsch@lilly.com'; 'usher_roland_w@lilly.com'
**Cc:** Kiedrow, Keith
**Subject:** Zyprexa and Symbyax Prior Approval Labeling Supplements

Good Day Christine and Roland,
Please refer to your submissions dated 9-1-09, providing for Prior Approval labelings supplements submitted to the Zyprexa (NDA 20-592/S-052, 21-086/S-0031 & 21-253/S-037) and Symbyax (NDA 21-520/S--23) applications.

We have completed our review of your supplements, and we would like to negotiate labeling so that a final action can be taken on these pending supplements. Please review our revisions, below, and let me know if they are acceptable.

Thanks,
Paul
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

Yellow highlights represent Lilly's proposed changes/deletions, and blue font represents the Agency's revisions

**Symbyax**

(b) (4)

(b) (4)

## Zyprexa

(b) (4)

## David, Paul A

**From:** Christine Ann Phillips [PHILLIPS_CHRISTINE_ANN@LILLY.COM]
**Sent:** Thursday, January 14, 2010 4:30 PM
**To:** David, Paul A
**Cc:** Kiedrow, Keith; phillipsch@lilly.com; usher_roland_w@lilly.com
**Subject:** Re: Zyprexa and Symbyax Prior Approval Labeling Supplements

**Attachments:** Zyprexa and Symbyax USPI Text to FDA (14Jan2010).docx

Zyprexa and
ymbyax USPI Text .

Hi Paul,

We accept the majority of changes suggested by FDA. We propose a couple of modifications to the footnotes, as shown in the enclosed document. Reasons are provided in comments. Thank you for the acceptance of the creatine phosphokinase language in the Symbyax USPI. Please let me know if you'd like to discuss further.

In addition, I'd like to ask (b) (4)

Regards,
Christine

(See attached file: Zyprexa and Symbyax USPI Text to FDA (14Jan2010).docx)

Christine Phillips, PhD, RAC
Eli Lilly and Company
US Regulatory Affairs
317.276.7239 (office)
317.625.6045 (mobile)
phillipsch@lilly.com

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"David, Paul A"
<Paul.David@fda.h
hs.gov>
01/12/2010 02:31
PM

To
<phillipsch@lilly.com>,
<usher_roland_w@lilly.com>
cc
"Kiedrow, Keith"
<Keith.Kiedrow@fda.hhs.gov>
Subject
Zyprexa and Symbyax Prior Approval
Labeling Supplements

Good Day Christine and Roland,
Please refer to your submissions dated 9-1-09, providing for Prior Approval labelings supplements submitted to the Zyprexa (NDA 20-592/S-052,
21-086/S-0031 & 21-253/S-037) and Symbyax (NDA 21-520/S--23) applications.

We have completed our review of your supplements, and we would like to negotiate labeling so that a final action can be taken on these pending supplements. Please review our revisions, below, and let me know if they are acceptable.

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CAPT Paul A. David, R.Ph.
Chief, Project Management Staff
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Phone: 301-796-1058
Fax: 301-796-9838
paul.david@fda.hhs.gov

Yellow highlights represent Lilly's proposed changes/deletions, and blue font represents the Agency's revisions

Symbyax

(b) (4)

(b) (4)

Proposed Labeling Changes for Creatine phosphokinase [These changes are acceptable.]

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.

An increase in creatine phosphokinase has been reported very rarely in SYMBYAX-treated patients and infrequently in clinical trials of olanzapine treated patients.

Zyprexa
As with other drugs that antagonize dopamine D2 receptors, olanzapine elevates prolactin levels, and a modestthe elevation persists during chronic 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 which 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.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

**Zyprexa USPI – Proposed Changes from Eli Lilly and Company (14 January 2010)**

5.15 Hyperprolactinemia

(b) (4)

[redacted]

**Symbyax USPI – Proposed Changes from Eli Lilly and Company (14 January 2010)**

(b) (4)

(b) (4)

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| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-20592 | SUPPL-52 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |
| NDA-21520 | SUPPL-23 | ELI LILLY AND CO | SYMBYAX |
| NDA-21086 | SUPPL-31 | ELI LILLY AND CO | ZYPREXA ZYDIS(OLANZAPINE)5/10/15/20/ MGTS |
| NDA-21253 | SUPPL-37 | ELI LILLY AND CO | ZYPREXA IM (OLANZAPINE) 10MG VIALS INJ |

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/s/

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PAUL A DAVID
01/26/2010

**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: | October 1, 2009 |
| To: | Thomas Laughren, MD, Director<br>**Division of Psychiatry Products (DPP)** |
| Through: | Claudia Karwoski, PharmD, Director<br>**Division of Risk Management (DRISK)** |
| | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Patient Product Information Reviewer, Acting Team Leader<br>**Division of Risk Management** |
| From: | Sharon R. Mills, BSN,RN, CCRP<br>Senior Patient Product Information Reviewer, Acting Team Leader<br>**Division of Risk Management** |
| Subject: | DRISK Review of Patient Labeling (Medication Guide), |
| Drug Name(s): | Zyprexa (olanzapine) Tablet and Zyprexa Zydis (olanzapine) Tablet, Orally Disintegrating |
| Application Type/Number: | NDA 20-592 |
| Submission Number: | S-040 and S-041 |
| Applicant/sponsor: | Eli Lilly and Company |
| OSE RCM #: | 2009-1412 |

## 1 INTRODUCTION

This review is written in response to a request by the Division of Psychiatry Products (DPP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Zyprexa (olanzapine) Tablet and Zyprexa Zydis (olanzapine) Tablet, Orally Disintegrating. Please let us know if DPP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. The proposed REMS revision is being reviewed by DRISK and will be provided to DPP under separate cover.

## 2 MATERIAL REVIEWED

- Draft Zyprexa (olanzapine) Tablet and Zyprexa Zydis (olanzapine) Tablet, Orally Disintegrating Prescribing Information (PI) submitted May 5, 2009 and revised by the Review Division throughout the current review cycle, most recent revision dated September 9, 2009.
- Draft Zyprexa (olanzapine) Tablet and Zyprexa Zydis (olanzapine) Tablet, Orally Disintegrating Medication Guide (MG) submitted on May 5, 2009 and revised by the review division throughout the review cycle, most recent version dated September 9, 2009.

## 3 RESULTS OF REVIEW

Since DRISK previously reviewed the Zyprexa MG in February 2009 and March 2009, we have limited this review to the identified PI revisions, in particular relating to the addition of information about adolescents, and changes to the Indications for Use. In our review of the MG we have:

- simplified wording and clarified concepts where possible
- made minimal reformatting changes to enhance readability
- ensured that the MG is consistent with the PI
- 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)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

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/s/

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SHARON R MILLS
10/01/2009

CLAUDIA B KARWOSKI
10/01/2009
concur

**REGULATORY PROJECT MANAGER**
**LABELING REVIEW**

Date: August 12, 2008
DRUG/NDA: Zyprexa (olanzapine) tablets (NDA 20-592), Zyprexa Zydis (olanzapine) orally disintegrating tablets (NDA 21-086), and Zyprexa IntraMuscular (olanzapine) injection (NDA 21-253)
Sponsor: Lilly
Indications: Schizophrenia

Supplements:

| NDA | Supplement | Dated | Action |
|---|---|---|---|
| **Zyprexa (olanzapine) tablets (NDA 20-592)** | | | |
| 20-592 | SLR-042 | 12-7-06 | AP letter dated 7-6-07 |
| 20-592 | SLR-049 | 7-8-08 | Open |
| **Zyprexa Zydis (olanzapine) orally disintegrating tablets (NDA 21-086)** | | | |
| 21-086 | SLR-022 | 12-7-06 | AP letter dated 7-6-07 |
| 21-086 | SLR-028 | 7-8-08 | Open |
| **Zyprexa IntraMuscular (olanzapine) injection (NDA 21-253)** | | | |
| 21-253 | SLR-026 dated | | AP letter dated 7-6-07 |
| 21-253 | SLR-033 dated 7-8-08 | | Open |

**Background:**

1. The Agency requested class labeling changes for all of the conventional antipsychotics to treat schizophrenia in a supplement request letter dated 6-16-08. Specifically, the Agency requested that the sponsors add a black box warning pertaining to mortality in elderly patients treated with antipsychotics.

**REVIEW**

**NDA 20-592/SLR-049**
**NDA 21-086/SLR-028**
**NDA 21-253/SLR-033**
**Date:** 7-8-08
**CBE:** No, Prior Approval
**Reviewed by Medical Officer:** No
These supplemental applications provide for the following changes to product labeling:

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

**WARNING**

**Increased Mortality in Elderly Patients with Dementia-Related Psychosis** —
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Zyprexa (olanzapine) is not approved for the treatment of patients with dementia-related psychosis (*see* **WARNINGS**).

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

**WARNINGS**

**Increased Mortality in Elderly Patients with Dementia-Related Psychosis** —
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Zyprexa is not approved for the treatment of patients with dementia-related psychosis (*see* **BOXED WARNING**).

**CONCLUSIONS**

1. These supplements only provide for the above labeling changes when compared to the last approved supplements. I have also attached annotated labeling to this review.
2. Additionally, (b) (4)
3. Given that the sponsor has agreed to our labeling changes, verbatim, I recommend that this review alone be sufficient to take an approval action for the above labeling supplements.

*{See appended electronic signature page}*

Paul David, R.Ph., DPP CPMS

Attachments: Annotated labeling

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/s/
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Paul David
8/13/2008 07:22:22 AM
CSO

**REGULATORY PROJECT MANAGER**
**LABELING REVIEW**

**Date:** August 6, 2009

**Drug/NDA:** Zyprexa (olanzapine): See Table Below for NDAs and Dosage Forms and Strengths

**Applicant:** Eli Lilly and Company

**Labeling Change**: Agranulocytosis Class Labeling

**Supplements:** See Table below

| Product Name | NDA / S-# | Date | Recommend |
|---|---|---|---|
| Zyprexa Oral Tablets<br>2.5, 5, 7.5, 10, 15, 20 mg | 20-592 S-051 | 03AUG09 | AP |
| Zyprexa Zydis<br>Orally Disintegrating Tablet<br>5, 10, 15, 20 mg | 21-086 S-030 | 03AUG09 | AP |
| Zyprexa IM Injection<br>10 mg/vial | 21-253 S-036 | 03AUG09 | AP |

**Background, Material Reviewed**

Last AP labeling: FDA letter dated March 19, 2009.

FDA requested labeling change: FDA Order Letter dated July 19, 2009.

Firm's proposed labeling: SNDA dated August 3, 2009.

For administrative history of this class labeling request, see FDA letters dated 05APR09, 02JUN09; FDA email dated 09JUN09. The 05APR09 letter was the initial request for class labeling for this product line. Lilly responded 05MAY09 to contest the request and propose alternate language. FDA extended the discussion period by another 30 days on 02JUN09, and provided slightly modified language on 09JUN09 via email. On 17JUN09 and 24JUN09, Lilly responded contesting the language again and proposing further modifications.

On 19JUL09, the Order Letter was issued. The text required in the Order letter follows:

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

Leukopenia, Neutropenia, and Agranulocytosis: has been reported with antipsychotics, including Zyprexa. Patients with a history of a clinically significant low white blood count (WBC) or a drug induced leukopenia/neutropenia should their complete blood count (CBC) monitored frequently during the first few months of therapy and

discontinuation of Zyprexa should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

**WARNING AND PRECAUTIONS**

**Leukopenia, Neutropenia and Agranulocytosis**

*Class Effect:* In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including Zyprexa. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of Zyprexa should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm3) should discontinue Zyprexa and have their WBC followed until recovery.

Lilly complied with the order letter and submitted the required labeling supplement on 03AUG09.

The pertinent excerpt from this labeling is shown below:

from Highlights:

*Leukopenia, Neutropenia, and Agranulocytosis:* Has been reported with antipsychotics, including ZYPREXA. Patients with a history of a clinically significant low white blood cell count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors (5.9)

from Warnings And Precautions:

5.9 Leukopenia, Neutropenia, and Agranulocytosis

Class Effect — In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including ZYPREXA. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm3) should discontinue ZYPREXA and have their WBC followed until recovery.

**Comments:**

- Firm's amended changes for the suspension labeling above correspond verbatim to those ordered by FDA on 19JUL09, with the following exceptions:
  - 'a' has been removed from 'or a drug-induced leukopenia'; this is acceptable US usage.
  - the product name has been capitalized.
  - other necessary editorial changes have been made, including addition of heading and renumbering of subsections within Section 5 of the label.
  - internal references to Section 17 subsections have been added and are appropriate.
- Reference in Highlights to changes that are one year old or older are slated for removal, per PLR: acceptable.
- Font changes to emphasize headers in Section 6 are proposed and acceptable.
- Other minor editorial changes ['two' to 2, 'per' to '/', are also acceptable.
- The labeling otherwise corresponds to the last approved labeling.

**Important Note Regarding MedGuide:**

This label, and the labeling for Symbyax, both include MedGuides. The MedGuides were required to address the issue of suicidality with antidepressant use to support the approved usage in depression and bipolar depression for both drugs [Zyprexa taken in combination with Prozac = Symbyax, for bipolar depression].

Under FDAAA, all MedGuides are now supposed to be used in conjunction with a REMS. A REMS exists for both Zyprexa and Symbyax MedGuides. Also under FDAAA, any revision to a MedGuide, other than the addition of a toll free number for reporting of AEs, requires submission of a REMS assessment and REMS review.

Not all antipsychotic labeling includes MedGuides at this time. None of the prior AP actions for this labeling change included revisions to a MedGuide. If the existing MedGuides for Zyprexa and Symbyax are revised to incorporate this agranulocytosis language, then we should consider

[a] requiring all other antipsychotics with MedGuides to make similar revisions

[b] requiring all antipsychotics with such warnings to include a MedGuide

[c] note that [b] requires a REMS for every affected product.

Rather than make a decision of this scope in connection with this specific action, which is on a 30-day clock under FDAAA and must be completed by September 2 [or 17 if discussions continue to Day 45], I recommend that we approve the labeling text above, without modification of the MedGuide at this time.

**Conclusions and Recommendations:**

1. The applicant has incorporated our changes as requested into the proposed labeling for the Zyprexa product line.

2. The proposed labeling only provides for those changes noted above when compared to the last approved labeling for Zyprexa, allowing for editorial modifications to eliminate minor typos, correct internal references, and add references to Section 17.

3. The issue of MedGuide revision to incorporate this language points to the possible need for MedGuides, and associated REMSs, for all antipsychotics carrying similar class labeling. I recommend deferral of this decision until we have completed the action on this labeling and on Symbyax.

4. With the provisos noted above, I recommend approval of these supplemental applications.

*{See appended electronic signature page}*

Doris J. Bates, Ph.D.
Safety Project Manager

**Attachments:**
1) Annotated labeling from firm.

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/s/

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DORIS J BATES
08/31/2009

VICTOR D CRENTSIL
08/31/2009

**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<br>**Division of Psychiatry Products (DPP)** |
| Through: | Claudia Karwoski, PharmD, Director (Acting)<br>**Division of Risk Managment**<br><br>Jodi Duckhorn, M.A., Team Leader<br>**Patient Labeling and Education Team**<br>**Division of Risk Management (DRISK)** |
| From: | Sharon R. Mills, BSN, RN, CCRP<br>Patient Product Information Specialist<br>**Patient Labeling and Education Team**<br>**Division of Risk Management (DRISK)** |
| Subject: | DRISK Review of Patient Labeling (Medication Guide), and Proposed Risk Evaluation and Mitigation Strategy (REMS), Review #2 |
| Drug Name(s): | • Zyprexa (olanzapine) Tablets; NDA 20-592/S039, 040, 041<br>• Zyprexa Zydis (olanzapine) Tablets, Orally Disintegrating; NDA 21-086/S-021 |
| 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 Assessements of the effectiveness of the REMS.

FDA has determined that Zyprexa (olanzapine) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Zyprexa (olanzapine). FDA has determined that Zyprexa (olanzapine) meets two of the three criteria for a Medication Guide as set forth in 21 CFR 208.1: Zyprexa (olanzapine) 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; Zyprexa (olanzapine) is a product for which patient labeling could help prevent serious adverse events.

# 2 MATERIAL REVIEWED

- Proposed Zyprexa (olanzapine) Risk Evaluation and Mitigation Strategy (REMS), submitted on December 1, 2008, and the Amendment to the Proposed REMS submitted on February 27, 2009.
- Draft Zyprexa (olanzapine) Medication Guide, revised and submitted on March 4, 2009

# 3 BACKGROUND

DRISK previously reviewed the sponsor's proposed Medication Guide and Risk Evaluation and Mitigation Strategy (REMS) for Zyprexa (olanzapine), on February 24, 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 Zyprexa (olanzapine) 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.

# 4 DISCUSSION

## 4.1 MEDICATION GUIDE

Since DRISK previously provided a line-by-line review of the sponsor's proposed MG previously, this review focuses on the proposed changes submitted by the sponsor.

The revised draft MG submitted by the sponsor has a Flesch Kincaid grade level of 8.7, and a Flesch Reading Ease score of 58.3%. 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%.

In our review of the MG, we have:

- ensured that the sponsor's proposed MG changes are consistent with the PI
- provided rationale for adding back certain information that was recommended in DRISK's prior review of the MG
- 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).

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 with 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.

## 4.2 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 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 Assessements 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.

The sponsor will submit the assessments within 60 days of the close of the intervals as noted above.

## 5 CONCLUSIONS AND RECOMMENDATIONS

DRISK believes that the sponsor's Amended proposed REMS for Zyprexa (olanzapine) generally meets the statutory requirements outlined in 21 CFR 208 and in accordance with 505-1. Below we have additional recommendations on the proposed REMS and Medication Guide. If the revisions are not acceptable to DPP, DRISK would like to review this material again prior to approval.

**Recommendations to be conveyed to Sponsor**

1. See the appended Zyprexa (olanzapine) REMS proposal (Appendix A) for 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 assessment 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 asesss 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 an amendment 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 Symbayx 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 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.

**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 Zyprexa (olanzapine)
    - 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

**We have the following comments on the sponsor's proposed MG revisions:**

6. We deleted all of the sponsor's shaded text boxes.
7. In the section "What is the most important information I should know about Zyprexa?":
    - We revised the first sentence of the section. DRISK stands by the language in our previous formal review. This is the standard language that we currently use at the beginning of this section of the MG, and is consistent with other MGs. To

enhance patient comprehension in a wide range of audiences, including those with lower levels of literacy, we recommend that the MG not include phrases such as "(b) (4)." Use patient-friendly language. Additionally, these are not just risks; rather they are actual side effects that happen. Hyperglycemia, elevated cholesterol and triglycerides, and weight gain, are the serious and significant public health concerns that require the distribution of a MG for Zyprexa and should be clearly conveyed to patients and caregivers.

- In the bullet for "high blood sugar (hyperglycemia):" DPP should confer with DDMAC to determine if it is acceptable to include mitigating language such as proposed by the sponsor. If this is acceptable, we recommend more patient friendly language, such as "Rarely" instead of "In rare cases."
- In the bullet for "high cholesterol and triglyceride levels in the blood (fat in the blood)": We recommend not using language such as "(b) (4)," in patient directed materials. We recommend telling patients that certain things may or can happen with TRADENAME. DRISK does not feel that the additional language proposed by the sponsor is needed because we already state that Zyprexa can cause serious side effects, and it is discussed here.
- In the bullet "Increase in weight (weight gain)": In general, DRISK recommends using active voice in patient directed materials. We agree with the sponsor that it is ok to remove the word "(b) (4)" here because it is stated above. However, we have changed the language to active voice and patient-friendly terminology.

8. In the section "What is Zyprexa?"
   - We agree with the sponsor's proposed change to the first statement so that it reads: "Zyprexa is a prescription medicine used (b) (4)" and is followed by four bullets. All of the labeled indications include "in adults" or "in adult patients."
   - The sponsor added back information about the onset of feeling better and improvement of symptoms. DRISK deleted this in our prior MG review. We recommend consulting with DDMAC for their input regarding the appropriateness of including this information in the MG. Additionally, if based on consultation with DDMAC this language is to remain in the MG, we recommend against using "(b) (4)" statements.
9. In the section "What should I tell my doctor before taking Zyprexa?"
   - We agree with the sponsor's suggestion to add a bullet for "heart problems."
   - We concur with the sponsor's suggestion to delete the information about (b) (4) (b) (4) from this section.
   - Under "Tell your doctor about all the medicines you take…" we agree with taking out the list of medicines.
10. In the section "What are the possible side effects of Zyprexa?"
    - We added back the statement "(b) (4)." This is currently our standard statement at the beginning of this section, and is consistent with the first sentence in the section "What is the most important information I should know about Zyprexa?"

- DRISK disagrees and has revised this section. The most serious side effects are placed first; however, all side effects from the Warnings and Precautions section are listed. Generally this is done in the order that they appear in the PI, and descriptions are provided of what is important for the patient to know. DPP should consider the placement of NMS in the MG because it appears before the metabolic issues and implies that this adverse reaction is of greater importance.
- Regarding the bullet for elderly patients with dementia-related psychosis: The sponsor's proposed change makes the bullet too complex. Additionally, "incidence" is not a patient-friendly term. In a Memo to File, from OSE to DPP dated January 2009[1], OSE stated that a MG is not appropriate for the conventional and atypical antipsychotics to address the issue of increased mortality in elderly patients with dementia related psychosis. However, since Zyprexa now requires a MG due to the risk of metabolic side effects, we must address this with patients. We do not usually put language in patient directed materials stating that 'TRADENAME is not approved for…' Rather we state what the labeled indications are. The product is not contraindicated in this patient population. DRISK believes that the review division should consider whether to add a statement to the PI indicating that use of Zyprexa is not recommended in this patient population. If such language is added to the PI, a statement such as "Elderly patients who have psychosis related to dementia should not take Zyprexa" could be added to the MG. The MG must be consistent with the PI.
- In the bullet "Neuroleptic malignant syndrome (NMS)" we concur with the sponsor (b) (4) . However, because of the seriousness of this condition, DRISK does not believe that patients should be told to simply call their doctor right away if they have any of these symptoms. It is important to get treated in a hospital and we are concerned about delay in treatment if patients can not reach their doctor in a timely manner, such as on the weekend or a holiday.
- In the bullet "Decreased blood pressure when you change positions," we disagree with the sponsor's proposed changes to this bullet. The sponsor's changes (b) (4) . We have changed this bullet in accordance with the recommendation in our prior review. DPP should review this bullet and determine if DRISK's description is accurate. We recommend adding an instruction to PI section 17.7 regarding how to avoid orthostatic hypotension and what to do if it happens. We have added back that patients should tell their doctor if they have dizziness, fast heartbeat, or fainting. Section 5.8 indicates that more gradual titration of Zyprexa may be needed. We have added slow heart beat because bradycardia is also listed in section 5.8.
- In the bullet " (b) (4) ," the sponsor's change removes information about the possibility of aspiration into the lungs that can happen in people who take

[1] OSE Memo to File re: Issue of a Medication Guide for Conventional and Atypical Antipsychotic Drugs; January 2009: RCM #: 2008-1200

antipsychotic medicines, including Zyprexa." We added the language from our prior review and further revised it to clarify that these problems are a common cause of sickness and death in people with advanced Alzheimer's disease, and can happen in people who take antipsychotic medicines, such as Zyprexa.

- In the bullet "Problems with control of body temperature" the sponsor's language does not appear to be consistent with PI section 5.13 which states "Disruption of the body's ability to reduce core body temperature..." Zyprexa has anticholinergic-like effects; with some other medicines that have anticholinergic activity, the concern is about heat prostration due to decreased ability to sweat. The sponsor states that there is "excessive sweating". This should be clarified. Also, the word "excessive" is not patient-friendly; use another word or phrase, such as "too much." In the meeting between the DRISK Patient Labeling Reviewer, Paul David, and Dr. Mathis on February 18, 2009, it was discussed and agreed that it is a good idea to tell patients to drink plenty of fluids to prevent dehydration. This addresses the issue of dehydration in PI section 5.13. There is currently no instruction in the PI to address this. An instruction should be added to section 17 to instruct healthcare providers to educate patients about avoiding dehydration while taking Zyprexa.
- DRISK disagrees with the sponsor's proposal to (b) (4) (b) (4). Although Zyprexa is not currently indicated in adolescents, the review division has decided to add the safety information to the labeling at this time; therefore, the common side effects that pertain to adolescents should be added to the MG to be consistent with the labeling that is currently being negotiated. The MG was determined to be necessary because data indicates that patients across the age spectrum are at risk for the metabolic side effects highlighted in the section "What is the most important information I should know about ZYPREXA?" Therefore, DRISK believes that it is appropriate to include common side effects in adolescents in the MG.
- We revised the side effect statement as follows:

  *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 in accordance with 21 CFR 208.20 (b) (7) (iii). The sponsor may not change the statement.

Please let us know if you have any questions.

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/s/
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Sharon Mills
3/12/2009 02:54:37 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
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DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
3/12/2009 03:33:34 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 23, 2009 |
| To: | Thomas Laughren, M.D., Director<br>**Division of Psychiatry Products (DPP)** |
| Through: | Jodi Duckhorn, M.A., Team Leader<br>**Patient Labeling and Education Team**<br>**Division of Risk Management (DRISK)** |
| From: | Sharon R. Mills, BSN, RN, CCRP<br>Patient Product Information Specialist<br>**Patient Labeling and Education Team**<br>**Division of Risk Management (DRISK)** |
| Subject: | DRISK Review of Patient Labeling (Medication Guide) and Proposed Risk Evaluation and Mitigation Strategy (REMS) |
| Drug Name(s): | • Zyprexa (olanzapine) Tablets; NDA 20-592/ S039, 040, 041<br>• Zyprexa Zydis (olanzapine) Tablets, Orally Disintegrating; NDA 21-086/S-021 |
| 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'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 Assessements of the effectiveness of the REMS.

FDA has determined that Zyprexa (olanzapine) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Zyprexa (olanzapine). FDA has determined that Zyprexa (olanzapine) meets two of the three criteria for a Medication Guide as set forth in 21 CFR 208.1: Zyprexa (olanzapine) 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; Zyprexa (olanzapine) is a product for which patient labeling could help prevent serious adverse events.

# 2 MATERIAL REVIEWED

- Draft Zyprexa (olanzapine) Prescribing Information (PI) submitted September 19, 2008 and revised by the Review Division on February 9, 2009.
- Draft Zyprexa (olanzapine) Medication Guide (MG) submitted on September 19, 2008.
- Proposed Zyprexa (olanzapine) Risk Evaluation and Mitigation Strategy (REMS), submitted on September 19, 2008.

# 3 BACKGROUND

Eli Lilly & Company submitted New Drug Applications, NDA 20-592 for Zyprexa (olanzapine) Tablets on September 30, 1996, and NDA 21-086 for Zyprexa Zydis (olanzapine) Table, Orally Disintegrating, on April 6, 2000. Zyprexa is indicated as follows:

**Bipolar I Disorder (Manic or Mixed Episodes)**

- **Monotherapy:** Oral Zyprexa is indicated for acute treatment of manic or mixed episodes associated with Bipolar I Disorder (monotherapy and in combination with lithium or valproate) and maintenance treatment of Bipolar I Disorder (monotherapy) in adults.
- **Combination Therapy:** The combination of oral Zyprexa with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults.

**Zyprexa and Fluoxetine in combination: Depressive Episodes Associated with Bipolar I Disorder**

- Oral Zyprexa and fluoxetine in combination is indicated for the acute treatment of depressive episodes associated with Bipolar I Disorder in adult Patients.
- Zyprexa monotherapy is not indicated for the treatment of depressive episodes associated with Bipolar I Disorder.

**Zyprexa and Fluoxetine in Combination: Treatment Resistant Depression**

- Oral Zyprexa and fluoxetine in combination is indicated for the acute treatment of 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).

- Zyprexa monotherapy is not indicated for treatment of treatment resistant depression.

Since Zyprexa was approved in 1996, DPP has become aware of new safety information from analysis of data related to an increased risk of hyperglycemia, hyperlipidemia, and weight gain in adolescents associated with olanzapine treatment. This information was not available when Zyprexa 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 Zyprexa (olanzapine). 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 Zyprexa (olanzapine) 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 9.6. To enhance patient comprehension, materials should be written at a 6$^{th}$ to 8$^{th}$ grade reading level. Our revised MG has a Flesch Kinkaid grade level of 8.5.

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:

   *The goal of the REMS is to inform patients of the serious risks associated with the use of Zyprexa (olanzapine), including the risks of hyperglycemia, hyperlipidemia, and weight gain.*
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 *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.

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 *Zyprexa (olanzapine)* 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 Zyprexa:

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 Zyprexa is under review. We will provide subsequent comments about the scope of the MG in the future. The Symbyax 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 note that this question does not pertain to Zyprexa or the Zyprexa REMS; however, it is included in the sponsor's Complete Response for Zyprexa. We defer to the review division to address this with the sponsor.**

3.3 Clarify Espectations 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:**

  ***The goal of the REMS is to inform patients of the serious risks associated with the use of Zyprexa (olanzapine), including the risks of hyperglycemia, hyperlipidemia, and weight gain.***

- **The sponsor's proposed timetable for assessments annually after approval of the REMS is acceptable; however, the assessments must be submitted separately and not as part of a Periodic Safety Update Report (PSUR). The sponsor should submit for review a detailed plan to evaluate patients' understanding about the safe use of *Zyprexa (olanzapine)* 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. In the section "What is the most important information I should know about Zyprexa?"
    - 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 Zyprexa.*
      This instruction should be added to section 17.4 of the PI.
9. In the section "What is Zyprexa?"
    - 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 "What is Zyprexa?" 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 "How should I take Zyprexa?"
    - The following statement is not consistent with the current draft labeling:
      *Zyprexa is not approved in children under the age of 13 years.*
      [redacted] (b) (4)

10. In the section "What should I tell my doctor before taking Zyprexa?

    - In the first paragraph, we deleted "[redacted] (b) (4)." The patient's medical conditions are relevant, [redacted] (b) (4).
    - A bullet was added for "bowel obstruction" to convey the "paralytic ileus."
    - The two statements at the end of the section relate to the indication and have been moved to the section "What is Zyprexa?" and have been modified to be consistent with the PI.

11. In the section "How should I take Zyprexa?"
    - The instruction to "[redacted] (b) (4)," is not in the PI. If the sponsor wishes to include this language, then it should be added to the PI. The language in the MG must be consistent with the language in the PI.
    - 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 Zyprexa. The language in the MG must be consistent with the language in the PI.

12. In the section "What should I avoid while taking Zyprexa?" the review division should clarify if using the term "react quickly" accurately addresses the issue of "motor skills" as proposed by the sponsor."

13. In the section "What are the possible side effects of Zyprexa?"
    - 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 Zyprexa.

- 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.
- 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. Give further consideration as to whether there are distinctions between teens and adults. 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]

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.

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.

1. Background

2. Goals

3. Supporting Information on Proposed REMS Elements

    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System
    d. Timetable for Assessment of the REMS

4. Information Needed for Assessments

5. Other Relevant Information

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

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/s/

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Sharon Mills
2/23/2009 04:54:57 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
2/24/2009 08:55:28 AM
DRUG SAFETY OFFICE REVIEWER

**REGULATORY PROJECT MANAGER**
**LABELING REVIEW**

Date: August 12, 2008
DRUG/NDA: Zyprexa (olanzapine) tablets (NDA 20-592), Zyprexa Zydis (olanzapine) orally disintegrating tablets (NDA 21-086), and Zyprexa IntraMuscular (olanzapine) injection (NDA 21-253)
Sponsor: Lilly
Indications: Schizophrenia

Supplements:

| NDA | Supplement | Dated | Action |
|---|---|---|---|
| **Zyprexa (olanzapine) tablets (NDA 20-592)** | | | |
| 20-592 | SLR-042 | 12-7-06 | AP letter dated 7-6-07 |
| 20-592 | SLR-049 | 7-8-08 | Open |
| **Zyprexa Zydis (olanzapine) orally disintegrating tablets (NDA 21-086)** | | | |
| 21-086 | SLR-022 | 12-7-06 | AP letter dated 7-6-07 |
| 21-086 | SLR-028 | 7-8-08 | Open |
| **Zyprexa IntraMuscular (olanzapine) injection (NDA 21-253)** | | | |
| 21-253 | SLR-026 dated | | AP letter dated 7-6-07 |
| 21-253 | SLR-033 dated 7-8-08 | | Open |

**Background:**

1. The Agency requested class labeling changes for all of the conventional antipsychotics to treat schizophrenia in a supplement request letter dated 6-16-08. Specifically, the Agency requested that the sponsors add a black box warning pertaining to mortality in elderly patients treated with antipsychotics.

**REVIEW**

**NDA 20-592/SLR-049**
**NDA 21-086/SLR-028**
**NDA 21-253/SLR-033**
**Date:** 7-8-08
**CBE:** No, Prior Approval
**Reviewed by Medical Officer:** No
These supplemental applications provide for the following changes to product labeling:

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

**WARNING**

**Increased Mortality in Elderly Patients with Dementia-Related Psychosis** —
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Zyprexa (olanzapine) is not approved for the treatment of patients with dementia-related psychosis (*see* **WARNINGS**).

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

**WARNINGS**

**Increased Mortality in Elderly Patients with Dementia-Related Psychosis** —
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Zyprexa is not approved for the treatment of patients with dementia-related psychosis (*see* **BOXED WARNING**).

**CONCLUSIONS**

1. These supplements only provide for the above labeling changes when compared to the last approved supplements. I have also attached annotated labeling to this review.
2. Additionally, (b) (4)
3. Given that the sponsor has agreed to our labeling changes, verbatim, I recommend that this review alone be sufficient to take an approval action for the above labeling supplements.

*{See appended electronic signature page}*

Paul David, R.Ph., DPP CPMS

Attachments: Annotated labeling

36 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

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/s/
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Paul David
8/13/2008 07:22:22 AM
CSO

**DRUGS: ZYPREXA, PROZAC** **PRIMARY REVIEWER**: Andre Jackson

**ZYPREXA**

| | |
|---|---|
| NDA 20-592 (b) (4) (4) | Submission dates : (b) (4) |
| NDA 21-086/ (b) (4) (4) | Submission dates : |
| NDA 20-592/SE8-039 | Submission date : 2-4-08 |
| NDA 21-086/SE8-021 | Submission date : 2-4-08 |
| NDA 20-592/SE5-040 | Submission date : 2-5-08 |
| NDA 20-592/SE5-041 | Submission date : 2-5-08 |
| NDA 21-253/ (b) (4) (4) | Submission date : (b) (4) |
| NDA 21-086/ (b) (4)) | Submission date : (b) (4) |

**SYMBYAX (Zyprexa/Prozac)**

| | |
|---|---|
| NDA 21-520/SE1-012 | Submission date : 2-1-08 |
| NDA 21-520 (b) (4)) | Submission dates : (b) (4) |

**PROZAC**

| | |
|---|---|
| NDA 18-936/SE8-077 | Submission date : 2-4-08 |
| NDA 18-936/SLR-075 | 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 S-(b) (4)( (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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(b) (4)

[redacted]

## 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. [ Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism.-Relocated to this position by OCP]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 <18 years of age *[see Warnings and Precautions (5.15), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

2.4 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. [Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism.-Relocated to this position by OCP]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 <18 years of age *[see Warnings and Precautions (5.15), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

## *B. Supplements for Zyprexa Zydis NDA 21-086*

o S-[redacted]

o S-021 (PAS for use of Zyprexa and Prozac in combination to treat treatment-resistant depression)

o S-[redacted]

**FDA RESPONSE for Zyprexa Zydis NDA 21-086**
**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 S (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*

8 Pages of Draft Labeling have been Withheld as b4(CCI/TS) immediately following this page

(b) (4)

## FDA LABEL CHANGES FOR PROZAC

### 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. [Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism.-Relocated to this position by OCP] 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 <18 years of age *[see Warnings and Precautions (5.10), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

### 2.4 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. [Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism.-Relocated to this position by OCP] 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 <18 years of age *[see Warnings and Precautions (5.10), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

## 7. DRUG INTERACTIONS

### 7.3 CNS acting drugs

The risk of using PROZAC in combination with other CNS active drugs, [except olanzapine,-The sponsor should explain the origin of this data to the FDA] has not been systematically evaluated. Nonetheless, caution is advised if the concomitant administration of PROZAC and such drugs is required.

### 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)

[redacted]

## FDA LABEL CHANGES FOR SYMBYAX

2.3 Special Populations

The starting dose of SYMBYAX 3 mg/25 mg - 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. Relocated to this position by OCP] When indicated, dose escalation should be performed with caution in these patients. SYMBYAX has not been systematically studied in patients over 65 years of age or in patients <18 years of age *[see Warnings and Precautions (5.20), Use in Specific Populations (8.4 and 8.5), and Clinical Pharmacology (12.3)]*.

**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 *[see Clinical Pharmacology (12.3)]*. [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. Relocated to this position by OCP]

**7 DRUG INTERACTIONS**

**7.7 CNS Acting Drugs**

(b) (4)

[redacted]

**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 *[see Clinical Pharmacology (12.3)]* should be allowed after stopping SYMBYAX before starting an MAOI. *[See Contraindications (4)]*.-This section has been moved from Contraindications by the sponsor to the Drug Interaction section and should be noted by the Medical Officer]

**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)]*.-This section has been moved from Contraindications by the sponsor to the Drug Interaction section and should be noted by the Medical Officer]

**12.3 Pharmacokinetics**

Absorption and Bioavailability

Distribution

Metabolism and Elimination-These 3 subheadings under pharmacokinetics were bolded in the approved label but are not in the proposed version from the firm, they need to be bolded for easier reading.

**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/

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Andre Jackson
7/15/2008 10:50:49 AM
BIOPHARMACEUTICS

Raman Baweja
7/15/2008 03:25:37 PM
BIOPHARMACEUTICS

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**020592 / S-035, 039, 040, 041, 049,053, 055**

**021086 / S-21, 031, 032, 034**

**021253 / S-037, 039, 043**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

# EXCLUSIVITY SUMMARY

NDA # 020592 SUPPL # 040 & 041 HFD # 130

Trade Name Zyprexa tablets

Generic Name olanzapine

Applicant Name Eli Lilly and Company

Approval Date, If Known 12/4/2009

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE5

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020592 Zyprexa (olanzapine) tablets

NDA# 021086 Zyprexa Zydis (olanzapine) orally disintegrating tablets

NDA# 021253 Zyprexa IM (olanzapine) injection

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

## PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

F1D-MC-HGIN
F1D-MC-HGIU
F1D-MC-HGMF
F1D-SB-LOAY

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

| | | |
|---|---|---|
| Investigation #1 | YES ☐ | NO ☒ |
| Investigation #2 | YES ☐ | NO ☒ |

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

| | | |
|---|---|---|
| Investigation #1 | YES ☐ | NO ☒ |
| Investigation #2 | YES ☐ | NO ☒ |

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

F1D-MC-HGIN; F1D-MC-HGIU; F1D-MC-HGMF; F1D-SB-LOAY

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # 028705 YES ☒ ! NO ☐

! Explain:

Investigation #2 !

IND # 028705 YES ☒ ! NO ☐

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

| | |
|---|---|
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |
| | ! |
| Investigation #2 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Kimberly Updegraff
Title: Project Manager
Date: 12/07/09

Name of Office/Division Director signing form: Thomas Laughren
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-20592 | SUPPL-40 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |
| NDA-20592 | SUPPL-41 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |

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/s/

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KIMBERLY S UPDEGRAFF
12/11/2009

THOMAS P LAUGHREN
12/11/2009

# EXCLUSIVITY SUMMARY

NDA # 20-592 & 21-086 SUPPL # 039 & 021 HFD # 130

Trade Name Zyprexa

Generic Name olanzapine tablets (20-592) & oral disintegrating tablets (21-086)

Applicant Name Lilly

Approval Date, If Known 3-19-09

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Both the Prozac (18-936/SE8-077) and Zyprexa (20-592/SE8-039 & 21-086/SE8-021) efficacy supplements are labeling supplements in which clinical data are referenced to the Symbyax efficacy supplement 21-520/SE1-012. Symbyax, a combination of fluoxetine and olanzapine, is approved for depressive episodes associated with bipolar disorder

(approval date 12-24-03) and treatment resistant depression (approval date 3-19-09). The applicant has received approval to place these 2 indications into the individual product's labeling stating the indications when used concomitantly with the other individual product.

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years, for the TRD claim

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-592 Zyprexa (olanzapine)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

## PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

One positive study (HDAO-2) and 2 supportive studies (Studies HGFR & HGIE)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 28705 YES ☒ ! NO ☐
! Explain:

Investigation #2

IND # 28705 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

| | |
|---|---|
| Investigation #1 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

| | |
|---|---|
| Investigation #2 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☒ NO ☒

If yes, explain:

DPP believes that exclusivity should extend to the treatment resistant indication (approved on 3-19-09). However, exclusivity should not extend to the depressive episodes associated with bipolar disorder indication (approval date 12-24-03) since this indication was approved more than 5 years ago. Regardless, if the decision is to allow generic sponsors to place either or both of these indications in the individual fluoxetine or olanzapine labelings, all of the safety information, pertaining to concomitant use of both products, should also be placed into labeling.

==========

Name of person completing form: Paul David
Title: CPMS
Date: 3-30-09

Name of Office/Division Director signing form: Thomas Laughren, MD
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

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/s/
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Thomas Laughren
3/30/2009 11:39:03 AM

**MEMORANDUM**

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

**DATE:** 3 December 2009

**FROM:** Mitchell V. Mathis, M.D.
Deputy Director
Division of Psychiatry Products, HFD-130

**TO:** File NDA 20-592 S-040, S-041

**SUBJECT:** Approval Recommendation for Zyprexa [olanzapine] Tablets for the Treatment of Schizophrenia and the Acute Treatment of Manic or Mixed Episodes Associated with Bipolar Disorder in Adolescents (ages 13-17)

## BACKGROUND AND REGULATORY HISTORY

Zyprexa is an atypical antipsychotic approved (as an oral formulation) in adults for the treatment of schizophrenia, and the acute treatment of manic or mixed episodes associated with bipolar I disorder (monotherapy or adjunctive therapy to lithium or valproic acid). The sponsor submitted one positive short-term trial in adolescents with schizophrenia (ages 13-17) and in one trial of adolescents with manic or mixed episodes associated with bipolar I disorder (ages 13-17), as well as pharmacokinetic data to support dosing in this population, and longer-term (6 months) safety data.

The Division was prepared to approve these applications after reviewing the data (see team member reviews, this NDA), but decided to first take this application (along with two others pending for similar indications) to the Psychopharmacologic Drugs Advisory Committee (PDAC) for a public discussion among experts in the fields of child psychiatry, general psychiatry, drug safety, cardiology, and endocrinology. We were specifically interested in expert opinion about expanding the indications of atypical antipsychotics into broader populations, especially given the adverse metabolic profile and yet unquantified risk of tardive dyskinesia with this class of medications.

Zyprexa (and others in the atypical antipsychotic class) has an adverse impact on glucose, lipids, and weight gain. In fact, although there are limited comparative safety data, it is our impression from having evaluated the controlled trial data for each of the atypicals that Zyprexa poses a greater risk of metabolic changes than do the others in the class (except for perhaps clozapine). Since schizophrenia and bipolar I disorder are life-long illnesses, our concern was that pediatric patients with these disorders would be treated earlier in life and for an extended period of time compared to adults, therefore increasing exposure-related risks of adverse reactions associated with drugs in this class. Zyprexa appears to have a greater adverse metabolic impact than the other drugs being evaluated in children/adolescents, and we felt like a public discussion of how to differentially label this drug would be in order.

Our safety review revealed that younger patients experienced qualitatively similar adverse reactions as adults, but there were some quantitative differences related to adverse changes in metabolic

parameters, as well as other adverse events. Our belief has been that pediatric patients represent a more treatment-naïve population, and so effects on glucose, lipids and weight are more apparent in this population, but we wanted to hear from experts and discuss these issues in public before taking a final action.

## PEDIATRIC ADVISORY COMMITTEE MEETING (PDAC)

The PDAC met on June 9-10, 2009. The members agreed with us that efficacy had been established in the studied populations for both indications. We then discussed the safety issues of concern with the committee. From a discussion of the facts and from the experience of treating physicians, it was obvious that schizophrenia and bipolar I disorder affect the pediatric population (in fact these diseases often onset during the pediatric years) and that the availability of multiple treatment options is important to the clinical management of these routinely devastating disorders. It was noted that the American Academy of Child and Adolescent Psychiatry (AACAP) recommends in its practice guidelines that antipsychotics be used in both disorders, and it was routinely accepted as fact that children and adolescents were already being treated with atypical antipsychotics, including Zyprexa, because their safety profiles are considered by many clinicians to be superior to the typical antipsychotics which have a known exposure-related risk of tardive dyskinesia. The Sponsor presented their data, and also indicated their acceptance of the Division's proposed labeling language which states that the increased potential in adolescents compared to adults for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first.

The votes of the PDAC were as follows:

- Schizophrenia
  - Effective? 11 yes; 5 no, 2 abstain
  - Safe? 10 yes; 4 no; 4 abstain
- Bipolar mania/mixed episodes
  - Effective? 17 yes; 0 no; 1 abstain
  - Safe? 11 yes; 4 no; 2 abstain

## LABELING/MEDICATION GUIDE

The labeling and Medication Guide were updated to include the pediatric indications, and pediatric safety data (which had already been included in labeling prior to our evaluation of these supplements). We also included a new section in labeling entitled *Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder*, which states that (b) (4) [redacted]. *Dosing and Administration* describes what we learned from the trials about dosing younger patients, and is presented in an easy to read tabular form in Highlights. The Medication Guide was updated to include a comprehensive description of what can be expected when using the drug, and when the patient/parent should call the prescriber. The Office of Safety and Epidemiology were consulted to evaluate the Medication Guide and the safety review team reviewed the final REMS documents.

## CONCLUSIONS

The safety and efficacy of Zyprexa has been established in pediatric patients with schizophrenia and manic or mixed episodes associated with bipolar I disorder. My recommendation to the Director is to approve these indications, with the expanded labeling and Medication Guide. This action will provide clinicians treating these patients with the proper information about dosing, a complete description of the risks of treating pediatric patients with Zyprexa (including our labeling stating that other drugs should be tried first in adolescent patients secondary to adverse metabolic effects), and a comprehensive Medication Guide to provide to patients with their prescription. These approvals would provide another treatment option for clinicians treating pediatric patients suffering from these debilitating diseases.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-20592 | SUPPL-40 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |
| NDA-20592 | SUPPL-41 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |

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

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/s/

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MITCHELL V Mathis
12/04/2009

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION[1]

| | | |
|---|---|---|
| NDA # 020592 BLA # | NDA Supplement # 040 & 041 BLA STN # | If NDA, Efficacy Supplement Type: SE5 |
| Proprietary Name: Zyprexa<br>Established/Proper Name: olanzapine<br>Dosage Form: tablets | | Applicant: Lilly<br>Agent for Applicant (if applicable): |
| RPM: Kimberly Updegraff | | Division: HFD-130 |

NDAs:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ If no listed drug, check here and explain:

**Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.**

☐ No changes ☐ Updated
Date of check:

**If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.**

**<u>On the day of approval</u>, check the Orange Book again for any new patents or pediatric exclusivity.**

| ❖ Actions | |
|---|---|
| • Proposed action<br>• User Fee Goal Date is 03/19/2009 | ☒ AP ☐ TA ☐ CR |
| • Previous actions *(specify type and date for each action taken)* | ☐ None<br>AE 04/30/2007<br>AE 08/01/2008 |

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

| | |
|---|---|
| ❖ If accelerated approval, were promotional materials received?<br>Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ | ☐ Received |
| ❖ Application Characteristics [2] | |

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☒ Submitted in response to a Pediatric Written Request

Comments:

| | |
|---|---|
| BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)* | ☐ Yes, date |
| ❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)* | ☐ Yes ☐ No |
| ❖ Public communications *(approvals only)* | |
| • Office of Executive Programs (OEP) liaison has been notified of action | ☒ Yes ☐ No |
| • Press Office notified of action (by OEP) | ☒ Yes ☐ No |
| • Indicate what types (if any) of information dissemination are anticipated | ☐ None<br>☐ HHS Press Release<br>☐ FDA Talk Paper<br>☐ CDER Q&As<br>☒ Other |

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

| | |
|---|---|
| ❖ Exclusivity | |
| • Is approval of this application blocked by any type of exclusivity? | ☒ No ☐ Yes |
| • NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.* | ☒ No ☐ Yes<br>If, yes, NDA/BLA # and date exclusivity expires: |
| • (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)* | ☐ No ☐ Yes<br>If yes, NDA # and date exclusivity expires: |
| • (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)* | ☐ No ☐ Yes<br>If yes, NDA # and date exclusivity expires: |
| • (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)* | ☐ No ☐ Yes<br>If yes, NDA # and date exclusivity expires: |
| • NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)* | ☒ No ☐ Yes<br>If yes, NDA # and date 10-year limitation expires: |
| ❖ Patent Information (NDAs only) | |
| • Patent Information:<br>Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | ☒ Verified<br>☐ Not applicable because drug is an old antibiotic. |
| • Patent Certification [505(b)(2) applications]:<br>Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(*i*)(A)<br>☐ Verified<br><br>21 CFR 314.50(i)(1)<br>☐ (ii) ☐ (iii) |
| • [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | ☐ No paragraph III certification<br>Date patent will expire |
| • [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).* | ☐ N/A (no paragraph IV certification)<br>☐ Verified |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

| | |
|---|---|
| (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?<br><br>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).<br><br>*If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*<br><br>*If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.* | ☐ Yes ☐ No |

## CONTENTS OF ACTION PACKAGE

| | |
|---|---|
| ❖ Copy of this Action Package Checklist[3] | Yes |
| **Officer/Employee List** | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)* | ☒ Included |
| Documentation of consent/non-consent by officers/employees | ☒ Included |
| **Action Letters** | |
| ❖ Copies of all action letters *(including approval letter with final labeling)* | Action(s) and date(s)<br>AP 12/04/2009<br>AE 08/01/2008<br>AE 04/30/2007 |
| **Labeling** | |
| ❖ Package Insert *(write submission/communication date at upper right of first page of PI)* | |
| • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | 11/10/2009 |
| • Original applicant-proposed labeling | 09/19/2008 |
| • Example of class labeling, if applicable | NA |

[3] Fill in blanks with dates of reviews, letters, etc.

| | |
|---|---|
| Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)* | ☒ Medication Guide<br>☐ Patient Package Insert<br>☐ Instructions for Use<br>☐ None |
| • Most-recent draft labeling. If it is division-proposed labeling, it should be in ttrack-changes format. | 11/10/2009 |
| • Original applicant-proposed labeling | 09/19/2008 |
| • Example of class labeling, if applicable | NA |
| ❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)* | |
| • Most-recent draft labeling | NA |
| ❖ Proprietary Name<br>• Acceptability/non-acceptability letter(s) *(indicate date(s))*<br>• Review(s) *(indicate date(s))* | NA |
| ❖ Labeling reviews *(indicate dates of reviews and meetings)* | ☐ RPM<br>☐ DMEDP<br>☒ DRISK<br>10/01/2009<br>03/12/2009<br>☐ DDMAC<br>☐ CSS<br>☐ Other reviews |
| **Administrative / Regulatory Documents** | |
| ❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* | Filing Review & Filing Meeting Minutes: 1/04/2007 |
| ❖ NDAs only: Exclusivity Summary *(signed by Division Director)* | ☒ Included |
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| • Applicant in on the AIP | ☐ Yes ☒ No |
| • This application is on the AIP<br>o If yes, Center Director's Exception for Review memo *(indicate date)*<br>o If yes, OC clearance for approval *(indicate date of clearance communication)* | ☐ Yes ☒ No<br>☐ Not an AP action |
| ❖ Pediatrics *(approvals only)*<br>• Date reviewed by PeRC 06/22/2009<br>If PeRC review not necessary, explain: _____<br>• Pediatric Page *(approvals only, must be reviewed by PERC before finalized)* | ☒ Included |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)* | ☒ Verified, statement is acceptable |
| ❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)* | Included |
| ❖ Internal memoranda, telecons, etc. | Included |

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

| | |
|---|---|
| ❖ Minutes of Meetings | |
| • Pre-Approval Safety Conference *(indicate date of mtg; approvals only)* | Not applicable |
| • Regulatory Briefing *(indicate date of mtg)* | ☒ No mtg |
| • If not the first review cycle, any end-of-review meeting *(indicate date of mtg)* | ☒ N/A or no mtg |
| • Pre-NDA/BLA meeting *(indicate date of mtg)* | ☐ No mtg |
| • EOP2 meeting *(indicate date of mtg)* | ☐ No mtg |
| • Other milestone meetings (e.g., EOP2a, CMC pilot programs) *(indicates dates)* | |
| ❖ Advisory Committee Meeting(s) | ☐ No AC meeting |
| • Date(s) of Meeting(s) | 6/09/2009 & 6/10/2009 |
| • 48-hour alert or minutes, if available *(do not include transcript)* | |
| **Decisional and Summary Memos** | |
| ❖ Office Director Decisional Memo *(indicate date for each review)* | ☒ None |
| Division Director Summary Review *(indicate date for each review)* | ☐ None<br>12/4/2009<br>4/29/2007 |
| Cross-Discipline Team Leader Review *(indicate date for each review)* | ☐ None<br>4/19/2007 |
| PMR/PMC Development Templates *(indicate total number)* | ☒ None |
| **Clinical Information[5]** | |
| Clinical Reviews | |
| • Clinical Team Leader Review(s) *(indicate date for each review)* | 4/12/2007 |
| • Clinical review(s) *(indicate date for each review)* | 7/18/2008<br>5/21/2007<br>4/18/2007<br>4/18/2007 |
| • Social scientist review(s) (if OTC drug) *(indicate date for each review)* | ☒ None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)* | See Clinical review dated 4/18/2007 |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)* | ☒ None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)* | ☒ Not applicable |
| ❖ Risk Management<br>• REMS Document and Supporting Statement *(indicate date(s) of submission(s))*<br>• REMS Memo *(indicate date)*<br>• Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* | 10/13/2009<br>11/29/2009<br>☐ None<br>10/6/2009 & 10/16/2009 email<br>04/19/2007 |
| ❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)* | ☒ None requested |

[5] Filing reviews should be filed with the discipline reviews.

| | |
|---|---|
| **Clinical Microbiology** ☒ None | |
| ❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)* | ☐ None |
| Clinical Microbiology Review(s) *(indicate date for each review)* | ☐ None |
| **Biostatistics** ☐ None | |
| ❖ Statistical Division Director Review(s) *(indicate date for each review)* | ☒ None |
| Statistical Team Leader Review(s) *(indicate date for each review)* | ☒ None |
| Statistical Review(s) *(indicate date for each review)* | ☐ None<br>4/27/2007<br>4/6/2007 |
| **Clinical Pharmacology** ☐ None | |
| ❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)* | ☒ None |
| Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)* | ☐ None 4/2/2007 |
| Clinical Pharmacology review(s) *(indicate date for each review)* | ☐ None 3/27/2007 |
| ❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)* | ☒ None |
| **Nonclinical** ☒ None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) *(indicate date for each review)* | ☐ None |
| • Supervisory Review(s) *(indicate date for each review)* | ☐ None |
| • Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | ☐ None |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)* | ☐ None |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | ☐ No carc |
| ❖ ECAC/CAC report/memo of meeting | ☐ None<br>Included in P/T review, page |
| ❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)* | ☐ None requested |
| **Product Quality** ☐ None | |
| ❖ Product Quality Discipline Reviews | |
| • ONDQA/OBP Division Director Review(s) *(indicate date for each review)* | ☒ None |
| • Branch Chief/Team Leader Review(s) *(indicate date for each review)* | ☒ None |
| • Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)* | ☐ None 1/17/2007 |
| ❖ Microbiology Reviews<br>☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)*<br>☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)* | ☒ Not needed |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)* | ☒ None |

| | |
|---|---|
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)* | 1/17/2007 |
| ☐ Review & FONSI *(indicate date of review)* | |
| ☐ Review & Environmental Impact Statement *(indicate date of each review)* | |
| ❖ Facilities Review/Inspection | |
| ☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date)* | Date completed:<br>☒ Acceptable<br>☐ Withhold recommendation |
| ☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date)* | Date completed:<br>☐ Acceptable<br>☐ Withhold recommendation |
| ❖ NDAs: Methods Validation *(check box only, do not include documents)* | ☐ Completed<br>☐ Requested<br>☐ Not yet requested<br>☐ Not needed |

## Appendix A to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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 ADRA.

**SUPPLEMENT NDA 20-592 S-040/S-041**
**REMS ASSESSMENT TO SUPPORT PROPOSED REMS MODIFICATION**

Per FDCA 505-1(g), Eli Lilly and Company, Inc. (Lilly) has assessed the REMS for Zyprexa tablets (approved 19 March 2009) and determined that a modification to the Medication Guide is necessary to extend the population for the indications of schizophrenia and mixed or manic episodes associated with bipolar I disorder to include adolescents (13-17 years). The goal of the REMS remains unchanged. Lilly believes the Medication Guide included in this submission is adequate to achieve its purpose. Lilly will continue to assess the REMS per the timetable approved on 19 March 2009.

**NDA 20-592, ZYPREXA (olanzapine) Tablet for Oral Use**
**NDA 21-086, ZYPREXA ZYDIS (olanzapine) Tablet, Orally Disintegrating for Oral Use**

Deleting contact information as not required per FDA communication on 20 March 2009

(b) (4)

[redacted]

## PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

### I. Goals(s)

The goal of the REMS is to inform patients of the serious risks associated with the use of Zyprexa (olanzapine) Tablet for Oral Use and Tablet, Orally Disintegrating for Oral Use, including the risks of hyperglycemia, hyperlipidemia, and weight gain.

### II. REMS Elements

### A. Medication Guide

The Medication Guide will be dispensed with each Zyprexa prescription in accordance with 21 CFR 208.24.

### B. Communication Plan

This REMS for Zyprexa does not include a Communication Plan.

### C. Elements to Assure Safe Use

This REMS for Zyprexa does not include elements to assure safe use.

### D. Implementation System

Because this REMS for Zyprexa does not include elements to assure safe use, an implementation system is not required.

Revised timetable as requested by FDA on 7 October 2009. Deleted text shown as strike-through, new text shown in red.

### E. Timetable for Submission of Assessments

The Timetable for Assessments is as follows:

(b) (4)

[redacted]

- The first assessment is due 18 months from the original approval date of the REMS (September 19, 2010)
- The second assessment is due 3 years from the original approval date of the REMS (March 19, 2012)
- The third assessment is due 7 years from the original approval date of the REMS (March 19, 2016)

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Eli Lilly and Company will submit each assessment so it will be received by the FDA on or before the due dates listed above.

**REMS MEMO – NEW APPROVAL TEMPLATE**
**October 21, 2009**

## Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**
**Office of Drug Evaluation I**
**Division of Psychiatry Products**

| | |
|---|---|
| **NDA/BLA #s:** | 020592/S040/S041 |
| **Products:** | ZYPREXA (olanzapine) oral tablets<br>ZYPREXA ZYDIS (olanzapine) orally disintegrating tablets |
| **APPLICANT:** | Eli Lilly and Company |
| **FROM:** | Thomas Laughren, MD, Director, Division of Psychiatry Products |
| **DATE:** | November 13, 2009 |

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

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 outweigh the risks of weight gain, hyperglycemia and hyperlipidemia associated with all forms of ZYPREXA (olanzapine). In reaching this determination, we considered the following:

A. Schizophrenia affects about 1% of the population (DSM-IV-TR, APA 2000). The estimated number of patients in the United States with schizophrenia is about 2.4 million (Regier et. al., 1993).

   The estimated prevalence of bipolar disorder is about 0.4 to 1.6% ( DSM-IV-TR, APA 2000). The estimated number of patients in the United States with bipolar disorder is about 5.7 million (Kessler et. al., 2005).

B. Schizophrenia is a serious mental illness that includes disorder of thinking, disorganized behavior, deficits in cognition, affect, and social functioning. It is a chronic and debilitating illness that affects many aspects of a patient's life and has

been associated with reduced life expectancy (AACAP 2001, APA 2000a, APA 2004). Adolescents with schizophrenia, like affected adults, have significant impairment, including similar thought disorder, deficits in cognition, affect, and social functioning. Childhood onset schizophrenia is a clinically severe form of schizophrenia in which the disruption in cognitive, linguistic, and social development can occur before the appearance of psychotic symptoms (Jacobsen and Rapoport 1998).

Bipolar disorder is a lifelong psychiatric illness that is characterized by significant morbidity and mortality and is often progressive (Lish et al 1994). Children and adolescents with mania, like affected adults, have significant social impairment leading to conflict within the family, repeated hospitalization, and increased economic burden on the family (Findling et al 2003, Papolos and Papolos 1999). Adolescents with bipolar disorder have an increased risk of substance-abuse disorders (Wilens et al 1999).

C. Prior to approval of this set of NDA supplements for adolescents with schizophrenia and bipolar disorder, there were there were limited therapeutic options approved for adolescent patients with schizophrenia and bipolar mania. ZYPREXA (olanzapine) demonstrated efficacy as compared to placebo in two clinical trials (one in adolescents with schizophrenia 13 to 17 years of age and one in adolescents with bipolar). ZYPREXA (olanzapine) has been shown to reduce the psychotic signs and symptoms in adolescent patients with schizophrenia and to reduce manic symptoms in adolescent patients with bipolar mania when compared to placebo in clinical trials. ZYPREXA (olanzapine) is approved in the US for the treatment of adult patients with schizophrenia and mania.

D. The expected duration of therapy with ZYPREXA (olanzapine) in patients who obtain a clinical response will minimally be 6 months to a year, and may be for many years; schizophrenia and bipolar disorder are considered life-long diseases, although the severity of symptoms may vary over time.

E. Several safety concerns have been identified in the adult clinical trials programs for olanzapine. Known potential safety signals include weight gain, hyperlipidemia, and hyperglycemia. Based on the DPP review of safety data included in the pending pediatric efficacy supplements for schizophrenia and bipolar disorder under NDA-20592/S-040 and 041, the submissions revealed consistent findings with the previously observed safety profile of ZYPREXA (olanzapine) in adult clinical trials.

The current ZYPREXA(olanzapine) label contains Warning language describing an association with hyperglycemia, diabetes mellitus, weight gain, and lipid elevations. The label also contains the standard Boxed Warning regarding increased risk of mortality in elderly patients with dementia related psychosis. This risk has been addressed in the revised Medication Guide for ZYPREXA (olanzapine).

F. ZYPREXA (olanzapine) is not a new molecular entity (NME).

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for ZYPREXA (olanzapine). FDA has determined that ZYPREXA (olanzapine) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of ZYPREXA (olanzapine). FDA has determined that ZYPREXA (olanzapine) has 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 ZYPREXA (olanzapine).

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

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

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-20592 | SUPPL-40 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |
| NDA-20592 | SUPPL-41 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |

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/s/

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KIMBERLY S UPDEGRAFF
11/28/2009

THOMAS P LAUGHREN
11/29/2009

**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: October 6, 2009

To: Thomas Laughren, M.D., Director
**Division of Psychiatry Products (DPP)**

Through: Claudia Karwoski, PharmD, Director
**Division of Risk Management**

From: Jessica M. Diaz, RN, BSN
Patient Product Information Reviewer
**Division of Risk Management**

Subject: Review of ZYPREXA REMS (originally approved March 19, 2009), submitted with S040 and S041

Drug Name(s): ZYPREXA (olanzapine) tablets

Application Type/Number: NDA 20-592 S040 & 041

Applicant/sponsor: Eli Lilly and Company

OSE RCM #: 2009-1412

This memorandum serves as a review of the ZYPREXA (olanzapine) tablets Risk Evaluation and Mitigation Strategy (REMS) approved March 19, 2009. Eli Lilly and Company submitted the REMS and an updated Medication Guide as part of the proposed labeling to pediatric supplements S040 and S041. DRISK completed a review of the Medication Guide on October 1, 2009. In addition, to the changes to the Medication Guide there are some minor modifications that are needed, specifically to the Timetable for Submission of Assessments for the already approved REMS to ensure clarity around the REMS Assessments due date . The language in the REMS should be revised as follows:

**Timetable for Submission of Assessments**

- The first assessment is due 18 months from the original approval date of the REMS (September 19, 2010)
- The second assessment is due 3 years from the original approval date of the REMS (March 19, 2012)
- The third assessment is due 7 years from the original approval date of the REMS (March 19, 2016)

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Eli Lilly and Company will submit each assessment so it will be received by the FDA on or before the due dates listed above.

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/s/

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JESSICA M DIAZ
10/06/2009

CLAUDIA B KARWOSKI
10/06/2009
concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20-592 S-040/S-041

**REMS Modification Notification**

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Attention: Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs

Dear Dr. Brophy:

We are reviewing your supplemental new drug applications dated and received on September 19, 2008, for Zyprexa (olanzapine) tablets, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg. These supplements provide for the use of Zyprexa (olanzapine) tablets in treating manic or mixed episodes of bipolar I disorder and schizophrenia in adolescents.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENT**

The Risk Evaluation and Mitigation Strategy (REMS) for Zyprexa (olanzapine) tablets was approved on March 19, 2009. The REMS consisted of a Medication Guide and a timetable for submission of assessments of the REMS. As these supplemental new drug applications provide for a new indication -- the use of Zyprexa (olanzapine) tablets in the adolescent population-- in accordance with section 505-1(g)(2)(A), you are required to submit an assessment and may propose a modification of the existing REMS. You have proposed modifications to the Medication Guide to extend the current warnings and precautions to include adolescents ages 13 to 17, but you have not yet submitted an assessment of the REMS. Where the REMS consists solely of a Medication Guide, the REMS assessment may consist of a statement that the Medication Guide would be adequate with the proposed modifications to achieve its purpose. Your proposed REMS modification submission should include the REMS document that was approved on March 19, 2009, in addition to your revised Medication Guide. The timetable for submission of assessments of the REMS may remain the same as that approved on March 19, 2009.

We request that you submit your modified REMS and REMS Assessment as described above to these supplements by the close of business on October 16, 2009. The modified REMS, once approved, will create enforceable obligations.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**SUPPLEMENT NDA 20-592 S-040/S-041**
**PROPOSED REMS MODIFICATION**

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

**SUPPLEMENT NDA 20-592 S-040/S-041**
**PROPOSED REMS MODIFICATION-AMENDMENT**

If you do not submit electronically, please send 5 copies of your submission.

If you have any questions, please call Kimberly Updegraff, M.S., Senior Regulatory Project Manager, at (301) 796-2201.

Sincerely yours,

*{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

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-20592 | SUPPL-40 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |
| NDA-20592 | SUPPL-41 | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/ |

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/s/

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THOMAS P LAUGHREN
10/06/2009

## Updegraff, Kimberly

**From:** Updegraff, Kimberly
**Sent:** Monday, April 13, 2009 5:34 PM
**To:** Christine Ann Phillips
**Cc:** Updegraff, Kimberly
**Subject:** NDA 20-592 S040/S041

Dear Christine,

Please refer to your submissions dated December 1, 2008 for NDA 20-592 S-040 and S-041 providing for the use of Zyprexa for the treatment of manic or mixed episodes associated with bipolar disorder and schizophrenia in adolescents.

- Please provide a list of investigators for all trials (not just the pivotal trials) for each indication (schizophrenia/bipolar).

Thanks,

*Kim*

Kimberly Updegraff
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation
Phone: (301)796-2201

**M E M O R A N D U M**

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) Zydis, 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 March10, 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 seamed 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 written to convey, "the particular serious and significant pubic 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/

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Mitchell Mathis
3/19/2009 12:20:43 PM
MEDICAL OFFICER

## 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:

o 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

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

Sincerely,
Rimmy

Appendix A.pdf (62 KB)

---

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

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/s/

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

## David, Paul A

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

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

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

- **We are aware that the sponsor was not provided with a REMS template prior to submission of the REMS as part of their Complete Response. As a result, the proposed REMS does not follow the recommended format.**
- **We request that the sponsor revise and resubmit the proposed REMS to follow the template that the review division provides. We are attaching the REMS template below.**
- **We recommend the REMS goal be revised for [Zyprexa (olanzapine)] or [Symbyax (olanzapine and fluoxetine)], as follows:**

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

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

Of note, the sponsor's submitted (b) (4) This may not be used in place of actual assessments because the participants did not receive the approved Medication Guide.

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

CAPT Paul A. David, R.Ph.
Chief, Project Management Staff
Division of Psychiatry Products/HFD-130
Food and Drug Administration

10903 New Hampshire Avenue, Building 22, Room 4100
Silver Spring, Maryland 20993-0002

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

11/25/08

**APPENDIX A- REMS TEMPLATE**
<<If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.>>

**Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name
Address
Contact Information

**PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

## I. GOAL(S):

List the goals and objectives of the REMS.

## II. REMS ELEMENTS:

### A. Medication Guide or PPI

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

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

### B. Communication Plan

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

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

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

### C. Elements To Assure Safe Use

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

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

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

**D. Implementation System**

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

**E. Timetable for Submission of Assessments**

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

11/25/08

APPEARS THIS WAY ON ORIGINAL

11/25/08

**Appendix B**

## REMS Supporting Document Template

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

1. Background

2. Goals

3. Supporting Information on Proposed REMS Elements

    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System
    d. Timetable for Assessment of the REMS

4. Information Needed for Assessments

5. Other Relevant Information

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/s/

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

**Bates, Doris J**

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

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

Dear Dr. Phillips and Dr. Brophy:

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

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

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

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

Sincerely,

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

## Updegraff, Kimberly

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

**Importance:** High

Hi Kimberly,

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

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

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

Thank you.

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

Please consider the environment before printing this e-mail.

## Updegraff, Kimberly

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

**Importance:** High

Hello Sarah,

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

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

Best Regards,

Jess

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

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

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

Enjoy your weekend,
Sarah

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

Dear Sarah,

## Grewal, Renmeet

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

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

Regards,
Rimmy

---

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

Hi Christine,
Regarding your submission dated and received on September 19, 2008. After an initial review of the submission the agency has decided this is a complete response to the August 1, 2008 approvable letter. This is considered a class 2 submission and the PDUFA date is March 19, 2008, however if the agency completes 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*
*Fax: (301) 796-9838*

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/s/

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

## Grewal, Renmeet

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

Hi Christine,

Regarding your submission dated and received on September 19, 2008. After an initial review of the submission the agency has decided this is a complete response to the August 1, 2008 approvable letter. This is considered a class 2 submission and the PDUFA date is March 19, 2008, however if the agency completes 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*
*Fax: (301) 796-9838*

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/s/

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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 | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| 9/25/08 | | 20-592/s-039/040/041<br>21-520/012, 21-086/021,18-936/077 | REMS: addition of a Medguide | 9/19/08 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| Olanzapine | | | **PDUFA: 3-19-09**<br>**WANT TO ACT SOONER** |

NAME OF FIRM: Eli Lilly

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- X SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER (SPECIFY BELOW): |

**III. BIOPHARMACEUTICS**

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

- ☐ CLINICAL
- ☐ PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**

Hi Mary,

This is a response to an approvable letter sent (8-1-08) to the sponsor including a REMS to respond with a MEDGUIDE. The sponsor has responded to our approvable letter. Since this contains a medguide we are coding it a 6 month clock however we would like to act on these supplements sooner. I have attached the links to the sponsor's response.

The network location for Zyprexa is : \\FDSWA150\NONECTD\N20592\S_040\2008-09-19
The network location for Symbyax is : \\FDSWA150\NONECTD\N21520\S_012\2008-09-19
The network location for Prozac is : \\FDSWA150\NONECTD\N18936\S_075\2008-09-19

If you have any further questions please contact me at either renmeet.grewal@fda.hhs.gov or 301-796-1080.

Thanks,
Rimmy

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) |
|---|---|
| Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager<br>301-796-1080<br>Renmeet.grewal@fda.hhs.gov | ☐ MAIL ☐ HAND |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

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/s/

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

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

Dear Dr. Melfi:

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

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

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

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

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

**WARNING**

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

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

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

> **WARNINGS**
>
> **Increased Mortality in Elderly Patients with Dementia-Related Psychosis** — Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Zyprexa is not approved for the treatment of patients with dementia-related psychosis (*see* **BOXED WARNING**).

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

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(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, text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved supplements NDAs 20-592/S-049, 21-086/S-028, & 21-253/S-033.**"

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

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

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

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

**PROMOTIONAL MATERIALS**

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

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

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

**LETTERS TO HEALTH CARE PROFESSIONALS**

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

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

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

If you have any questions, call LCDR Sonny Saini, Pharm. D., Safety Project Manager, at (301) 796-0532.

Sincerely,

*{See appended electronic signature page}*

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

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Thomas Laughren
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# 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<br>Zyprexa (olanzapine) tablets<br>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 dyskinisia, 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/
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Thomas Laughren
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MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

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

Dear Dr. Phillips:

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

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

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

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

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

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

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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Thomas Laughren
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

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

Dear Dr. Melfi:

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

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

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

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

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

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

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

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

Sincerely,

*{See appended electronic signature page}*

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

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Thomas Laughren
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**M E M O R A N D U M** **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** April 29, 2007

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

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

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

## 1.0 BACKGROUND

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

## 2.0 CHEMISTRY

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

## 3.0 PHARMACOLOGY

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

## 4.0 BIOPHARMACEUTICS

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

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

## 5.0 CLINICAL DATA

### 5.1 Efficacy Data

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

#### 5.1.1 Study HGIU (Acute Mania in Bipolar I Disorder)

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

#### 5.1.2 Study HGIN (Acute Schizophrenia)

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

Highly Non-Significant Results on the MMRM and OC Analyses

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

> Comment: In my tertiary evaluation, I found this discrepancy between LOCF and MMRM quite unusual, in my experience, and asked for further exploration. As it turned out, Dr. Kong's MMRM analysis was quite discrepant with the sponsor's MMRM analysis (p=0.015). Upon further evaluation, Dr. Kong discovered that the program he had used to conduct the analysis included, as a default, a variance-covariance structure that required independence between the repeated observations for any subject. This is an unusual requirement, and not the variance-covariance structure that we generally recommend. In fact, we almost always recommend an unstructured variance-covariance structure, i.e., the same one used by the sponsor, and a goodness-of-fit exploration for different variance-covariance structures revealed the best fit for this structure. Thus the biometrics group has now recommended that we accept the sponsor's highly significant MMRM result (see addendum to original biometrics review).
>
> Regarding the OC analysis, this remains a discrepancy with the LOCF and the revised MMRM analyses. However, I am not as troubled by this outcome on the OC analysis. As noted, the dropouts on placebo were very substantial, and I'm inclined to view the patients completing a study such as this to 6 weeks on placebo as quite different than the remaining patients. I think the diagnosis of schizophrenia in this younger population is challenging, and likely results in the inclusion of some patients who improve spontaneously, and thus, are doing as well as drug-treated patients at 6 weeks simply because they represent a very different group of patients. This, I think the OC results for this trial can be largely discounted.

Treatment by Geographic Region Interaction

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

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

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

### 5.1.3 Summary of Efficacy

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

## 5.2 Safety Data

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

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

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

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

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

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

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

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

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

### 5.3 Clinical Sections of Labeling

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

## 6.0 WORLD LITERATURE

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

## 7.0 FOREIGN REGULATORY ACTIONS

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

## 8.0 DSI INSPECTIONS

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

## 9.0 LABELING AND APPROVABLE LETTER

### 10.1 Labeling

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

### 10.2 Foreign Labeling

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

### 10.3 Approvable Letter

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

## 10.0 CONCLUSIONS AND RECOMMENDATIONS

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

cc:
Orig NDA 20-592/S-040 and 041
HFD-130/TLaughren/MMathis/NKhin/CAlfaro/KKiedrow/DBates/SHardeman

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/s/
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Thomas Laughren
4/29/2007 10:55:29 AM
MEDICAL OFFICER

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

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Date: April 19, 2007

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

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

From: OSE Risk Management Team

Drug Name: Zyprexa (olanzapine)

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

Sponsor: Eli Lilly

OSE RCM#: 2006-1170

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

## 1 INTRODUCTION

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

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

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

## 2 MATERIALS REVIEWED

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

## 3 RESULTS OF REVIEW

### *3.1 Safety Risks*

#### 3.1.1 Sponsor's Safety Concerns

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

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

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

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

### 3.1.2 DPP Safety Concerns

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

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

## *3.2 Sponsor's Proposed Risk Management Plan*

### 3.2.1 Pharmacovigilance Activities

Eli Lilly proposes the following pharmacovigilance activities:

### 3.2.2 Risk Minimization Activities

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

## 4 DISCUSSION AND CONCLUSION

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

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

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

OSE Risk Management Team
Claudia Karwoski, Pharm.D., Risk Management Team Leader, OSE-IO
Mary Dempsey, Risk Management Program Coordinator, OSE-IO

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

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/s/

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

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

**Bates, Doris J**

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

Dear Dr. Melfi:

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

1. For the Acute Placebo Controlled Combined Database, please provide a subgroup analysis for age (< 15, >= 15) for the variable "weight in kg" similar to Table 2.7.4.70 in the summary-clin-safety document.

2. Please provide a subgroup analysis for age (< 15 and >=15) and gender for the variable "PCS weight change (> 7%)" for the Acute Placebo Controlled Combined Database.

3. It appears that the study report for HGIN includes all vital signs analyses for all subgroups (e.g. Table HGIN.14.47) while these analyses are only included in the study report for HGIU if the treatment by subgroups analysis was significant (e.g. HGIU.12.45). Please provide the subgroup analyses for HGIU similar to that provided in Table HGIN.14.47.

4. In section 2.7.4.7.5 of the summary-clin-safe-app document, analyses are provided for suicide-related adverse events. In reviewing Table APP.2.7.4.7.5.9 (patients with possible suicidal behavior or ideation - combined database), there appear to be 3 cases that do not have narratives listed in this document or in the Table of Significant and Notable Patients document. Please provide case narratives for the following cases: HGMF-008-0805, LOAY-401-4012 and LOAY-407-4077.

5. In the summary-clin-safe-app document, section 2.7.4.7.1.3.2.6 presents correlation coefficients between weight and a number of factors for the Overall Olanzapine Exposure Combined Database. Please provide these data for the Acute Placebo Controlled Database.

6. In the summary-clin-safe-app document, section 2.7.4.7.1.3.3 compares data between the adolescent and adult populations. For these population comparisons, the Overall Olanzapine Exposure Combined Database is used. Is a comparison of these populations including only the acute, double-blind trial data available?

7. In proposed labeling, some adverse events have been removed from the sections "other adverse events observed during the clinical trial evaluation of oral olanzapine" and "other adverse events observed during the clinical trial evaluation of intramuscular olanzapine for injection". In the former section, it appears that all of the frequently occurring AEs ("frequent") have been removed. In both sections, many adverse events that were included in the infrequent and rare categories have been removed. Please provide a justification for removal of these adverse events from proposed product labeling.

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

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

Dear Dr. Melfi:

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

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

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

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

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

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

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

Thank you, and best regards,

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

**M E M O R A N D U M**

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

**DATE:** April 18, 2007

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

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

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

## 1. BACKGROUND

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

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

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

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

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

## 2.0 CHEMISTRY

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

## 3.0 PHARMACOLOGY/TOXICOLOGY

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

## 4.0 CLINICAL PHARMACOLOGY

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

In brief, the sponsor reported that olanzapine pharmacokinetics was similar in adolescents and adults. The sponsor also claimed in their proposed labeling that (b) (4) However, Dr. Jackson noted that due to the poor quality of the prediction of the true steady-state values with the model, only the observed range of steady-state values was used. As Dr. Jackson pointed out in his review that in clinical studies, most adolescents had a lower average body weight compared to adults, resulting in an average range of olanzapine exposure that was approximately 30-63% higher in adolescents than adult patients. Dr. Jackson provided labeling comments to reflect these findings.

## 5.0 CLINICAL DATA

### 5.1 Efficacy Data

#### 5.1.1 Overview of Studies Pertinent to Efficacy

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

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

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

### 5.1.2 Summary of Studies Pertinent to Efficacy Claim

#### 5.1.2.1 Study F1D-MC-HGIN (Schizophrenia)

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

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

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

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

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

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

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

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

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

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

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

Comment:

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

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

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

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

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

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

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

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

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

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

Comment:

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

### 5.1.3 Comments on Other Important Efficacy Issues

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

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

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

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

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

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

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

### 5.1.4 Conclusions Regarding Efficacy Data

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

## 5.2 Safety Data

### 5.2.1 Safety Database

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

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

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

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

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

### 5.2.2 Safety Findings and Issues of Particular Interest

#### 5.2.2.1 Common and Drug-Related Adverse Events

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

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

#### 5.2.2.2 Weight Gain

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

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

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

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

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

### 5.2.2.3 Abnormal Laboratory Tests

**Liver function tests**

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

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

**Lipid profile (Hypertriglyceridemia, Hypercholesterolemia)**

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

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

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

**Hyperglycemia**

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

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

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

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

**Hyperprolactinemia**

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

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

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

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

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

**Elevated CPK**

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

**5.2.2.4 Vital signs and ECG changes**

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

**5.2.2.5 Extrapyrimidal Symptoms**

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

**5.2.2.6 Suicidality**

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

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

### 5.2.2.7 Risk Management Plan

The sponsor's proposed risk management plan includes (b) (4) [redacted]. The OSE was consulted on this proposed risk management plan. The OSE has stated that they would provide their input on the appropriateness of the RMP after the sponsor submits a complete response to the action letter.

### 5.2.3 Conclusion Regarding Safety Data

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

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

## 6.0 WORLD LITERATURE

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

## 7.0 FOREIGN REGULATORY ACTION

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

## 8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

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

## 9.0 DSI INSPECTIONS

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

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

## 10.0 LABELING AND ACTION LETTER

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

## 11.0 CONCLUSION AND RECOMMENDATION

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

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

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

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/s/

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

**MEMORANDUM**
**SERVICES**

**DEPARTMENT OF HEALTH AND HUMAN**

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

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# CLINICAL INSPECTION SUMMARY

DATE: 4/12/2007

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

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

FROM: Khairy Malek, Medical Officer

SUBJECT: Evaluation of Clinical Inspections

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

APPLICANT: Eli Lilly & Co., Inc.

DRUG: Zyprexa (olanzapine)

THERAPEUTIC CLASSIFICATION: Priority

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

CONSULTATION REQUEST DATE: December 1, 2006

DIVISION ACTION GOAL DATE: April 30, 2007

PDUFA DATE: April 30, 2007

I. BACKGROUND:

Olanzapine is a psychotropic agent approved by the FDA in 1996 in the treatment of psychotic disorders including schizophrenia and also approved for the treatment of acute manic episode associated with adult bipolar 1 disorder.
The two new supplements are for the same indications in the pediatric population and the protocols included adolescents 13-17 years old. Supplement SE5-040, protocol F1D-MC-HGIU(a) is titled "Olanzapine Versus Placebo in the Treatment of Mania in Adolescents with Bipolar 1 Disorder". Supplement SE5-041, protocol F1D-MC-HGIN(c) is titled "Olanzapine Versus Placebo in the Treatment of Adolescents with Schizophrenia"

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

Summary Report of U.S. and Foreign Inspections

II. RESULTS (by protocol/site):

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

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

A. Protocol # HGIU

1. Robert Riesenberg-Atlanta Georgia

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

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

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

2. Melissa DelBello-Cincinnati, Ohio

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

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

B. Protocol HGIN:

1. Robert Riesenberg-Atlanta, Georgia

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

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

2. Melissa DelBello-Cincinnati, Ohio

At this site six subjects enrolled in the study. The field investigator audited all the records in the study. No violations were observed.
There was no limitation to the inspection.

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

3. Leonid Bardenstein-Moscow, Russia.

At this site ten subjects were enrolled, but 6 subjects completed the double-blind portion of the study. Four subjects were discontinued during that phase, 2 due to physician perceived lack of efficacy, I due to subject perceived lack of efficacy and one because of elevated liver enzymes. Nine subjects completed the open-label period of the study (all except the one with elevated liver enzymes).
The field investigator reviewed the records of all subjects in the study. Few protocol violations were observed:

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

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

There was no limitation of the inspection.

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

4. Valery Kransov-Moscow, Russia

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

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

There was no limitation of the inspection.

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

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

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

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

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

Khairy Malek
Medical Officer

{See appended electronic signature page}

CONCURRENCE:

{See appended electronic signature page}

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

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

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

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

**Bates, Doris J**

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

Dear Dr. Melfi:

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

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

1. It is unclear whether there was greater weight gain in patients with lower BMI at baseline (and visa versa). Please provide an analysis of weight gain based on the patient's baseline BMI to address this question.

2. Please provide the numbers of patients in both the placebo and olanzapine treatment groups who were obese (BMI > 30) at baseline and at end of study. Was there a statistical difference?

3. Please provide a subgroup analysis for laboratory data (similar to the summary in Table 2.7.4.33 in summary-clin-safety). Include all olanzapine patients who gained greater than 3.9 kg (mean weight gain from baseline) compared to all placebo patients.

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

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

Sincerely,

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

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

**FILING COMMUNICATION**

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

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

Dear Ms. Wojcieszek:

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

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

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

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

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

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

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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

**Bates, Doris J**

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

Good morning Dr. Melfi:

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

**********

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

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

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

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

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

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

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

**********

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

**********

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

**********

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

Thank you, and best regards,

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

**Bates, Doris J**

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

Dear Dr. Melfi:

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

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

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

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

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

With best regards,

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

**Bates, Doris J**

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

Hi Dr. Melfi:

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

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

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

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

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

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

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

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

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

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

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

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

Hi Doris:

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

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

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

Thanks!

Cathy

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

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

email: melfi@lilly.com

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**MEMORANDUM**

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

**DATE:** February 14, 2007

**TO:** Administrative File

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

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

- The above three supplemental NDAs were submitted as efficacy supplements along with sNDA 21-520/S-012 (Symbyax) for the treatment of Treatment Resistant Depression (TRD). All four efficacy supplements were classified as priority reviews.

- The Agency filed sNDA 21-520/S-012 but refused to file the above three sNDAs since clinical studies for the TRD indication were only conducted with the Symbyax formulation.

- Eli Lilly (the sponsor) sent in a meeting request dated 1-4-07, and received 1-5-07, to discuss why the Agency refused to file the above three sNDAs. The meeting package was comprised of a justification for placing the combination product into each of the labelings for the individual products as well as an alternative labeling proposal to describe this information.

- The Agency granted the meeting. During the pre-meeting, it was decided, given the alternative labeling proposal and justification, the Agency would file these applications.

- The sponsor was informed that the 1-4-07 meeting package would constitute the resubmission date.

- The sponsor was also informed that these supplements would be coded as a standard review classification since approval was linked to the Agency's review of the Symbyax TRD applications.

- The DR was informed to change the UF coding to clinical data by reference.

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

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

---

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

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

Sincerely,
Rimmy

---

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

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/s/

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

**Bates, Doris J**

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

Good morning Dr. Melfi:

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

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

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

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

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

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

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

Thank you, and best regards,

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

**Bates, Doris J**

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

Good afternoon Dr. Melfi,

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

---

1. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF analysis (similar to table HGIN 14.20 for OC analysis) - with and without site 021.

2. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF and OC analysis for the US and Russia sites separately.

3. Provide patient baseline demographics and analysis for US vs. Russia sites (similar to HGIN.11.1 but comparing US vs. Russia).

4. It is noted that 50 patients were randomized at the 5 sites in Russia - 10 patients per site. Is it coincidental that 10 subjects were randomized at each of these sites? Were caps specified to the investigators such that each site could randomize no more than 10 patients?

---

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

Thank you and best regards,

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

# NDA REGULATORY FILING CHECKLIST

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

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

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

***NOTE:***

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

*(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

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

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

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

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

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

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

application? YES ☒ NO ☐
If yes, explain:
NDA 21253 intramuscular injection exclusivity expires 29MAR2007,
NDA 21086 orally disintegrating tablet exclusivity for long term tx of bipolar disorder expires 14JAN2007
NDA 20592 tablet exclusivity for long term tx of bipolar disorder expires 14JAN2007

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

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

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

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. ***Yes***

- List referenced IND numbers: ***IND 28,705 only***

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

## Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  ***Not applicable***
  YES ☐ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☒ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☐
  ***Not applicable***

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

## Chemistry

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

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/s/

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Doris Bates
1/4/2007 03:35:37 PM
CSO

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

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

DATE: 15 December 2006

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

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

| **Discipline** | **Participants** |
|---|---|
| Division Director | Thomas P. Laughren, M.D. |
| Deputy Director | [Mitchell Mathis, M.D.] |
| Clinical Team Leader and Reviewer: | Ni Aye Khin, M.D. / Cara Alfaro, Pharm.D. |
| Secondary Medical: | not applicable |
| Statistical Team Leader: and Reviewer | Peiling Yang, Ph.D. / Fanhui Kong, Ph.D. |
| Pharmacology Team Leader and Reviewer: | not applicable |
| Statistical Pharmacology: | not applicable |
| Chemistry PAL and Reviewer | [Janice Brown, Ph.D.] |
| Environmental Assessment (if needed): | [Janice Brown, Ph.D.] [categorical exclusion] |
| Biopharmaceutics Team Leader and Reviewer: | Ray Baweja, Ph.D. / Andre Jackson, Ph.D. |
| DSI: | [Khairy Malek, Ph.D.] |
| Regulatory Project Management: | Doris J. Bates, Ph.D. |
| HFD-130 Clinical Safety: | not applicable |
| ODS Clinical Safety (RiskMAP-IO): | Mary Dempsey |
| DDMAC: | not applicable |

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

CLINICAL FILE ☒ REFUSE TO FILE ☐

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

STATISTICS FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

***Categorical exclusion was omitted, has been requested and received.***

ELECTRONIC SUBMISSION: No comments.

REGULATORY CONCLUSIONS/DEFICIENCIES:
**(Refer to 21 CFR 314.101(d) for filing requirements.)**

☐ The application is unsuitable for filing. Explain why:

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

- ☐ No filing issues have been identified.
- ☒ Clinical review issues have been identified and are to be communicated by Day 74.

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

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

**Milestones for this project:**
Filing date: 12-29-06.
74-day letter date: 1-12-2007.
Pediatric Exclusivity Board Date: 1-10-07. Exclusivity Pkg due to PEB: 1-1-07.
PEB Exclusivity Finding Due Day 90: 1-29-07.
Midcycle meeting: 2-12-2007.
Internal Deadline for reviews to Team Leaders: 3-26-07
Internal Deadline for reviews to Clinical TL: 4-09-07
Internal Deadline for package to Dr. Laughren:: 4-16-07
Clinical and Clinical Pharmacology Summaries Due for Web Release by Day 175: 4-24-2007
PDUFA date: 4-30-2007

Doris J. Bates, Ph.D.
Regulatory Project Manager, HFD-130

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/s/

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Doris Bates
1/4/2007 03:39:57 PM
One meeting for both submissions under a common Written Request.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**FILING COMMUNICATION**
**ISSUES IDENTIFIED**

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

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

Dear Dr. Melfi:

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

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

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

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

1. In protocols HGIU and HGIN, height was obtained using "a measuring device supplied by the sponsor" that required calibration. Please provide a description of this measuring device.

2. The primary efficacy analysis in study HGIN excluded data from site 021 due to GCP issues at that site (it is noted that results are similar with and without this site). Please provide details regarding the GCP issues at this site or specify where this information may be found in the study report.

3. In protocol HGIN, it is noted that "The scoring of the anchored version of the BPRS-C is determined by interviews with both the patient and the parent/legal guardian at all visits. The reference score (as recorded in the CRFs) should be the higher of the two scores". Viewing the

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

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

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Thomas Laughren
1/4/2007 09:58:13 PM

**Bates, Doris J**

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

Dr. Jackson:

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

Included in this e-mail message is:
- The Note to the Reviewers
- 3 bioanalytical methods study reports, one for each of the studies:
  1.F1D-MC-HGGC
  2.F1D-MC-HGCS
  3.F1D-MC-HGMF

In a subsequent e-mail message, I will send the following 2 documents that provide detailed bioanalytical methods information:
- 820-0457: Automated Extraction of Olanzapine (LY170053) in Heparinized Human Plasma. [This report is relevant to all studies]
- 820-0192: The Measurement of Olanzapine in Heparinized Human Plasma [This report is relevant to study HGMF]

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

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

Cathy Melfi

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

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

12/14/2006 09:57 AM

To melfi@lilly.com

cc

Subject Assays

The NDA 20-592 has four studies:
1.F1D-MC-HGGC
2.F1D-MC-HGCS
3.F1D-MC-HGMF
4.F1D-SB-LOAY

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

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

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

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

Thanks

Andre Jackson
CDER/DCP1
301-796-1545
Please note new E-mail Address:
Andre.Jackson@fda.hhs.gov

**Bates, Doris J**

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

Cara:

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

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

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

Cathy

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

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

12/18/2006 10:35 AM

To Catherine Melfi <MELFI_CATHERINE@LILLY.COM>

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

Subject HGIU and HGIN Protocol Submissions

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

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

1/18/2007

Thank you.
Cara

*Cara Alfaro, Pharm.D., BCPP*
*Clinical Reviewer*
*Food and Drug Administration*
*CDER/Division of Psychiatry Products*
*10903 New Hampshire Avenue, Building 22, Room 4219*
*Silver Spring, MD 20993-0002*
*cara.alfaro@fda.hhs.gov*

1/18/2007

## Bates, Doris J

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

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

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

---

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

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

Cathy

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

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

12/06/2006 02:42 PM

To Catherine Melfi <MELFI_CATHERINE@LILLY.COM>

cc

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

Hi Cathy

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

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

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

---

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

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

Cathy Melfi

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

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

11/29/2006 03:10 PM

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

Investigators / Patients Randomized / Patients Completing at each site

Hi Cathy

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

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

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

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

Thanks in advance,

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

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.

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/

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Thomas Laughren
10/16/2006 01:29:43 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

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

Dear Ms. Wojcieszek:

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

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

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

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

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

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

**NDA ACKNOWLEDGMENT**

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

Dear Ms. Wojcieszek:

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

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

Review Priority Classification: Priority (P)

Date of Application: September 28, 2006

Date of Receipt: September 29, 2006

Our Reference Number: NDA 18-936

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

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

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and

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/

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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)*: | | | FROM: | |
|---|---|---|---|---|
| HFD- 860/Biopharm<br>Attention: Raman Baweja | | | HFD-130/ Division of Psychiatry Products | |
| DATE<br>10-06-06 | IND NO. | NDA NO.<br>21-520/S-12,20-592/S-39,21-086/S-21,18-936/S-77 | TYPE OF DOCUMENT<br>New Efficacy Supplements | DATE OF DOCUMENT<br>9-28-06 |
| NAME OF DRUG<br>Symbyax, Zyprexa Zyprexa Zydis, Prozac | PRIORITY CONSIDERATION<br>Priority Review | | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE<br>**Filing meeting: 11-7-06**<br>**PDUFA date: 3/29/07** |

NAME OF FIRM: (b) (4)

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER (SPECIFY BELOW): |

**III. BIOPHARMACEUTICS**

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

- ☐ CLINICAL
- ☐ PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**

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 | METHOD OF DELIVERY (Check one) |
|---|---|
| Renmeet Grewal, Pharm.D.<br>Regulatory Project Manager<br>301-796-1080<br>Renmeet.grewal@fda.hhs.gov | ☐ MAIL ☐ HAND |
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/s/

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Renmeet Gujral
10/10/2006 02:42:34 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# REQUEST FOR CONSULTATION

| TO *(Division/Office)*: | | | FROM: | |
|---|---|---|---|---|
| HFD- 710/Stat<br>Attention: Peiling Yang | | | HFD-130/ Division of Psychiatry Products | |
| DATE<br>10-10-06 | IND NO. | NDA NO.<br>21-520/S-12,20-592/S-39,21-086/S-21,18-936/S-77 | TYPE OF DOCUMENT<br>New Efficacy Supplements | DATE OF DOCUMENT<br>9-28-06 |
| NAME OF DRUG<br>Symbyax, Zyprexa Zyprexa Zydis, Prozac | PRIORITY CONSIDERATION<br>Priority Review | | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE<br>**Filing meeting: 11-7-06**<br>**PDUFA date: 3/29/07** |

NAME OF FIRM (b) (4)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
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- ☐ RESUBMISSION
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- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER (SPECIFY BELOW): |

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

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 | METHOD OF DELIVERY (Check one) |
|---|---|
| Renmeet Grewal, Pharm.D.<br>Regulatory Project Manager<br>301-796-1080<br>Renmeet.grewal@fda.hhs.gov | ☐ MAIL ☐ HAND |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

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/s/

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Renmeet Gujral
10/10/2006 02:44:54 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.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592

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

Dear Dr. Brophy:

Please refer to your correspondence dated May 21, 2002, requesting changes to FDA's November 30, 2001, Written Request for pediatric studies for Zyprexa (olanzapine).

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on November 30, 2001, and amended on April 9, 2002, remain the same.

- **Under ADOLESCENT SCHIZOPHRENIA; General Advice for Developing a Drug for Adolescent- Onset Schizophrenia; Specific Study Requirements for Development Program in Adolescent Schizophrenia; Study Design; Pediatric Efficacy and Safety Study**

  We have amended the clinical design for either inpatient or outpatient status as follows:

  "For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute inpatient or outpatient trial, with a recommended duration of at least 6 to 8 weeks."

We note your plans to include patients that meet the diagnostic criteria for schizophrenia, schizophreniform disorder and schizoaffective disorder. Our evaluation will focus on the schizophrenia patients.

- **Under ADOLESCENT BIPOLAR DISORDER; General Advice for Developing a Drug for Mania in Adolescent Bipolar Disorder; Specific Study Requirements for Development Program in Adolescent Mania in Association with Bipolar Disorder; Study Design; Pediatric Efficacy and Safety Study**

  We have amended the clinical design for either inpatient or outpatient status as follows:

  "For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute inpatient or outpatient trial, with a recommended duration of at least 3 weeks."

JUL 05 2002

- **Under Format of Reports to be Submitted**

  We have amended the "Format of reports to be submitted" section of your Written Request, which states the specific information on racial and ethnic minorities to be included in the final study report in accordance with Section 18 of the BPCA. Please note that we are changing the word "must" to "should" twice.

  "In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(s) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or White. For ethnicity, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino."

All other terms stated in our original Written Request or any subsequent amendments remain the same.

Reports of the studies that meet the terms of the Written Request dated November 30, 2001, as amended by our letter of April 9, 2002, and by this letter must be submitted to the Agency on or before November 30, 2006, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

COPY

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

*{See appended electronic signature page}*

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Robert Temple
6/29/05 02:20:26 PM

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JUL 05 2005

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA 20-592

Lilly Research Laboratories
Attn: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to the Written Request, originally issued on November 30, 2001, that you received from the Center for Drug Evaluation and Research, as well as the amendment issued in July 2002, from the Office of Counter-Terrorism and Pediatric Drug Development.

**BPCA § 18: Minority Children and Pediatric Exclusivity Program**

We are amending the "Format of reports to be submitted" section of your Written Request to require submitted reports to include more specific information on racial and ethnic minorities, in accordance with Section 18, *Minority Children and Pediatric-Exclusivity Program*, of the Best Pharmaceuticals for Children Act (BPCA) (Public Law 107-109). All other terms stated in our original Written Request remain the same.

> *Format of reports to be submitted:*
> In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(s) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

**BPCA § 9: Public Dissemination of Medical and Clinical Pharmacology Review Summaries for All Fileable Supplements Submitted in Response to Written Requests**

We note that the July 2002 re-issued Written Request notified you that an application submitted in response to a Written Request would be subject to the disclosure provisions of the BPCA. This letter also reminds you that in accordance with Section 9 of the BPCA, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request issued or re-issued under BPCA and filed by FDA, regardless of the following circumstances:

(1) the type of response to the Written Request (complete or partial);
(2) the status of the supplement (withdrawn after the supplement has been filed or pending);
(3) the action taken (i.e. approval, approvable, not approvable); or
(4) the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at [http://www.fda.gov/cder/pediatric/Summaryreview.htm] and publish in the Federal Register a notification of availability.

MAY 1 8 2004

G. Brophy

If you have any questions regarding this letter or the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. If you believe that the Written Request should be amended, please contact the review division directly.

Sincerely,

*{See appended electronic signature page}*

M. Dianne Murphy, M.D.
Director
Office of Counter-terrorism and Pediatric Drug Development
Center for Drug Evaluation and Research

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/s/
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Dianne Murphy
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA 20-592

Eli Lilly and Company
Attention: H. John Roth, Ph.D.
Sr. Reg. Res. Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Roth:

Please refer to the Written Request, originally issued on November 30, 2001, that you received from the Center for Drug Evaluation and Research. This Written Request was issued under Section 505A of the Federal Food, Drug, and Cosmetic Act to conduct pediatric studies using olanzapine. As you know, on January 4, 2002, the President signed into law the "Best Pharmaceuticals for Children Act," (BPCA) which both extended the pediatric exclusivity program established in the 1997 FDA Modernization Act (FDAMA) and provided new mechanisms for studying pediatric uses for drugs. The BPCA also contains new provisions of which you should be aware related to user fees, priority review, drug labeling, and disclosure of pediatric study results. FDA is revising its Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act to provide additional information on the pediatric drugs study provisions of the BPCA.

FDA has received questions about whether sponsors who were issued Written Requests to conduct pediatric studies prior to passage of the BPCA, but who had not as yet submitted the reports of the studies as of January 4, 2002, would be governed by the provisions of FDAMA or the BPCA. In order to maximize the benefit to be derived from the BPCA and to minimize uncertainty and delay in implementing the pediatric exclusivity program, FDA has decided to reissue those Written Requests originally issued prior to passage of the BPCA for which studies have not already been submitted.

This letter is your notification that the Written Request (and any subsequent amendments) described above is considered to be reissued as of the date of this letter. The terms of the Written Request are not otherwise altered by this letter. If you believe that the Written Request should be amended, please contact the division directly.

Please note that if the original Written Request was issued under Section 505A(a), it will now be considered to be issued under Section 505A(b), due to the reordering of the sections, as described in Section 19 of the BPCA. If the original Written Request was issued under Section 505A(c), it will still be considered to be issued under Section 505A(c).

An important change to note is that, if the drug for which FDA issued the Written Request under 505A(c) has listed patent or exclusivity protection, new section 505(d)(4)(A) states that within 180 days of receipt of this "reissued" Written Request, you must notify FDA when the pediatric studies will be initiated, or that you do not agree to conduct the requested studies. New provisions at Section 505(d)(4)(B)-(F) describe alternative methods for obtaining these pediatric studies.

If you have questions regarding the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. As noted above, requests to amend your Written Request should be directed to the review division.

Sincerely,

*{See appended electronic signature page}*

M. Dianne Murphy, M.D.
Director
Office of Counterterrorism and Pediatric Drug Development
Center for Drug Evaluation and Research

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/s/

Dianne Murphy
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592

Eli Lilly and Company
Attention: H. John Roth, Ph.D.
Sr. Reg. Res. Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Roth:

Please refer to your correspondence dated January 28, 2002, requesting changes to FDA's November 30, 2002, Written Request for pediatric studies for Zyprexa (olanzapine).

We reviewed your proposed changes and are amending the following section of the Written Request:

- **Under GENERAL REQUIREMENTS AND COMMENTS; Timeframe for Submitting Reports of the Study(ies)**

  We have amended the timeframe for submitting the reports of the studies from 3 years to 5 years (i.e., on or before November 30, 2006) as follows:

  "Reports of the above studies must be submitted to the Agency within 5 years from the date of this letter to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request."

Your requests to 1) omit the requirement to conduct a relapse prevention trial in adolescent schizophrenia, 2) revise the adolescent bipolar mania study to allow for a flexible dose design, and 3) allow the use of behavioral and/or dietary interventions for patients who gain weight during the trials will be dealt with in a separate letter. All other terms stated in our Written Request remain the same.

Reports of the studies that meet the terms of the Written Request dated November 30, 2002, as amended by this letter must be submitted to the Agency on or before November 30, 2006, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

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Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

*{See appended electronic signature page}*

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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Robert Temple
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592

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

Dear Dr. Brophy:

Reference is made to your Proposed Pediatric Study Request submitted on June 11, 1999, to your New Drug Application for Zyprexa (olanzapine) tablets (NDA 20-592).

We have completed our review of your submission and conclude that your proposed pediatric study request is incomplete.

To obtain needed pediatric information on olanzapine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from trials in pediatric patients with (1) schizophrenia, and with (2) acute mania, as part of bipolar I disorder, as described below.

**ADOLESCENT SCHIZOPHRENIA**

**General Advice for Developing a Drug for Adolescent-Onset Schizophrenia**

Schizophrenia is a chronic and debilitating illness that has an estimated lifetime adult prevalence of 0.5 to 1%. According to the DSM IV, the diagnostic criteria for schizophrenia are the same for the pediatric and adult populations, but the symptomatology and prevalence of schizophrenia in these two populations have been recognized to be somewhat different. Within the pediatric age group, a diagnosis of schizophrenia is most commonly made in adolescents, and the symptoms in this age group are generally similar to those in adults (APA Practice Parameters, 1997). Schizophrenia has also been described in children, but it is thought to be uncommon (AACAP Practice Parameters, 2001). Although there are not adequate epidemiological data, one author suggests that 0.1 to 1 % of schizophrenic psychoses will present prior to age 10 (Remschmidt, 1996). In addition, the symptoms in childhood schizophrenia differ from those typically seen in adult schizophrenia and the diagnosis is more difficult to establish in this younger population (Volkmar, 1996).

Given the finding that childhood onset schizophrenia may present with symptoms quite different from those of adult onset schizophrenia, it would be important to systematically study the efficacy of treatment within this pediatric population. The very low incidence of schizophrenia diagnosed prior to the age 13, however, makes it unlikely that it would be possible to conduct a sufficiently large study of this age group within a reasonable time. For this reason, and because there is still controversy about the validity of this diagnosis in children, this written request will be limited to the study of schizophrenia in adolescents aged 13 to 17 years.

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In issuing this request, we would like to stress the importance and challenge of accurately diagnosing schizophrenia in the pediatric population. The differential diagnosis may include bipolar disorder, mood disorder with psychosis, personality disorders, other psychotic disorders with organic etiologies, in addition to many disorders that classically present in childhood, such as the pervasive developmental disorders and developmental language disorders (AACAP Practice parameters, 2001). An indication of the difficulty of diagnosis is an NIMH study reporting that 7 of 31 (23%) children originally diagnosed with treatment-resistant childhood-onset schizophrenia were re-assessed after a 4 week medication free wash-out period and found not to have that disease; revised diagnoses included posttraumatic stress disorder, atypical psychosis, and personality disorder (Kumra, 1999).

Under FDAMA (1997), adequate assessment of adolescents (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. This approach is explicitly considered in the guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires that the adult data be considered reasonably relevant to the course of the disease and the effects of the drug in the pediatric populations. Although we are aware of only two published placebo controlled studies supporting the efficacy of neuroleptics (haloperidol & loxitane) in the treatment of pediatric schizophrenia (Spencer et al., 1992 & Pool et al., 1976), we believe that a sufficiently strong case has been made for continuity between adult and adolescent schizophrenia to permit a pediatric claim for a drug already approved in adults to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent schizophrenia. In addition, a pediatric schizophrenia program would need to include pharmacokinetic information and safety information in the relevant pediatric age group. For pediatric schizophrenia, we consider the relevant age group to include adolescents aged 13-17 years.

Bibliography

American Academy of Child and Adolescent Psychiatry. (2001). Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40(7, Supplement), 4S-23S.

American Psychiatric Association (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association.

American Psychiatric Association (1997). Practice guideline for the treatment of patients with schizophrenia. *American Journal of Psychiatry*, 154(4 Suppl): 1-63.

Kumra, S, Briguglio C, Lenane M, et al. (1999), Including Children and Adolescents with Schizophrenia in Medication-Free Research. *American Journal of Psychiatry*, 156:7: 1065-1068.

Pool D, Bloom W, Mielke DH et al. (1976), A controlled evaluation of loxitane in seventy-five adolescent schizophrenia patients. *Current Therapeutic Research Clinical and Experimental* 19:99-104.

Remschmidt H, Schulz E, Herpertz-Dahlmann B (1996), Schizophrenic Psychoses in Childhood and Adolescence *CNS Drugs* Aug: 6(2):100-112.

Spencer EK, Jafantaris V., Pardron-Gayol MV, et al. (1992), Haloperidol in schizophrenic children: early findings from a study in progress *Psychopharmacol Bull* 28:183-186.

Volkmar F (1996), Childhood and Adolescent Psychosis: a Review of the Past 10 Years *Journal of the American Academy of Child and Adolescent Psychiatry* 35(7):843-851.

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**Specific Study Requirements for Development Program in Adolescent Schizophrenia**

Types of Studies

Pediatric Efficacy and Safety Study

Pediatric Pharmacokinetic Study

Pediatric Safety Study

Objective/Rationale

The overall goal of the development program would be to establish the safety and efficacy of the study drug in the treatment of adolescent schizophrenia, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

Study Design

Pediatric Efficacy and Safety Study

- For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute inpatient trial, with a recommended duration of at least 6 to 8 weeks. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms are not adequately controlled to a specific extent at some point on assigned treatment or who worsen. At least 50% of patients assigned to active drug must complete to the nominal endpoint of this trial in order for it to be considered a completed trial. We strongly recommend that the trial be a fixed dose study including at least two fixed doses of the study drug. A relapse prevention trial should follow the acute treatment trial, in which responders to acute treatment would be randomized to study drug or placebo, with follow-up observation for relapse for a period of 6 months or more with assessment of time to relapse and treatment of relapsed patients. Both the acute and the relapse prevention trials should be limited to patients capable of giving assent to participate in the trial.

Pediatric Pharmacokinetic Study

- You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to the controlled efficacy trial or to other safety trials. Adequate pharmacokinetic data from studies in a single indication would be sufficient to meet this requirement. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Pediatric Safety Study

ZY 8264 560

- Safety data must be collected in the controlled efficacy trial. In addition, longer-term safety data, for a minimum duration of 6 months exposure to the drug, must be collected. The longer-term safety data could come from open studies, e.g., a longer-term open extension of the controlled efficacy trial populations, from separate longer-term open safety studies, or from controlled

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studies, e.g., a longer-term safety and efficacy trial. Adequate longer-term safety data from studies in a single indication would be sufficient to meet this requirement.

Age Group in Which Study(ies) will be Performed –All Studies

Adolescents (ages 13 to 17 years) must be included in the sample, and there must be a reasonable gender and age distribution within this sample.

Number of Patients to be Studied

Pediatric Efficacy and Safety Study

- The study must have a sufficient number of patients to provide reasonable statistical power to show a difference between drug and placebo. While it is difficult to specify the sample size needed to accomplish this, it should be noted that positive trials in adult schizophrenia have generally utilized samples of at least 60 patients per treatment arm. It will probably be necessary to conduct a multicentered study to ensure a sufficient population accurately diagnosed with schizophrenia.

Pediatric Pharmacokinetic Study

- A sufficient number of patients to adequately characterize the pharmacokinetics of the study drug in the above age group.

Pediatric Safety Study

- A sufficient number of pediatric patients to adequately characterize the safety of the study drug at clinically relevant doses for a sufficient duration. At least 100 patients exposed to drug for at least 6 months would be a minimum requirement for long-term safety.

Entry Criteria

The protocols must include a valid and reliable diagnostic method for recruiting and enrolling adolescents with schizophrenia. Given the difficulty in making the diagnosis for screening purposes, it is recommended that a clinical interview of children and their parents or caregivers be conducted by an adequately trained clinician (e.g. child psychiatrist) to assure accurate diagnosis. It is also recommended that the diagnosis be confirmed using a reliable and valid semi-structured interview.

Patient Evaluations and Study Endpoints

Pediatric Efficacy and Safety Study

- A scale specific to schizophrenia and sensitive to the effects of drug treatment of schizophrenia in the target population should be used. It may also be useful to add a global measure, e.g., the Clinical Global Impression (CGI). It is essential to identify a primary outcome (or outcomes if more than one is considered important) for the controlled efficacy trial; ordinarily this would be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trial.

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Pediatric Pharmacokinetic Study

- Pharmacokinetic assessments must be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite measured, the data collected should provide estimates of important pharmacokinetic parameters, e.g., AUC, half-life, $C_{max}$, $t_{max}$, and apparent oral clearance in pediatric subjects in the relevant age range. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available at [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].

Pediatric Safety Study

- Routine safety assessments must be collected at baseline and appropriate follow-up times, i.e., vital signs (pulse rate and blood pressure), weight, height, clinical laboratory measures (chemistry, hematology, and urinalysis), ECGs, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias). Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and we encourage you to consider longer-term studies of a year or more to address this question if the acute studies demonstrate efficacy in schizophrenia.

Statistical Information

Pediatric Efficacy and Safety Study

- This trial must have a detailed statistical plan. The trial should be designed with at least 80% statistical power to detect a reasonable treatment effect (probably best based on typical effects in adults) at conventional levels (alpha=0.05, 2-tailed) of statistical significance.

Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters.

Pediatric Safety Study

- Descriptive analysis of the safety data.

## ADOLESCENT BIPOLAR DISORDER

### General Advice for Developing a Drug for Mania in Adolescent Bipolar Disorder

According to the DSM IV, the diagnostic criteria for mania are the same for the pediatric and adult population. However, the lower end of the age range for bipolar disorder is not clear. Bipolar disorder below the age of 13 years is considered both uncommon and difficult to diagnose. On the other hand, bipolar disorder in the adolescent population is thought to be relatively common and phenomenologically similar to bipolar disorder seen in adults. Thus, the study of bipolar disorder in adolescents should be feasible and should yield useful information.

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Under FDAMA (1997), adequate assessment of adolescents (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. This approach is explicitly considered in the guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires that the adult data be considered reasonably relevant to the course of the disease and the effects of the drug in the pediatric populations. We believe that a sufficiently strong case has been made for continuity between adult and adolescent bipolar disorder to permit a pediatric claim for a drug already approved in adults for mania to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent mania in association with bipolar disorder. In addition, a pediatric mania program would need to include pharmacokinetic information and safety information in the relevant pediatric age group. For pediatric mania, we consider the relevant age group to include adolescents aged 13-17 years.

Bibliography

American Psychiatric Association (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association.

**Specific Study Requirements for Development Program in Adolescent Mania in Association with Bipolar Disorder**

Types of Studies

Pediatric Efficacy and Safety Study

Pediatric Pharmacokinetic Study

Pediatric Safety Study

Objective/Rationale

The overall goal of the development program would be to establish the safety and efficacy of the study drug in the treatment of adolescent mania in association with bipolar disorder, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

**Study Design**

Pediatric Efficacy and Safety Study ZY 8264 563

- For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute inpatient trial, with a recommended duration of at least 3 weeks. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms are not adequately controlled to a specific extent at some point on assigned treatment or who worsen. At least 50% of patients assigned to active drug must complete to the nominal endpoint of this trial in order for it to be considered a completed trial. We strongly recommend that the trial be a fixed dose study including at least two fixed doses of the study drug. Given the lack of a robust evidence base for the use of lithium in adolescent mania, there is uncertainty about the optimal therapeutic approach in this population. Thus, this could be a monotherapy trial, or an add-on trial, e.g., adding study drug or placebo to patients already taking lithium. In addition, you may consider a relapse prevention trial to follow from the acute treatment trial, in which responders to acute

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treatment would be randomized to study drug or placebo, with follow-up observation for relapse for a period of 6 months or more with assessment of time to relapse and treatment of relapsed patients. Both the acute and the relapse prevention trials should be limited to patients capable of giving assent to participate in the trial.

Pediatric Pharmacokinetic Study

- You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to the controlled efficacy trial or to other safety trials. Adequate pharmacokinetic data from studies in a single indication would be sufficient to meet this requirement. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Pediatric Safety Study

- Safety data must be collected in the controlled efficacy trial. You may consider collecting longer-term safety data. The longer-term safety data could come from open studies, e.g., a longer-term open extension from the controlled efficacy trial and/or in separate longer-term open safety studies, or from controlled studies, e.g., a longer-term safety and efficacy trial. Adequate longer-term safety data from studies in a single indication would be sufficient to meet this requirement.

Age Group in Which Study(ies) will be Performed –All Studies

Adolescents (ages 13 to 17 years) must be included in the sample, and there must be a reasonable gender and age distribution.

Number of Patients to be Studied

Pediatric Efficacy and Safety Study

- The study must have a sufficient number of patients to provide reasonable statistical power to show a difference between drug and placebo. While it is difficult to specify the sample size needed to accomplish this, it should be noted that positive trials in adult mania have generally utilized samples of at least 60 patients per treatment arm. It will probably be necessary to conduct a multicentered study to ensure a sufficient population accurately diagnosed with mania.

Pediatric Pharmacokinetic Study

- A sufficient number of patients to adequately characterize the pharmacokinetics of the study drug in the above age group.

Pediatric Safety Study

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- A sufficient number of pediatric patients in the above age group to adequately characterize the safety of the study drug at clinically relevant doses for a sufficient duration. At least 100 patients exposed to drug for at least 6 months would be a minimum requirement for long-term safety.

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Entry Criteria

The protocols must include a valid and reliable diagnostic method for recruiting and enrolling adolescents with mania. Given the difficulty in making the diagnosis for screening purposes, it is recommended that a clinical interview of children and their parents or caregivers be conducted by an adequately trained clinician (e.g. child psychiatrist) to assure accurate diagnosis. It is also recommended that the diagnosis be confirmed using a reliable and valid semi-structured interview.

Patient Evaluations and Study Endpoints

Pediatric Efficacy and Safety Study

- A scale specific to mania and sensitive to the effects of drug treatment of mania in the target population should be used. It may also be useful to add a global measure, e.g., the Clinical Global Impression (CGI). It is essential to identify a primary outcome (or outcomes if more than one is considered important) for the controlled efficacy trials, and ordinarily this would be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trials.

Pediatric Pharmacokinetic Study

- Pharmacokinetic assessments must be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite measured, the data collected should provide estimates of important pharmacokinetic parameters, e.g., AUC, half-life, $C_{max}$, $t_{max}$, and apparent oral clearance in pediatric subjects in the relevant age range. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available at [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].

Pediatric Safety Study

- Routine safety assessments must be collected at baseline and appropriate follow-up times, i.e., vital signs (pulse rate and blood pressure), weight, height, clinical laboratory measures (chemistry, hematology, and urinalysis), ECGs, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias). Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and you may consider longer-term studies of a year or more to address this question, if the acute studies and any longer-term efficacy studies that you may conduct demonstrate efficacy in bipolar disorder.

Statistical Information

Pediatric Efficacy and Safety Study

- This trial must have a detailed statistical plan. The trial should be designed with at least 80% statistical power to detect a reasonable treatment effect (probably best based on typical effects in adults) at conventional levels (alpha=0.05, 2-tailed) of statistical significance.

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Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters.

Pediatric Safety Study

- Descriptive analysis of the safety data.

## GENERAL REQUIREMENTS AND COMMENTS

### Drug Information

Use age appropriate formulations in the studies described above. Since the pediatric patient population consists of adolescents (ages 13 to 17), your marketed solid dosage formulation should be adequate for these studies.

### Drug Concerns

No specific concerns related to administration to schizophrenic or manic pediatric patients were identified while studying olanzapine in adults, nor have specific concerns been identified during the postmarketing experience.

### Labeling That May Result from the Studies

The pediatric schizophrenia and mania efficacy, safety, and pharmacokinetic studies described in this request could result in the addition to labeling of information pertinent to these studies.

### Format of Reports to be Submitted

Full study reports or analyses, not previously submitted to the Agency, addressing the issues outlined in this request, with full analysis, assessment, and interpretation.

### Timeframe for Submitting Reports of the Study(ies)

Reports of the above studies must be submitted to the Agency within 3 years from the date of this letter to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

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Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, contact Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely yours,

*{See appended electronic signature page}*

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Robert Temple
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